PRINCIPLES OF GENETICS

ELDON J. GARDNER
Utah State University

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University of Minnesota

SIXTH EDITION

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PREFACE

This revision is a continuing attempt to provide a general genetics text that is current, readable, and challenging for students; it is flexible in that it can serve as a textbook for university quarter, semester, or two-quarter courses. It is a beginning-level text, focused on the basic principles of genetics, but with sufficient rigor to satisfy the needs of biology majors. This edition has been reorganized and extensively rewritten. Historical material and applied aspects of plant and animal breeding have been reduced to make room for more extensive coverage of experimental data in molecular, population, and human genetics. In making the book more concise, basic aspects of genetics have been preserved and extended in depth. Coverage of molecular genetics has been considerably expanded in this edition.

The textbook begins with a concise Introduction, giving historical, functional, and human perspectives, as well as a perspective of the principles covered in the 17 chapters that follow. Chapter 2 provides a unified statement of Mendelian genetics followed in Chapter 3 by a description of the cellular mechanics that explain Mendelian principles. The biochemical nature of genes, their mode of replication, and the organization of DNA in chromosomes are introduced in Chapter 4. These early discussions of cellular and molecular biology provide background for the discussion of sex determination and sex linkage (Chapter 5), crossing over, bacterial recombination, mutations, genetic fine structure, and gene regulation in Chapters 6 to 11.

Linkage, chromosome mapping, tetrad analysis, gene conversion, and the molecular basis of crossing over are integrated in Chapter 6. Recombination mechanisms unique to bacteria—conjugation, transduction, and transformation—are covered in Chapter 7, along with plasmids, episomes, and insertion sequences. Chapter 8 covers the genetic control of metabolism, with emphasis on the one gene–one polypeptide concept, transcription, translation, and the genetic code. Chapter 9 describes the nature and molecular basis of spontaneous and induced mutation. Repair mechanisms, the consequences of defective repair pathways, and the correlation between mutagenicity and carcinogenicity are also discussed. The structure of genes and complex loci are covered in Chapter 10. Evidence for noncoding "intervening sequences" or "spacers" within genes of eukaryotes is presented, along with a discussion of the recombinant DNA and "gene-cloning" techniques used to detect these sequences. In Chapter 11, we have attempted to provide a concise description of what is known about the regulation of gene expression in both prokaryotic and eukaryotic systems.

Chromosomal structural aberrations and chromosomal numerical changes with their mechanisms and consequences are the topics of Chapters 12 and 13. Most extranuclear inheritance (Chapter 14) is attributed to evolutionary symbiosis that has brought free living bacterial cells with their own DNA into intimate association with eukaryotic organisms. Chapters 15 and 16 are devoted to quantitative inheritance and population genetics. Current aspects and the status of behavior genetics are outlined in Chapter 17. Examples from human genetics are given throughout the book, and the final chapter is devoted to basic genetics as applied to humans. Prospects for human genetic engineering and the behavior of genes in human populations are discussions included in Chapter 18. A glossary of terms, answers to all problems in the book, and a combined author and subject index complete the book.

Our thanks to students, teachers, and colleagues who have suggested improvements for the book. We especially thank Brian Davis,

Larry Puckett, Robert M. Fineman, Irene Uchida, A. Dean Stock, Scott W. Rogers, and John R. Simmons, who have made valuable suggestions and assisted with illustrations. Franklin D. Enfield read original drafts of seven chapters and made many important suggestions for their improvement. His contributions and the assistance of Jilleen Wandmacher in preparing the manuscript are gratefully acknowledged. We also gratefully acknowledge the assistance of Mr. Frederick Corey, editor, Mr. John Balbalis and staff of the Wiley Illustration Department, Ms. Kathy Bendo, photograph editor, Ms. Joan Knizeski, manuscript editor, and Ms. Linda Indig, production supervisor.

Credits for illustrations, tables, and quotations from other individuals or publications are given with the individual item.

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D. Peter Snustad

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ONE

INTRODUCTION

Genetics is a science of potentials. It deals with the transfer of biological information from cell to cell, from parents to offspring, and thus from generation to generation. Geneticists are concerned with the whys and hows of these transfers, which are the basis for certain differences and similarities that are recognized in groups of living organisms. Genetics deals with the physical and chemical nature of the information itself. What is the source of genetic variation? How are differences distributed in populations? Not all variation among living things, however, is inherited. Environmental and developmental factors are also significant and therefore of interest to the geneticist.

Long before humans began to wonder about genetic mechanisms, they were already operating effectively in nature. How and why were such mechanisms discovered? Populations of plants and animals are now known to have built-in potentials for constancy and change that are dependent on genetics. Change that becomes established through these mechanisms over long periods of time in a population of living things is called **evolution.**

Many potentials have been accomplished by human intervention in genetic mechanisms that now accrue to benefit human beings. Wild animals and plants have become domesticated. By selective breeding, domesticated organisms have been made to serve human society increasingly better than their wild, unselected counterparts. Improved quantity and quality of milk, eggs, meat, wool, maize, wheat, rice, cotton, and many other sources of food, fiber, and shelter attest to the successes of human interventions.

PERSPECTIVES IN GENETICS: HISTORICAL

BIRTH OF A SCIENCE

Gregor Mendel (1822–1884) is appropriately called the "father of genetics." His precedent-setting experiments with garden peas (*Pisum sativum;* published in 1866) were conducted in the limited space of a monastery garden (Fig. 1.1) while he was also employed as a substitute schoolteacher. The conclusions that he drew from his elegant investigations constitute the foundation of today's science of genetics. Why was Mendel so successful in discovering basic principles of genetics?

Mendel was not the first to perform hybridization experiments, but he was one of the first to consider the results in terms of single traits. His predecessors had considered whole organisms, which incorporate a nebulous complex of traits; thus, they could only observe that similarities and differences occurred among parents and progeny. They missed the significance of individual differences. Employing the scientific method, Mendel designed the necessary experiments, counted and classified the peas resulting from his crosses, compared the proportions with mathematical models, and formulated a hypothesis for these differences. Although Mendel devised a precise mathematical pattern for the transmission of hereditary units, he had no concept of the biological mechanism involved. Nevertheless, on the basis of his preliminary experiments and hypotheses, he predicted and subsequently verified his predictions with the results of later crosses.

In 1900, Mendel's paper was discovered

Fig. 1.1. Garden at Altbrünn. Monastery garden where Mendel's experiments on garden peas were conducted. (Courtesy of Professor Jaroslav Kříženecký.)

simultaneously by three botanists: Hugo de Vries in Holland, known for his mutation theory and studies on the evening primrose and maize; Carl Correns in Germany, who investigated maize, peas, and beans; and Eric von Tschermak-Seysenegg in Austria, who worked with several plants including garden peas. Each of these investigators obtained evidence for Mendel's principles from his own independent studies. They all found Mendel's report while searching the literature for related work and cited it in their own publications. William Bateson, an Englishman, gave this developing science the name "genetics" in 1905. He coined the term from a Greek word meaning "to generate."

CONCEPT OF THE GENE

In addition to naming the science, Bateson actively promoted Mendel's view of paired genes. He used the word "allelomorph," shortened to "allele," to identify members of pairs that control different alternative traits. Also during the early 1900s, a Frenchman, Lucien Cuénot, showed that genes controlled fur color in the mouse; an American, W. E. Castle, related genes to sex and to fur color and pattern in mammals; and a Dane, W. L. Johannsen, studied the influence of heredity and environment in plants. Johannsen began using the word "gene" from the last syllable of Darwin's term "pangene." The gene concept, however, had been implicit in Mendel's visualization of a physical element or factor (**Anlage**) that acts as the foundation for development of a trait. These men and their peers were able to build on the basic principles of cytology, which were established between 1865 (when Mendel's work was completed) and 1900 (when it was discovered). Why were Mendel's important discoveries not recognized for such a long time (35 years) after the studies were completed and reported?

CHROMOSOME THEORY

Wilhelm Roux had postulated as early as 1883 that chromosomes within the nucleus of the cell were the bearers of hereditary factors. The only model he was able to devise that would account for his observed genetic results was a row of lined-up objects that were duplicated exactly. To explain the mechanics of gene transmission from cell to cell, he therefore suggested that nuclei must have invisible structures held in rows or chains that duplicated themselves when the cell divided. Constituents of the nucleus that seemed best designed to carry genes and fill these requirements were **chromosomes.** Experiments of T. Boveri and W. S. Sutton in 1902 brought confirming evidence that a gene is part of a chromosome. The theory of the gene as a discrete unit of a chromosome was developed by T. H. Morgan and his associates from studies on the fruit fly, *Drosophila melanogaster*. H. J. Muller later promoted the merger of the two sciences that had contributed most to the chromosome theory: cytology (the study of cells) and genetics as **"cytogenetics."**

CHEMICAL NATURE OF THE GENE

In the 1930s G. W. Beadle, B. Ephrussi, E. L. Tatum, J. B. S. Haldane, and others provided a basis for understanding the functional properties of genes and suggested functional extensions of the classical gene concept. The gene was at first characterized as an indivisible unit of structure, unit of mutation, and unit of function, with all three of these attributes considered equivalent. Investigators then recalled that a physician, A. E. Garrod, had indicated in 1909 that genes in humans function through **enzymes.** Geneticists of the 1940s following Garrod's lead sought an ideal experimental system for investigating functional aspects of genes. Prokaryotes (organisms lacking well-defined nuclei and not undergoing meiosis, that is, bacteria and blue-green algae) were chosen for experimental material even though eukaryotes (organisms made up of cells with true nuclei bounded by envelopes and undergoing meiosis) had more practical significance for geneticists.

Early triumphs were the identification of macromolecules carrying genetic information in a bacterium by O. T. Avery and associates and in a virus by A. Hershey and M. Chase. The Avery et al. experiments showed that a chemical, deoxyribonucleic acid (**DNA**), could bring about genetic change (transformation) in a pneumococcus bacterium; Hershey and Chase demonstrated that the nucleic acid component (DNA) and not the protein is the genetic material carried by the bacteriophage. H. Fraenkel-Conrat and B. Singer showed that ribonucleic acid (**RNA**) is the genetic material in tobacco mosaic virus. Thus, in some viruses, RNA performs the functions that DNA performs in other organisms. J. D. Watson and F. H. C. Crick worked out the double helix structure of the chemical DNA. The central problem of genetics was thus resolved with the discovery that DNA is the genetic material. Genetic mechanisms could now be formulated in biochemical terms. How do units (genes) of DNA control specific traits in organisms, and how do assemblages of DNA units carried in fertilized eggs provide "blueprints" for development of entire organisms?

FUNCTIONAL PERSPECTIVE

Genes accomplish their function (1) through replication that results in more units like themselves and (2) through transcription and translation, whereby proteins that function as determiners in the metabolism of the cell are synthesized. Although genes are usually stable, they are susceptible to occasional change or mutation, which provides altered forms of genes (**alleles**). Mendel first postulated the existence of genes from their end effects, as expressed in altered characteristics. Now genes have been defined chemically and are known for what they do in directing the formation of traits through the specificity of protein enzymes. Thus DNA carries the speci-

fications for growth, differentiation, and functioning of cells in the organism.

In the animal body, the same set of genes is present in virtually all nucleated cells. Different genes, however, become active at different times during development. But how does this selective activation occur? At times of activity, information contained in a gene is known to be decoded by processes of transcription and translation to produce **proteins.** Proteins that are enzymes catalyze cellular biochemical reactions. But how does each cell or group of cells become activated at the proper time to take its place in the blueprint of a coordinated sequence to form an organism? Contents of a single fertilized cell include the information needed for the development of a finely adjusted organism—for example, a human being destined at one time to contain at least a million billion (10^{15}) cells. It is difficult to imagine how a complex organism is assembled. However, metabolic disorders often provide unique opportunities to combine genetic concepts with tools of biochemistry and to reconstruct some steps in normal development. At a different level of organization, the DNA in a species population is the evolutionary storehouse, carrying the information for that species.

PERSPECTIVE OF PRINCIPLES

This text is entitled "Principles" of Genetics. It is an attempt to present basic concepts that have been established by observation and experimentation as **principles** of genetics. In the text, each principle is developed with appropriate background, mechanisms, and applications. Since the entire book is devoted to the elucidation of principles, it is not expected that they will be fully understood at their first mention. Nevertheless, it does seem appropriate to briefly state the principles in the Introduction (1) to illustrate their precise nature and (2) to suggest the sequential discoveries by original investigators and the step-by-step sequence through which the known principles can be related and understood. Some of these principles are: (1) The gene is the unit of inheritance. (2) Genes are arranged in linear order on chromosomes. (3) Chromosomes are single units in reproductive cells (eggs and sperm), but they are paired in fertilized eggs and in body cells that develop from fertilized eggs. (4) Members of a pair of genes and chromosomes segregate to different reproductive cells. (5) Members of different gene pairs are assorted independently with respect to those of other gene pairs in the formation of eggs and sperm. (6) Genes are units of deoxyribose nucleic acid (DNA) and are capable of replication. They carry coded messages that can be transcribed and translated into polypeptides, which may be either enzymes or structural proteins. (7) Changes (mutations) occur in genes and chromosomes. (8) Multiple genes control the inheritance of quantitative traits (e.g., size, pigmentation). (9) Genes in populations establish an equilibrium, the level of which can be changed by such factors as mutation, migration, and selection—phenomena that provide the basis for race and species formation.

In this book, these and other genetic principles are discussed in detail as they apply to microorganisms, plants, and animals, with strong emphasis on humans. Behavior patterns that we see in animals (particularly in human beings) are also considered in terms of genetic principles.

The science of genetics will not end with the current principles and applications. Many questions remain to be answered through current and future research. For example, how are systems of genes regulated and coordinated in controlling complex phenotypes? Regulatory mechanisms have been discovered in prokaryotes, and those in higher organisms are being investigated. How is damaged DNA repaired? How does differentiation occur from a DNA "blueprint" in a totipotent zygote to a multicellular organism with specific cellular and regional structures and functions? How do normal cells become cancerous? How does

aging occur? What genetic changes are associated with mental retardation?

Not only are some genetic mechanisms of long-standing in nature presently unresolved, but humans are creating new problems for themselves and other inhabitants of the earth. Extensive use of synthetic chemicals in herbicides, insecticides, fungicides, food preservatives, or as artificial colors and flavors may alter nature's balance in human and other populations. To understand and to resolve these new challenges, we must find new applications of known principles or discover new principles.

Insidious forms of irradiation and other pollution in present and future environments will have direct effects on genetic material, as expressed in mutation rates that influence general health, cancer incidence, aging, and numerous health-related problems. Widespread use of aerosols on earth alters the protective shield in the upper atmosphere, allowing increased irradiation to damage the genetic system of humans and other organisms.

Biological warfare could devastate well-adjusted genetic systems and, indeed, threaten all life on earth. Recombinant DNA innocently produced in biology laboratories could have infectious properties for which immune systems have not developed in nature. Extent of risk is controversial, but all must agree that new living forms must be considered with respect and must be kept under control—if not by nature, by human intervention. Laboratory procedures for cloning of cells or embryos must be controlled judiciously for the future of humankind and our environment. Genetic engineering, designed to replace particular defective genes and thus prevent or cure genetic abnormalities, may eventually be used effectively for improving the lot of humans. On the other hand, uninformed tampering with well-adjusted genetic systems or misuse of such powerful procedures is fraught with grave danger. At present, there are very strict guidelines that have been established for recombinant DNA technology. These are observed by researchers in both academic and medical fields (Chapter 10).

PERSPECTIVE OF HUMAN GENETICS

With all the principles of genetics that have been discovered and evaluated for application to humans, what tools and choices are now available for improving the lot of present and future generations of humankind? Similar questions have been asked and answered with more or less success for earlier generations. Unfortunately, valid principles have on occasion been misapplied and abused. Well-known incidents perpetuated for political ends in Nazi Germany during the 1930s brought the so-called "eugenics" movement into disrepute. Current "human genetics" is designed to avoid errors of the past and to provide the scientific basis and counseling for present needs. But how can the rapidly accumulating data be applied to ensure individual freedom and human dignity and, at the same time, improve the lot of humans in a favorable environment? Certainly, an understanding of basic principles of human genetics is most helpful to people in making informed and democratic decisions. The first criterion, then, is that people themselves be well-informed concerning relevant principles and tools available to them in the application of genetics. The second criterion is that well-informed genetic counselors and diagnostic facilities be available to provide technical information needed to assist people in making their own decisions. It follows that choices in matters of health and reproduction be made by the people themselves and not be dictated by a state.

NEW TOOLS FOR DIAGNOSIS AND THERAPY

Early and accurate diagnosis makes possible intervention and "cure" or at least improvement in the symptoms of many inherited anomalies. The most striking example of diag-

nosis and treatment of an inherited disease is the work that has been done with phenylketonuria (PKU). This disease is caused by a mutant gene and can be detected by a simple test of urine in newborns. PKU infants detected at birth are given a diet low in phenylalanine during early infancy and thus are saved from mental retardation and other symptoms of untreated PKU. Treated children still carry the **defective gene.** When the "cured" females grow to maturity and approach motherhood, they must return to the low phenylalanine diet and thus provide a suitable prenatal environment for the fetus. Their progeny may require a low phenylalanine diet in early infancy to avoid PKU symptoms. Other early diagnoses and dietary "cures" are the milk-free diet for galactosemia and vitamin B_6 for cystathioninuria.

Chromosome analysis can be used to detect a large number of abnormalities in the fetus, the newborn, the child, and the adult. Like defective genes, chromosome aberrations are not "cured," but the symptoms of certain conditions such as the Turner (45,X) and the Klinefelter (47,XXY) syndromes can be treated with hormones to correct deficiencies and to promote or retard growth. Numerical aberrations in chromosomes result from failure of chromosomes to separate (nondisjunction) during cell division. Older mothers are more prone to nondisjunction and thus have a much higher proportion of ova with an extra chromosome than do younger mothers. Chromosome irregularities can be detected prenatally by withdrawing a sample of amniotic fluid and culturing the fetal cells. Dividing cultured cells are observed microscopically and photographed for the detection of chromosome aberrations. Several structural as well as numerical aberrations are associated with mental retardation and physical defects. These can also be detected through cultured fetal cells. In newborns, children, and adults, chromosome analysis can be accomplished from cell cultures developed from samples of blood, skin, or other tissues.

Direct enzyme assays are used to detect mucopolysaccharidosis and other storage diseases that result from enzyme defects. Indirect tests, such as abnormal excretion of amino acids in urine, are also used to detect genetic metabolic abnormalities. Alphafetoprotein (AFP) levels are elevated in amniotic fluid when open neural-tube defects, such as spina bifida and myelomeningocele, have occurred in the fetus.

The fetoscope, an instrument that can be inserted into the uterine cavity along with an attached light source, permits the viewing of the placenta and fetal parts. Ultrasound has also been used to obtain fetal images; for example, fine details of internal structures such as the heart, kidney, and bladder can be reconstructed. When abnormalities are detected prenatally, preparations can be made for surgical or therapeutic intervention at the time of birth.

In addition to screening for neonatal disease and monitoring the fetus, inroads have been made in the treatment of genetic diseases and other defects. Antihemophilic **globulin** is a protein replacement for hemophilia, **insulin** is a hormone replacement for diabetes, and leukocyte infusions provide **enzyme** replacements for the mucopolysaccharidoses. Surgical intervention is available for multiple polyposis of the colorectum, kidney transplants for inherited renal disease, and bone marrow infusions for immunodeficiencies. Alas, fortunate people who have been "cured" of hemophilia, diabetes, mucopolysaccharidosis, multiple polyposis and other genetic diseases still carry defective genes that may be transmitted to their children. Therapy on the defective gene itself is still in the future.

SUMMARY

Genetics deals with the inherent mechanisms that control constancy and change in living organisms. The science of genetics was born with the discovery of Mendelian principles at the turn of the twentieth century. It has taken a prominent place among the biological sciences with (1) the concept of the gene, (2) chromosome theory, and (3) the discovery that the chemical DNA is genetic material. A few basic principles represent the core of the science. Applications have developed through plant and animal breeding and through our increased understanding of the mechanisms of living systems, particularly in humans. Diagnosis, cure, and prevention are now available for the symptoms of many human genetic anomalies. People that are "cured" of genetic diseases still carry defective genes that may be transmitted to future generations.

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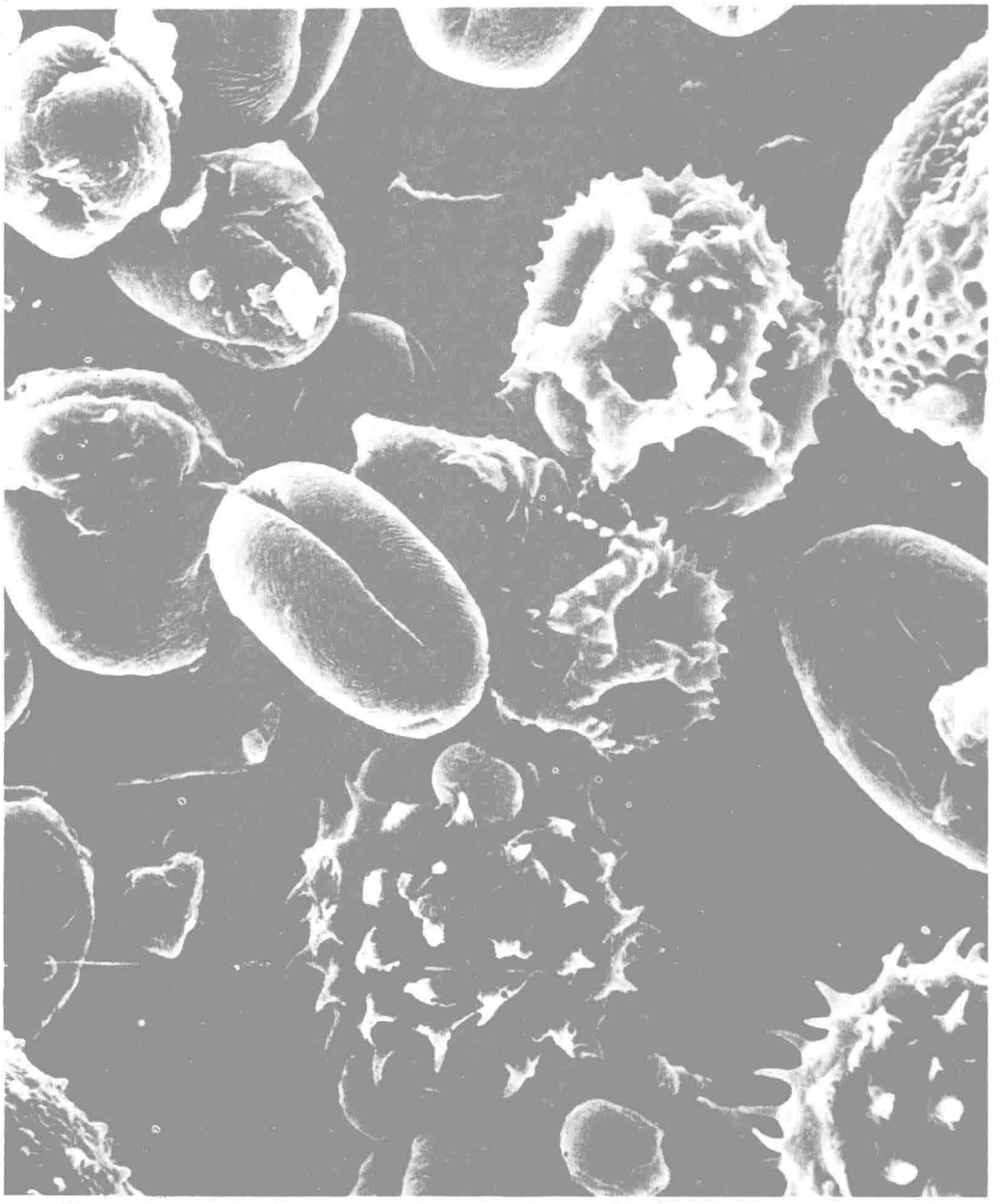

Scanning electron micrograph of pollen grains removed from the pollen basket of a honey bee returning from an alfalfa field (magnification × 750). (Courtesy of S. W. Rogers.)