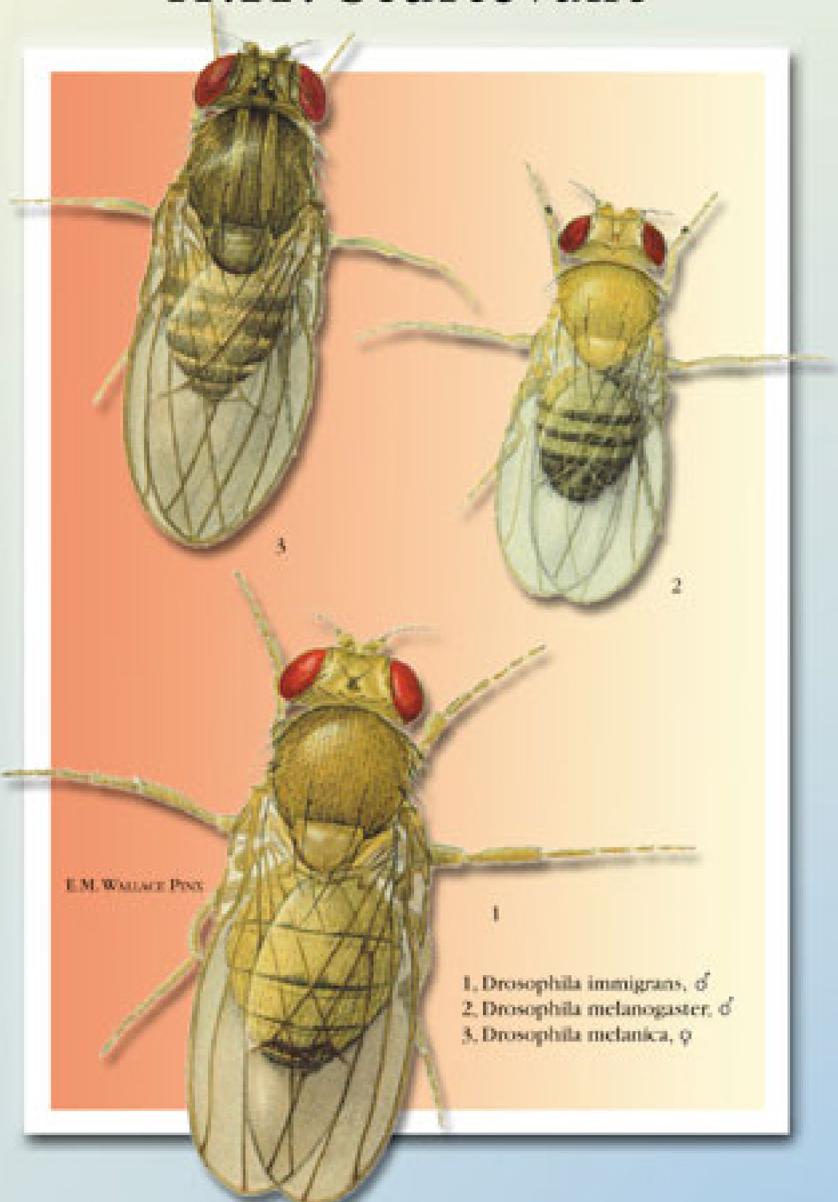
A History of Genetics

A.H. Sturtevant



with an introduction and afterword by

E.B. Lewis

Cold Spring Harbor Laboratory Press

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A HISTORY OF GENETICS

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WITH AN INTRODUCTION BY EDWARD B. LEWIS

Cold Spring Harbor Laboratory Press
Cold Spring Harbor, New York

Electronic Scholarly Publishing Project
http://www.esp.org

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Published by Cold Spring Harbor Laboratory Press and Electronic Scholarly Publishing Project

Electronic Scholarly Publishing Project
ESP Foundations Reprint Series: Classical Genetics
Series Editor: Robert J. Robbins
Electronic Production: Ana Dos Santos, William Landram

Cold Spring Harbor Laboratory Press
Acquisition Editor: John R. Inglis
Production Editor: Mala Mazzullo
Cover Designers: Robert J. Robbins / Danny deBruin

Front Cover: Species of Drosophila, by Edith M. Wallace, Plate 3, from *The North American Species of* Drosophila, by A. H. Sturtevant, 1921, Carnegie Institution of Washington.

Back Cover: Sex-linked inheritance, Figure 38 from *The Theory of the Gene*, by T. H. Morgan, 1926, Yale University Press.

Bibliographical Note: This CSHLP/ESP edition, first published in 2000, is a newly typeset, unabridged version of *A History of Genetics*, by A. H. Sturtevant, based on the second printing of the original 1965 book, published by Harper & Row in their Modern Perspectives in Biology series. All footnotes were taken from the original work. The figures have been redrawn for this edition.

Availability: A directory of Cold Spring Harbor Laboratory Press publications is available at http://www.cshl.org/books/directory.htm. All Electronic Scholarly Publishing Project publications may be obtained online, from http://www.esp.org.

Web site: The full text of this book, along with other supporting materials, including full-text copies of many of the works discussed by the author, may be obtained at the book's web site: http://www.esp.org/books/sturt/history.

Library of Congress Cataloging-in-Publication Data
Sturtevant, A. H. (Alfred Henry), 1891-
A history of genetics / A. H. Sturtevant
p. cm.
Previously published: New York: Harper & Row, 1965.
Includes bibliographical references and index.
ISBN 0-87969-607-9 (pbk.: alk. paper)
1. Genetics--History. I. Title
QH428 .S78 2000
576.5'09--dc21 00-052394

10 9 8 7 6 5 4 3 2 1

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NOTE FROM THE PUBLISHERS

This book is special in several rather diverse ways. First published by Alfred Sturtevant in 1965, it is one of the very few accounts of the early days of genetics by one who was there—the truths of a reporter rather than an historian. Sturtevant was one of an accomplished trio of Thomas Hunt Morgan's students, and although his name may resonate less with today's scientists than the names of his colleagues Bridges and Muller, his keen intelligence and broad scientific interests gave his book a scope of unusual breadth and interest. Yet it did not endure. A second printing appeared in 1967. Three years later Sturtevant was dead, and increasingly rare copies of his book were consigned to library shelves and second-hand shops as the concepts and techniques of molecular biology swept to dominance in the field of genetics.

This reprinted edition has its origins in two independent initiatives. Prompted by colleagues on the scientific staff, Cold Spring Harbor Laboratory Press has in recent years republished two long-out-of-print books with both historical interest and continued contemporary relevance: *The Biology of* Drosophila by Milislav Demerec and *The Structure and Reproduction of Corn* by Theodore Kiesselbach. The response to these volumes was warm and encouraging, so when the idea of reviving Sturtevant's classic was suggested, we were enthusiastic, particularly when it was pointed out that Sturtevant's student and recent Nobel Prize winner, Edward Lewis, might be persuaded to write a new introduction to the book. Dr. Lewis kindly agreed to the task and did his part quickly and well. However, the currently rapid rate of growth and expansion within the Press meant that momentum on the project slowed, since the project lacked the urgency of books with the latest research results that are our typical output.

Independently, Robert Robbins, a biologist turned information scientist with a long-standing interest in both the history of science and the technology of publishing, had become interested in seeing the book return to print. Intrigued by the possibilities of networked information, he had established the Electronic Scholarly Publishing Project, a web-based repository of historically interesting books and papers displayed in a way that leveraged the unique advantages of online delivery—full text-based searching, links to other electronic information sources, and personal annotation of the stored document. The ESP Project places a special emphasis on works related to the foundations of classical genetics.

Robbins' desire to add the Sturtevant book to this repository led him first to the Sturtevant family, then to Ed Lewis, then to Cold Spring Harbor Laboratory itself, with the result that the Electronic Scholarly Publishing Project and the Cold Spring Harbor Laboratory Press agreed to produce the book jointly, with an online and a print version to appear simultaneously.

The outcome is the book you hold in your hands. Along with the physical book, we have also produced a website associated with the project. At that site, readers may obtain full-text electronic versions of many of the key papers discussed by Sturtevant, including Sturtevant's own "The linear arrangement of six sex-linked factors in Drosophila, as shown by their mode of association," which contained the world's first genetic map. The book's website can be seen at http://www.esp.org/books/sturt/history.

The partnership of Cold Spring Harbor Laboratory Press with the Electronic Scholarly Publishing Project is an experiment, one of many being conducted in this era of new publishing paradigms. It is our hope that for the reader, this print–online combination will deliver the best of both media, as a vehicle of an exceptional work of scholarship that deserves fresh recognition by a new generation of scientists.

We are pleased that this book appears in the year 2000—a year with special significance for genetics and for the study of *Drosophila melanogaster*. This is the 100th anniversary of the founding of modern genetics with the rediscovery of Mendel's work, and it is the year in which the full DNA sequence of the Drosophila genome was obtained. The fruit fly is still at the center of genetic research, just as it was when Sturtevant first began his work in the "Fly Room" at Columbia University.

JOHN R. INGLIS
Cold Spring Harbor Laboratory Press

ROBERT J. ROBBINS
Electronic Scholarly Publishing Project

INTRODUCTION

The reprinting of this classic book provides students with one of the few authoritative, analytical works dealing with the early history of genetics. Those of us who had the privilege of knowing and working with Sturtevant benefited greatly from hearing first-hand his accounts of that history as he knew it and, in many instances, experienced it. Fortunately, Sturtevant put it all together in this book.

In his preface to the book, Sturtevant lists the persons that he knew personally and who were major players in the field, in addition to those who occupied the famous fly room (Chapter 7) at Columbia University. As a result, much of the history is based on first-hand contacts as well as on a scholarly and critical review of the literature of genetics and cytology.

Sturtevant was clearly present at the creation of modern genetics, if dated from 1910 when Morgan commenced work on Drosophila. Of Morgan's three students—Sturtevant, Bridges, and Muller—Sturtevant was ideally suited to write the history because of his remarkable memory, his knowledge of almost all aspects of biology, and a keen analytical ability that extended not only to his experimental work, but also to tracing the history of the underlying ideas.

Sturtevant was a gifted writer and also an authority on many of the subjects he covers. While he was a sophomore in college, he deduced the linear order of the genes. Later, he postulated the existence of inversions and duplications before they were verified cytologically. Sturtevant was especially interested in how genes produce their effects and, consequently, was the father of a field now called developmental genetics. In this area, his style was to analyze exceptions to the rule. In so doing, he identified the phenomenon of position effect, in which the position of a gene (that of the Bar, and double-Bar, eye mutations) can be shown to affect its function. He identified the first clear case of a non-autonomously expressed gene, vermilion, mutants of which produce a vermilion, instead of the normal red, eye color. This was an important exception to the rule that sex-linked mutants behaved autonomously in gynandromorphs. How this led to the field of biochemical genetics is explained in Chapter 16.

In the tradition of such biologists as Darwin, Galton, and Bateson and of many of the early Mendelians, Sturtevant was an ardent evolutionist. He had a seemingly inexhaustible knowledge of embryology, anatomy, morphology, and taxonomy that served him well in treating evolutionary concepts historically, as described in Chapter 17. It is a wide-ranging chapter that covers many topics, including the development of population genetics, the role of gene mutations in evolution, and, prophetically, the conservation of biochemical pathways in major groups from bacteria to vertebrates. His own experimental work, typically only briefly referred to, included his work on interracial and interspecific hybrids in the genus Drosophila, and the demonstration that the genetic content of different species of that genus is remarkably conserved, whether it be in the X chromosome or in each of the specific autosomal arms. Sturtevant always had a healthy skepticism, surely one of the most important qualities of a successful scientist. This is shown by his doubt of the value of many laboratory experiments in population genetics, on the basis that they cannot faithfully duplicate what really goes on in the great out-of-doors.

It may come as a surprise to many students to realize how much opposition there was in some quarters to the early discoveries of the Morgan school. Sturtevant's account of such controversies is a recurrent theme of this book, as it should be in a historical treatise.

Science has often been advanced by scientists who questioned existing dogma and found it flawed. Or, conversely, such dogma has probably in some cases slowed progress for years. Would advances in genetics have been more rapid had there not been the virtually universal belief that genes were proteins, or that development of an organism involved cytoplasmic rather than nuclear heredity? Sturtevant does not waste space speculating about such issues, but he does discuss several cases in which progress was held back because of failure to develop a satisfactory terminology and symbolism.

Sturtevant had a strong social consciousness that comes forth in Chapter 20. There he treats the history of human genetics, stressing the difficulties and pitfalls that plague studies in this field. He devotes considerable space to an objective and critical analysis of the so-called "nature vs. nurture" question.

In the last chapter, Sturtevant discusses how discoveries in science and particularly genetics tend to come about. He addresses in his typically analytical way the often-cited dictum: The time has to be ripe for a discovery to be made and that when that time comes someone is bound to make the discovery. He concludes that this attitude greatly oversimplifies what generally happens in science.

I believe Sturtevant's writing of this book after his retirement was one more intellectual exercise to stave off boredom. He had reduced his experimental work to an hour or so each day, and it must have been more difficult to keep up with the expanding literature of the field. His book is clearly a labor of love and his personality shines through every page.

July 2000 E. B. Lewis
Pasadena, California

AUTHOR'S PREFACE

The publication of Mendel's paper of 1866 is the outstanding event in the history of genetics; but, as is well known, 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. What was the state of knowledge about heredity in Mendel's day; what sort of man was Mendel, and how did he come to make his discovery; what happened between 1866 and 1900 to account for the different reaction to his results; how did his paper come to be found, and just what was the immediate reaction?

These questions are discussed in the first four chapters. From that point on, it has seemed more logical to treat the various topics separately rather than to follow a more nearly chronological order. The attempt has been, in each case, to trace the beginnings of a subject and to bring it down to the work currently being done—but not to discuss presently active fields of work, since these are adequately covered in current books and reviews. There is no definite terminal date, but work later than about 1950 is generally omitted or is referred to only briefly. In other fields the cutoff date is even earlier than this.

For Chapters 1 and 3 I have relied largely on secondary sources such as Sachs (1875), Zirkle (1935), Roberts (1929), and Wilson (1925). For the period after 1900 I have read or reread much of the original literature and, for general background, have been fortunate enough to have had some direct personal contact with many of the people discussed—including, among the early workers, de Vries, Bateson, Johannsen, Wilson, Morgan, McClung, East, Shull, Castle, Emerson, Davenport, Punnett, Nilsson-Ehle, Goldschmidt, and others. (I have seen Cuénot, Baur, Sutton, and Saunders but never really knew them.)

I am indebted to numerous colleagues who have read part or all of the manuscript and have made constructive suggestions. Especially to be named are Drs. N. H. Horowitz, E. B. Lewis, H. L. Roman, C. Stern, G. Hardin, and C. Fulton. Much of the material has been presented in a series of lectures at the California Institute of Technology and at the Universities of Washington, Texas, and Wisconsin; numerous discussions with colleagues at these institutions have been very helpful.

August 1965 A. H. STURTEVANT
Pasadena, California

CHAPTER 1

BEFORE MENDEL

In discussing the history of a subject it is usual to begin with Aristotle—and he forms a convenient starting point for genetics, though the real beginnings, even of theoretical genetics, go farther back. As a matter of fact, much of Aristotle's discussion of the subject is contained in his criticism of the earlier views of Hippocrates.

Hippocrates had developed a theory resembling that later proposed by Darwin, who called it "pangenesis." According to this view, each part of the body produces something (called "gemmules" by Darwin) which is then somehow collected in the "semen"—or as we should now say, the germ cells. These are the material basis of heredity, since they develop into the characters of the offspring. The view was developed, both by Hippocrates and by Darwin, largely to explain the supposed inheritance of acquired characters. Aristotle devoted a long passage to criticism of this hypothesis, which he discarded for several reasons. He pointed out that individuals sometimes resemble remote ancestors rather than their immediate parents (which is in fact one of the arguments used by Darwin *for*, rather than *against*, pangenesis, since Darwin did not suppose that the gemmules necessarily came to expression in the first generation and did not suppose, as did Hippocrates, that they were released from the parts of the body at the moment of copulation). Aristotle also pointed out that peculiarities of hair and nails, and even of gait and other habits of movement, may reappear in offspring, and that these are difficult to interpret in terms of a simple form of the hypothesis. Characters not yet present in an individual may also be inherited—such things as gray hair or type of beard from a young father—even before his beard or grayness develops. More important, he pointed out that the effects of mutilations or loss of parts, both in animals and in plants, are often not inherited. Aristotle, like everyone else until much later, accepted the inheritance of acquired characters; but he was nevertheless aware that there was no simple one-to-one relation between the presence of a part in parents and its development in their offspring. His general conclusion was that what is inherited is not characters themselves in any sense but only the potentiality of producing them. Today this sounds self-evident, but at that time it was an important conclusion, which was not always fully understood, even by the early Mendelians.

Aristotle was a naturalist and described many kinds of animals—some imaginary, others real and described in surprisingly accurate detail. He knew about the mule and supposed that other animals were species hybrids—that the giraffe, for example, was a hybrid between the camel and the leopard. According to him, in the dry country of Libya there are few places where water is available; therefore many kinds of animals congregate around the water holes. If they are somewhere near the same size, and have similar gestation periods, they may cross; this is the basis for the saying that "something new is always coming from Libya."

Some later authorities disregarded Aristotle's reasonable limitations on what forms might be expected to cross, as in the conclusion that the ostrich is a hybrid between the sparrow and the camel. There is a long history of such supposed hybrids—notably of the crossing between the viper and the eel, and of the hybrid between the horse and the cow. Zirkle records accounts of both of these as late as the seventeenth century.

The knowledge of sex in animals goes far back before the beginnings of history and was understood quite early even in plants—at least in two important food plants of the Near East, namely, the Smyrna fig and the date palm, both of which are dioecious (that is to say, have separate male and female trees). Zirkle shows that a special Near Eastern deity (the cherub) was supposed to preside over the date pollination, and that representations of this deity can be traced back to about 1000 B.C. There is, in fact, evidence that male and female trees were grown separately as early as 2400 B.C.

The condition found in these two trees was definitely related to the phenomenon of sex in animals, by Aristotle and others, but it was much later that it was realized that plants in general have a sexual process.

That the higher plants do have sexual reproduction and that the pollen represents the male element seems to have been first indicated as an important generalization by Nehemiah Grew in 1676. A sound experimental basis was first given by Camerarius (1691 to 1694). From that time on, the view was rather generally accepted, especially after Linnaeus presented more evidence and lent the prestige of his name in 1760.

More or less casual observations on natural or accidental hybrids in plants were made over a long period, beginning with the observations of Cotton Mather on maize in 1716. However, the systematic study of plant hybrids dates from the work of Kölreuter, published from 1761 to 1766. His work laid the foundations of the subject and was familiar to Darwin and to Mendel, both of whom discussed it a hundred years later.

Kölreuter made many crosses, studied the pollination process itself, and also recognized the importance of insects in natural pollination. He used a simple microscope to study the structure of pollen and was the first to describe the diversity of pollen grains found in seed plants. He also made studies on the germination of pollen. These studies on germination were carried out on pollen in water, with the result that the pollen tubes plasmolyzed almost immediately. This led Kölreuter to conclude that the fertilizing agent was the fluid released on the stigma, rather than a formed element from a particular pollen grain.

In another respect he reached a wrong conclusion that delayed the development of a clear understanding of fertilization, namely, the view that more than one pollen grain is necessary for the production of a normal seed. This view was based on experiments with counted numbers of pollen grains, which seemed conclusive to him. The result was generally accepted for some time, and even Darwin adopted it *(The Variation of Animals and Plants under Domestication*, Ch. 27) on the authority of Kölreuter, and of Gärtner, who later confirmed the experiments. Kölreuter supposed, as a result of his experiments, that he could recognize "half-hybrids," that is, individual plants derived from pollen that was partly from the seed parent and partly from a different plant. Like Aristotle and other predecessors, he thought of fertilization as resulting from a mixing of fluids, basing this in part on his direct observations of germinating pollen.

His observations on the hybrids themselves were of importance. He recognized that they were usually intermediate between the parents (he was nearly always using strains that differed in many respects), but he did record a few cases where they resembled one parent. He recognized the sterility often found in hybrids between widely different forms and showed that in some of these the pollen was empty. He emphasized the identity of the hybrids from reciprocal crosses—which is rather surprising, since plastid differences might have been expected in some of such a large number of reciprocal species hybrids.

Kölreuter reported a few instances of increased variability in the offspring of hybrids but laid no emphasis on this observation. He also observed the frequent great increase in the vegetative vigor of hybrids and suggested that it might be of economic importance, especially if hybrid timber trees could be produced.

Following Kölreuter, there were a number of men engaged in the study of plant hybrids. Detailed accounts of their work are given by Roberts (1929), but perhaps the most satisfactory general account of the state of knowledge in Mendel's time is to be found in Darwin's discussion in *The Variation in Animals and Plants under Domestication* (1868).*

Darwin collected a vast amount of information from the works of the plant hybridizers, from works on the practical breeding of domestic animals and cultivated plants, and from gardeners, sportsmen, and fanciers. He himself carried out numerous experiments with pigeons and with various plants. The book is still interesting, as a source of information and of curious observations. Darwin was looking for generalizations, and extracting them from masses of observations was his special ability. But, in the case of heredity, the method yielded very little. He recognized two more or less distinct types of variations—those that came to be known as continuous and discontinuous, respectively. The latter, sometimes called "sports," he recognized as sometimes showing dominance, and as being often transmitted unchanged through many generations. But he felt that they were relatively unimportant as compared to the continuously varying characters, which could be changed gradually by selection and which gave intermediate hybrids on crossing. He concluded that crossing has a unifying effect. Since hybrids are generally intermediate between their parents, crossing tends to keep populations uniform, while inbreeding tends to lead to differences between populations; this same conclusion is shared by modern genetics, though the arguments are not quite the same as Darwin's.

He reported crosses which led to increased variability in the second and later generations, but he was interested in them chiefly because of their bearing on the question of reversion to ancestral types. He also recognized the increase in vigor that often results from crossing and observed the usual decline due to continued inbreeding. He carried out numerous detailed experiments in this field, which are elaborated in one of his later books, *(The Effects of Cross and Self Fertilization in the Vegetable Kingdom*, 1876).

On the origin of variability, Darwin had little to say that sounds

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* Darwin's books were extensively altered in successive editions, and it is not always safe to consult a later edition and then to assign the views given therein to the date of the first edition. Although I have not seen the first edition of the book, I have no reason to suppose that its date is misleading in this connection.

modern. He thought that changed conditions, such as domestication, stimulated variability and also affected the inheritance both in selection within a strain and in crosses between strains. The effects of selection were familiar to him, but he was not aware of the basic distinction between genetically and environmentally produced small variations.

Darwin's own theory of heredity (pangenesis) was not generally well received, but it did apparently serve to suggest the particulate theories of Weismann and of de Vries, which paved the way in 1900 for the appreciation of Mendel's work.

The development of ideas about inheritance in animals and in plants was rather independent, for in plants the early experiments were directed largely toward the demonstration of sexual reproduction, which needed no demonstration in animals. This led to the study of hybrid plants, but in animals the development was largely in the hands of practical breeders, who were more concerned with selection than with crossing. One of the striking things about Darwin was that he had a detailed firsthand knowledge of both animals and plants, and of the literature on both. In his work we find the modern custom of discussing theory without regard to the distinction between animals and plants. It is true that this had been done before—by Aristotle, for example—but not to the extent that Darwin introduced. It may be noted that the previous hybridizers referred to in Mendel's paper (Kölreuter, Gärtner, Herbert, Lecoq, and Wichura) were all botanists. Since Mendel referred to them, we may suppose that they influenced his work; therefore there follow brief accounts of the last four, since Kölreuter has already been discussed.

Gärtner's work was published largely in 1839 and in 1849. He made a large number of crosses. Roberts says that "he carried out nearly 10,000 separate experiments in crossing, among 700 species, belonging to 80 different genera of plants, and obtained in all some 350 different hybrid plants." In general, he confirmed much of Kölreuter's work, but added little that was new, except for an insistence on the greater variability of F_2 (the second generation) compared to F_1 (the first generation). He did not often describe the separate characters of his plants but rather treated them as whole organisms—a habit common to many of the older hybridizers. Mendel gave a good deal of space to a discussion of Gärtner's results. He interpreted them as due in part to the multiplicity of gene differences between the plants crossed—which in F_2 resulted in great rarity of individuals closely resembling the parents. Gärtner also carried out experiments with several plants that involved back-crossing hybrids in successive generations to one of the parental species, in an effort to see how many such backcrosses would be needed to eliminate the characters of the other parent. Mendel did a few experiments of this kind with peas and found, as he expected, that the result depends on the proportion of dominant genes in the parent to which the back-crossing is done. He suggested that this factor must always complicate experiments of the kind carried out by Gärtner (and earlier similar crosses made by Kölreuter).

The work of Herbert, published between 1819 and 1847, dealt chiefly with crosses among ornamental plants. Perhaps his most important contribution was his discussion of the idea that crosses between species are unsuccessful or yield sterile hybrids, while crosses between varieties yield fertile offspring. He pointed out that there is no sharp line here, and that the degree of structural difference between two forms is not an invariable index of the fertility of their hybrids. In short, the argument is a circular one: infertility between species and fertility between varieties can be concluded only if fertility and sterility are made the criteria by which species and varieties are defined.

Lecoq (published 1827 to 1862) was interested in the breeding of improved agricultural plants. He made many crosses and discussed the results of other hybridizers, but seems to have added little that advanced the subject.

Wichura's chief paper appeared in 1865, after Mendel's experiments were completed; he therefore could scarcely have influenced the planning of Mendel's crosses. His work was on the crossing of willows; perhaps the most striking passages have to do with the necessity for extreme care in preventing unwanted pollen from confusing the experiments, and his strong insistence on the identity of reciprocal hybrids—the latter being a point that Lecoq had believed was not correct.

Two other people in this period should be discussed, since both have been cited as having in some respects anticipated Mendel's point of view.

Maupertuis was even earlier than Kölreuter, his work having been published between 1744 and 1756. He reported on a human pedigree showing polydactylism, and discussed albinism in man and a color pattern in dogs. He also developed a theory of heredity somewhat like Darwin's pangenesis. Glass (1947) has reviewed this work in detail; he sees Maupertuis, in some respects, as a forerunner of Mendel. This is, to my mind, based largely on the interpretation of rather obscure passages in terms of what we now know. In any case, it is clear that Maupertuis had little or no effect on later developments in the study of heredity.

Naudin, a contemporary of Mendel, published his accounts between 1855 and 1869. He studied a series of crosses involving several genera of plants. In several respects he made real advances. Like several of his predecessors, he emphasized the identity of reciprocal hybrids. He also emphasized the relative uniformity of F_1 as contrasted to the great variability of F_2; and he saw the recombination of parental differences in F_2. But there was no analytical approach, no ratios were recognized, and no simple and testable interpretations were presented. The expression "laws of Naudin-Mendel," sometimes seen in the literature, is wholly unjustified.

Mendel's analysis could not have been made without some knowledge of the facts of fertilization—specifically, that one egg and one sperm unite to form the zygote. This was not known until a few years before his time and was not generally recognized even then. Darwin, for example, thought that more than one sperm was needed for each egg, both in animals and in plants.

Direct observations on fertilization had to wait for the development of microscopes. Leeuwenhoek saw animal spermatozoa under a microscope in 1677 and thought that one was sufficient to fertilize an egg—but this was neither directly observed, nor generally accepted, for animals, until two hundred years later (see Chapter 3).* In the lower plants, fertilization was observed by Thuret in 1853 (Fucus), Pringsheim in 1856 (Oedogonium), and De Bary in 1861 (fungi). In seed plants, the work of Amici was especially important. In 1823 he recorded the production of the pollen tube, which in 1830 he traced to the ovary and even to the micropyle. In 1846 he showed that in orchids, there is a cell already present in the ovule, which, inactive until the pollen tube arrives, then develops into the embryo. This work was confirmed and extended by Hofmeister and others, so that Mendel could write in his paper: "In the opinion of renowned physiologists, for the purpose of propagation one pollen cell and one egg cell unite in Phanerogams into a single cell, which is capable by assimilation and formation of new cells, of becoming an independent organism." Nevertheless, there was not general agreement on the point. Naudin (1863) repeated the experiments of Kölreuter and of Gärtner, placing counted numbers of pollen grains on stigmas and concluding that a fully viable seed required more than one grain. It appears, from his let-

* Leeuwenhoek also saw conjugation in ciliated Protozoa (1695), but this observation was not understood until the unicellular nature of these animals was made out two centuries later.

ters to Nägeli, that Mendel himself also repeated this experiment (using Mirabilis, as had Naudin) and found that a single grain was sufficient. He did not publish this result, and does not refer to this approach to the question in his paper.

CHAPTER 2

MENDEL

Gregor Johann Mendel was born in 1822 in the village of Heinzendorf in northern Moravia—then a part of Austria, now in Czechoslovakia, near the Polish border. The area had long been populated by people of German and Czech ancestry, living side by side and presumably intermarrying. Mendel's native tongue was the peculiar Silesian dialect of German; in later life he had to learn to speak Czech. He came of peasant stock, and only by persistence and hard work was he able to get a start in education. In 1843 he was admitted as a novice at the Augustinian monastery at Brünn; four years later he became a priest. He took an examination for a teaching certificate in natural science and failed (1850). It has been suggested that the examining board was biased because he was a priest or because his scientific views were unorthodox; the plain fact seems to be that he was inadequately prepared. In order to remedy this, he spent four terms, between 1851 and 1853, at the University of Vienna, where he studied physics, chemistry, mathematics, zoology, entomology, botany, and paleontology. In the first term he took work in experimental physics under the famous Doppler and was for a time, an "assistant demonstrator" in physics. He also had courses with Ettinghausen, a mathematician and physicist, and with Redtenbacher, an organic chemist—both productive research men. We may surmise that this background led to his use of quantitative and experimental methods in biological work. Another of his professors at Vienna, Unger in botany, was also an outstanding figure. Unger was one of the important men in the development of the cell theory; he had demonstrated the antherozoids of mosses and correctly interpreted them as the male generative cells, and he had shown (in opposition to Schleiden) that the meristematic cells of higher plants arise by division. In 1855 Unger published a book on the anatomy and physiology of plants that is rated by Sachs as the best of its time; in this book he made the first suggestion that the fluid content of animal cells and that of plant cells are essentially similar. Mendel was thus in contact with at least two first-rate research scientists, and evidence of their influences upon him shows in his major paper.

Mendel returned to Brünn after the summer term of 1853 at Vienna. At a meeting of the Vienna Zoological-Botanical Society in April, 1854, his teacher Kollar read a letter from him, in which he discussed the pea weevil (*Bruchus pisi*). In the summer of 1854, Mendel grew thirty-four strains of peas; he tested them for constancy in 1855. In 1856 he began the series of experiments that led to his paper, which was read to the Brünn Society for Natural History in 1865 and was published in their proceedings in 1866. Before discussing this paper and its consequences, it will be well to describe some later events in Mendel's life.

He was interested in honeybees and was an active member of the local beekeepers' society. He attempted to cross strains of bees, apparently without success. It has been suggested by Whiting and by Zirkle that he probably knew of the work of Dzierzon on bees, and that Dzierzon's description of segregation in the drone offspring of the hybrid queen may have given Mendel the clue that led to his studies of peas. He is also known to have kept mice, and Iltis and others have suggested that he may have first worked out his results with them, but hesitated, as a priest, to publish on mammalian genetics. These suggestions both seem unlikely to me; there seems no reason to doubt Mendel's own statement: "Experience of artificial fertilization, such as is effected with ornamental plants in order to obtain new variations in color, has led to the experiments which will here be discussed." Perhaps the selection of peas as his experimental material was due in part to Gärtners's account of the work of Knight on peas.

Mendel was also interested in meteorology. At least as early as 1859, he was the Brünn correspondent for Austrian regional reports, and he continued to make daily records of rainfall, temperature, humidity, and barometric pressure to the end of his life. He also kept records of sunspots and of the level of ground water as measured by the height of the water in the monastery well. In 1870 a tornado passed over the monastery, and Mendel published a detailed account of it in the *Proceedings of the Brünn Society*. He noted that the spiral motion was clockwise, whereas the usual direction is counterclockwise. He gave many details, and attempted a physical interpretation. This paper was stillborn, as was his earlier one on peas, published in the same journal. According to Iltis, a catalogue issued in 1917 lists 258 tornadoes observed in Europe but does not include Mendel's account.

In 1868 Mendel was elected abbot of the Brünn monastery. This led to administrative duties and, beginning in 1875, to a controversy with the government on taxation of monastery property. It appears that he continued his meteorological and horticultural observations, but his productive scientific work was finished about 1871. He died January 6, 1884.

Mendel sent a copy of his major paper to Nägeli, together with a letter in which he stated that he was continuing his experiments, using Hieracium, Cirsium, and Geum. Nägeli was professor of botany at Munich and a major figure of his time in biology. He was also interested in heredity and was actively working on it. He completely failed to appreciate Mendel's work and made some rather pointless criticisms of it in his reply to Mendel's letter. He did not refer to it in his publications. He was greatly interested in Hieracium, however, which fact led to a correspondence with Mendel. Nägeli's letters have been lost, but he kept some of Mendel's letters to him. Found among his papers, these were published by Correns in 1905 (I have used the translation in *The Birth of Genetics,* issued in 1950 as a supplement to Volume 35 of *Genetics).* There are ten of these letters, written between 1866 and 1873, and they give a picture of Mendel's biological work during the period. Because of Nägeli's interest, much of the account has to do with Hieracium, the subject of Mendel's only other published paper in genetics (published in 1870 in the *Proceedings of the Brünn Society* for 1869; a translation may be found in Bateson's *Mendel's Principles,* 1909).

The work on Hieracium must have been a great disappointment to Mendel. He obtained several hybrids by dint of much hard work, and all of them bred true. It is now known that this occurs because the seeds are usually produced by apomixis, that is, they are purely maternal in origin and arise without the intervention of meiosis or fertilization (Raunkiär 1903, Ostenfeld 1904). In other words, this was the worst possible choice of material for the study of segregation and recombination—for reasons that could not be guessed at the time.

It appears from Mendel's letters to Nägeli that he was very actively engaged in genetic studies on several other kinds of plants through 1870. His experiments (previously mentioned) with single pollen grains of Mirabilis were repeated in two different years with the same result. He reports studies on Mirabilis, maize, and stocks. Of these three he says "Their hybrids behave exactly like those of Pisum." The character studied in stocks was hairiness; with respect to flower color in this plant, he says the experiments had lasted six years and were being continued—this in 1870. He had grown 1500 specimens for the purpose in that year; his difficulty arose from the mutiplicity of shades that were hard to separate.

In Mirabilis he had seen and understood the intermediate color of a heterozygote and had made the appropriate tests to establish this interpretation. He also mentioned experiments with several other plants—Aquilegia, Linaria, Ipomoea, Cheiranthus, Tropaeolum, and Lychnis.

The picture that emerges is of a man very actively and effectively experimenting, aware of the importance of his discovery, and testing and extending it on a wide variety of forms. None of these results were published; it is difficult to suppose that his work would have been so completely ignored if he had presented this confirmatory evidence, even though it was not enough to convince Nägeli.

This, in outline, is the man. I have tried to give an account of him in order to form a basis for judging his paper—how it came about that he did the work, and what one is to think in view of the analysis by Fisher that will be discussed. A fuller account of Mendel will be found in the biography by Iltis.

There are a number of new procedures in Mendel's work. He himself said in the paper, ". . . among all the numerous experiments made [by his predecessors], not one has been carried out to such an extent and in such a way as to make it possible to determine the number of different forms under which the offspring of hybrids appear, or to arrange these forms with certainty according to their separate generations, or definitely to ascertain their statistical relations." One may agree with Bateson's comment on this passage: "It is to the clear conception of these three primary necessities that the whole success of Mendel's work is due. So far as I know this conception was absolutely new in his day."

This was his experimental approach, but it was effective because he also developed a simple interpretation of the ratios that he obtained and then carried out direct and convincing experiments to test this hypothesis. The paper must be read to be appreciated. As has often been observed, it is difficult to see how the experiments could have been carried out more efficiently than they were.

As Fisher (1936) puts it, it is as though Mendel knew the answer before he started, and was producing a demonstration. Fisher has attempted to reconstruct the experiments as carried out year by year, knowing the garden space available and the number of years involved.* He concludes

* Fisher's dates are wrong. He gives them as 1857 to 1864, but it is clear from Mendel's letters to Nägeli that the final year was 1863. Fisher includes the two years of preliminary testing in the eight years that Mendel says the experiments lasted. I have interpreted the statement to mean that these two years preceded the eight years of actual experiments—an interpretation also given by Yule (1902). Fisher's interpretation may be right, but if Yule and I are right there are two more years available and Fisher's year-by-year reconstruction needs revision. It may also be pointed out that Mendel

that the crosses were carried out in the order in which they are described. He also points out several other aspects of the work that seem significant. For example, in testing F_2 individuals to distinguish homozygous dominants from heterozygotes, Mendel must have had a much larger number of seeds illustrating the 3 : 1 ratio than those recorded in F_2; but he did not report these numbers (if he even troubled to count them). Evidently he felt that larger numbers were of no importance.

The most serious matter discussed by Fisher is that Mendel's ratios are consistently closer to expectation than sampling theory would lead one to expect. For yellow vs. green seeds, his F_2 numbers were 6022 : 2001—a deviation of 5 (from 3 : 1), whereas a deviation of 26 or more would be expected in half of a large number of trials, each including 8023 seeds. Fisher shows that this same extremely close fit runs through all Mendel's data. He calculates that, taking the whole series, the chance of getting as close a fit to expectation is only .00007, that is, in only 1 trial of 14,000 would one expect so close an agreement with expectation.

If this were all, one might not be too disturbed, for it is possible to question the logic of the argument that a fit is too close to expectation. If I report that I tossed 1000 coins and got exactly 500 heads and 500 tails, a statistician will raise his eyebrows, though this is the most probable exactly specified result. If I report 480 heads and 520 tails, the statistician will say that is about what one would expect—though this result is less probable than the 500 : 500 one. He will arrive at this by adding the probabilities for all results between 480 : 520 and 520 : 480, whereas for the exact agreement he will consider only the probability of 500 : 500 itself. If now I report that I tossed 1000 coins ten times, and got 500 : 500 every time, our statistician will surely conclude that I am lying, though this is the most probable result thus exactly specified. The argument comes perilously close to saying that no such experiment can be carried out, since every single exactly specified result has a vanishingly small probability of occurring.

In the present case, however, it appears that in one series of experi-

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probably used some time and garden space in the later years of this period to carry out the experiments with beans and hawkweeds and with the several other plants referred to in the letters to Nägeli.

Fisher also quotes extensively from a paper by Nägeli (1865), and concludes that "it is difficult to suppose that these remarks were not intended to discourage Mendel personally, without drawing attention to his researches." But this paper of Nägeli's was published before Mendel's—clearly before Nägeli could have known anything about Mendel's work!

ments Mendel got an equally close fit to a *wrong* expectation. He tested his F_2 plants that showed dominant characters to see which were homozygous and which were heterozygous, since his scheme required that these occur in the ratio of 1 : 2. For the seed characters (yellow vs. green, round vs. wrinkled), it was necessary only to plant the F_2 seed and observe the seeds the resulting plants produced when allowed to self-pollinate. For the other characters, it was necessary to plant the F_3 seeds and see what kinds of plants they produced. For this purpose, Mendel planted 10 seeds from each tested F_2 dominant. If the tested plant was heterozygous, one-fourth of its offspring would show the recessive. Fisher points out that there is an uncertainty here that was not taken into account by Mendel. For a plant that is heterozygous, the chance that any one offspring will not be a homozygous recessive is .75. The chance that none of 10 will be a homozygous recessive therefore is $(.75)^{10} = .0563$. That is to say, by this test between 5 and 6 percent of the actual heterozygotes will be classified as homozygotes. Fisher shows that Mendel's results are very close to the 2 : 1 ratio expected without this correction and are not in close agreement with the corrected expectation of 1.8874 to 1.1126—in fact as poor an agreement (with the corrected expectation) as Mendel recorded would be expected to occur rather less often than once in 2000 tries.

The argument that a fit to expectation is not close enough is not subject to the criticisms that were levelled earlier against the argument that a fit is too close. There are, however, some further aspects that need discussion. The critical passage in Mendel's paper reads: "Für jeden einzelnen von den nachfolgenden Versuchen wurden 100 Pflanzen ausgewählt, welche in der ersten [second, by current terminology] Generation das dominierende Merkmal besassen, und um die Bedeutung desselben zu prüfen, von jeder 10 Samen angebaut." Fisher is right if only 10 seeds were planted from each tested F_2 dominant. If the experiment included at least 10 seeds but often more than 10, then the correction to the 2 : 1 expectation will be less, and Fisher's most telling point will be weakened. The statement by Mendel seems unequivocal, but the possibility remains that he may have used more than 10 seeds in some or many tests.

There is a possible slight error in Fisher's expectations. In the pea flower, the anthers are closely apposed to the style, and if a plant is allowed to self-pollinate it may be expected that, as a rule, one anther will break at one point. The pollen grains near the break will then be first on the stigma and will be the ones that function. Under these conditions, it may be that the functioning pollen will not be a random sample but will represent all or most of the grains from one or a few pollen-mother-cells. This does not seem likely to be an important factor, since there are so few seeds per flower; but in the limiting case it could result in the sampling error (from a self-pollinated heterozygote) being limited to the eggs alone. Calculations based on this improbable limiting assumption indicate that Fisher's general conclusions would still hold good; but the point remains that in any such analysis one needs to examine the assumptions very carefully, to make sure there may not be some alternative explanation.

Mendel's experiments have been repeated by many investigators, and the question arises: have they also reported unexpectedly close agreement with expectation? For the F_2 ratio for yellow vs. green seeds, the data from several sources have been tabulated by Johannsen, and the statistical calculations have been carried out by him, with the results shown in Table 1.

TABLE 1. F_2 RESULTS, PEA CROSSES

Source	Yellow	Green	Total	Dev. from 3 in 4	Prob. Error	Dev. ÷ P.E.
Mendel, 1866	6,022	2,001	8,023	+ .0024	± .0130	.18
Correns, 1900	1,394	453	1,847	+ .0189	± .0272	.70
Tschermak, 1900	3,580	1,190	4,770	+ .0021	± .0169	.12
Hurst, 1904	1,310	445	1,775	– .0142	± .0279	.51
Bateson, 1905	11,902	3,903	15,806	+ .0123	± .0093	1.32
Lock, 1905	1,438	514	1,952	– .0533	± .0264	2.04
Darbishire, 1909	109,060	36,186	145,246	+ .0035	± .0030	1.16
Winge, 1924	19,195	6,553	25,748	– .0180	± .0125	1.44
Total	153,902	51,245	205,147	+ .0008	± .0038	.21

SOURCE: Johannsen, 1926.

Evidently this is in good agreement with expectation. It would be expected that the values in the last column would be more than 1.00 in half of the series, less than 1.00 in half—which happens to be just what is observed. One observer, Tschermak, achieved an even closer approach to 3 : 1 than did Mendel. Of the eight observers, five (including Mendel) obtained a small excess of dominants, three got a small deficiency. The poorest fit (that of Lock) would be expected to occur in about 1 out of 6 tries, and it did occur in 1 of 8 series. The over-all impression is that the agreement with expectation is neither too good nor too poor.

In summary, then, Fisher's analysis of Mendel's data must stand essentially as he stated it. There remains the question of how the data came