The Science of Genetics:

An Introduction to Heredity

THIRD EDITION

GEORGE W. BURNS

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Preface

It has been pointed out that genetic knowledge now doubles every two years. In the four years that have elapsed since publication of the second edition of *The Science of Genetics,* then, the problem has increasingly become one of selecting material so that an up-to-date treatment can be maintained within the bounds of a one-term course.

Because of the growing information about human genetics, and because of interest in oneself as a genetic organism, emphasis on human genetic patterns has been increased in this edition, and examples are drawn from this field wherever possible. New or expanded treatments of sex determination, sex anomalies, chromosome aberrations, polygenic traits, and genetic polymorphism of mankind have been included. More information has been added on the human karyotype, both normal and abnormal, with emphasis on contributions from fluorescence microscopy and other recent studies. Legal implications of blood group genetics have been updated in the light of new laws and court cases. Treatment of possible genetic damage in man by a variety of drugs has been expanded.

Fruits of current research on DNA and RNA structure and behavior, ribosome structure, transcription, translation, and gene regulation have been included. Mutation and mutagenic agents have received greater coverage. The topic of population genetics has been expanded to include examination of the combined effect of mutation and selection on gene frequencies; at the same time the mathematics has been kept understandable for the general student. Implications of the "new genetics" (e.g., genetic engineering) for the future of the human race have been broadened in the light of current and ongoing research and controversy. Problems have been revised and augmented, and many new references have been added. Most of the latter are referred to directly within the chapters themselves, but a few significant, more general references have also been included.

Although most of the book has been completely rewritten for this edition, the problem approach has been retained, using work of the men and women who have contributed most to the development of the science. Topics are developed inductively, from observation to explanation to principle. The historical theme—starting with "classical" genetics and progressing through molecular genetics, wherein the story of our increasing knowledge about the field unfolds for the student as it has over the years for mankind—has been employed again in this edition. However, no loss of coherence will result if, for example, one wishes to proceed to DNA and molecular genetics early, for example, after considering monohybrid and dihybrid genetics.

This book is intended for undergraduates who have had a previous college course in one of the life sciences. However, salient points of cell structure and behavior are reviewed where needed. Appendixes contain answers to problems, life cycles of animals and plants used in genetic research, structural formulas of the biologically important amino acids, a summary of mathematical formulas, ratios and statistical tests that have been developed in the text, a table of metric values, and a list of journals and reviews. The glossary has been expanded.

The help of many persons who have made this book possible is gratefully acknowledged. Special thanks for their invaluable help are due to Jeffrey and Susan Carpenter Laycock for assistance on legal implications of blood group genetics and to Dawn DeLozier, John Derr, Gary Bock, and Chris Arn for providing or helping to secure photographic material. Mrs. Laycock, Miss DeLozier, Mr. Derr, Mr. Bock, and Miss Arn are former students of mine, and their interest is therefore particularly gratifying. In addition, many persons active in genetic research have most graciously provided other photographs of their own; these have added immeasurably to accounts of several topics. These latter persons include Drs. Theodore A. Baramki, Mihaly Bartalos, E. J. DuPraw, Richard C. Juberg, C. C. Lin, and Herbert A Lubs. Dr. S.-H. Kim kindly permitted use of a three-dimensional diagram of transfer RNA, and the National Foundation–March of Dimes generously gave permission to reproduce certain drawings and tables from *Paris Conference (1971): Standardization in Human Cytogenetics.* Full acknowledgment is given with each figure or table. I am also indebted to the Literary Executor of the late Sir Ronald A. Fisher, F.R.S., and to Oliver and Boyd, Ltd., Edinburgh, for their permission to reprint Table 3 from their book *Statistical Methods for Research Workers.* Sincere thanks are due also to the many professional associates, users of previous editions of *The Science of Genetics,* who responded so helpfully to requests for comments and suggestions. No expression of gratitude would be complete without recognition of the wisdom and continuing helpful counsel of Mr. Charles E. Stewart, Jr., Biology Editor, and Mr. Ronald Harris, Production Supervisor, of the Macmillan staff. Finally, to my students who have always made the teaching of genetics an exciting and rewarding experience, this book is dedicated with real affection.

G. W. B.

Contents

CHAPTER 1
Introduction

CERTAINLY one of the most exciting fields of biological science, if not of all science, is genetics. This is the study of the mechanisms of heredity by which traits or characteristics are passed from generation to generation. Not only has modern genetics had a compact history, being essentially a product of the twentieth century, but it has made almost explosive progress from the rediscovery in 1900 of Mendel's basic observations of the 1860s to a fairly full comprehension of underlying principles at the molecular level. As our knowledge of these operating mechanisms developed, it became apparent that they are remarkably similar in their fundamental behavior for all kinds of organisms, whether man or mouse, bacterium or corn. But geneticists' quest for truth and understanding is far from completed; as in other sciences, the answer to one question raises new ones and opens whole new avenues of inquiry.

Genetics is personally relevant to everyone. Man is a genetic animal; each of us is the product of a long series of matings. People differ among themselves with regard to the expression of many traits; one has some inherited characteristics of his father and certain ones of his mother, but often, as well, some not exhibited by either parent. Familiar examples abound in persons of your own acquaintance—hair or eye color, curly or straight hair, height, intelligence, and baldness, to list but a few. Less obvious genetic traits include such diverse ones as form of ear lobes (Fig. 1-1), ability to roll the tongue (Fig. 1-2), ability to taste the chemical phenylthiocarbamide (PTC), red-green color blindness, hemophilia or "bleeder's disease," extra fingers or toes, or ability to produce insulin (lack of which results in diabetes). Note that some of these characteristics seem purely morphological, being concerned primarily with form and structure, whereas others are clearly physiological. Look about you at your friends and family for points of difference or similarity. Most of these characteristics have genetic bases. You are undoubtedly aware also of mentally retarded persons in our population, and of infants so grossly deformed that they are born dead or die within a very short time. Many of these unfortunate cases have underlying genetic and/or cytological causes. The determination of one's sex and the occurrence of sex intermediates (hermaphrodites and pseudohermaphrodites) also have genetic and cytological causes.

Although a survey of man's long interest in heredity is outside the scope of this book, it is well established that as much as 6,000 years ago he kept records of pedigrees of such domestic animals as the horse or of crop plants like rice. Because certain animals and plants were necessary for his survival and culture, man has, since the beginning of recorded history at least, attempted to develop improved varieties. But the story of man's concern with heredity during his

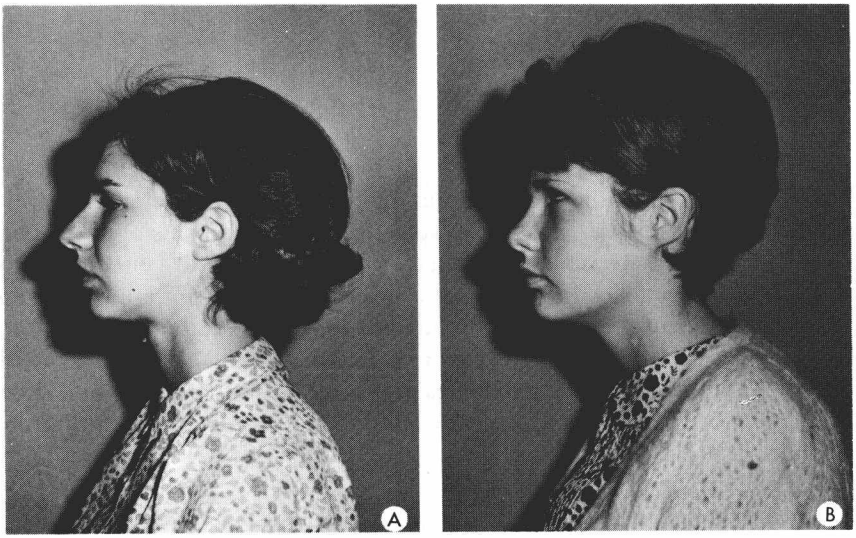

FIGURE 1-1. *Inherited difference in form of ear lobe. (A) Free ear lobe, the result of a dominant gene. (B) Attached ear lobe, caused by a recessive allele.*

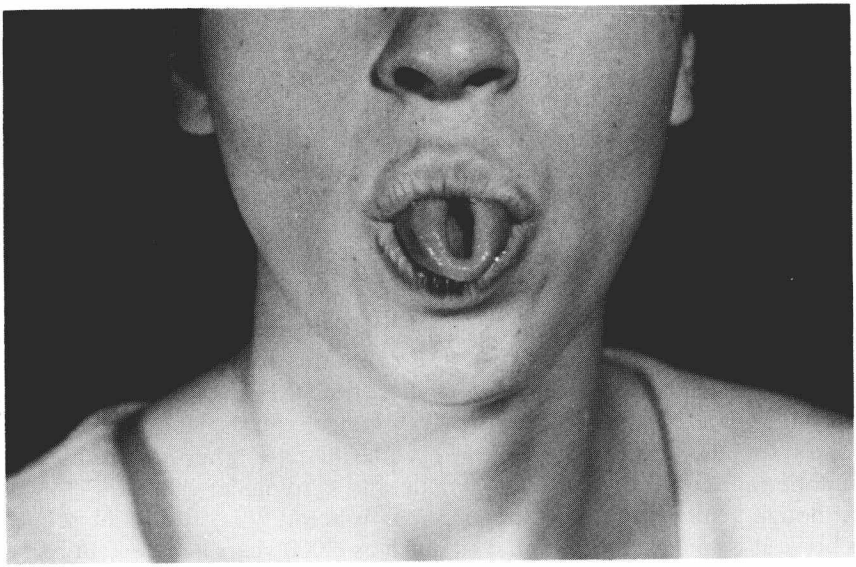

FIGURE 1-2. *Genetic or learned trait? Ability to roll the tongue has been ascribed to action of a dominant gene. A less commonly encountered trait, ability to fold the tip of the tongue back toward its base, is often described as resulting from another dominant gene. However, Martin (1975) finds no evidence for a genetic basis to tongue rolling.*

lifetime on this planet has been, until recently, one of interest largely in results rather than in fundamental understanding of the mechanisms involved.

As one examines the development of ideas relating to these mechanisms, he finds the way replete with misconceptions, many of them naïve in the light of modern knowledge. These theories may be divided roughly into three categories: (1) "*vapors and fluids,*" (2) *preformation,* and (3) *particulate inheritance.* Such early Greek philosophers as Pythagoras (500 B.C.) proposed that "vapors" derived from various organs unite to form a new individual. Then Aristotle assigned a "vitalizing" effect to semen, which, he suggested, was highly purified blood, a notion that was to influence thinking for almost 2,000 years.

By the seventeenth century sperm and egg had been discovered, and the Dutch scientist Swammerdam theorized that sex cells contained miniatures of the adult. Literature of that time contains drawings of models or manikins within sperm heads which imaginative workers reported seeing (Fig. 1-3). Such theories of preformation persisted well into the eighteenth century, by which time the German investigator Wolff offered experimental evidence that no preformed embryo existed in the egg of the chicken.

But Maupertuis in France, recognizing that preformation could not easily account for transmission of traits to the offspring from both parents, had pro-

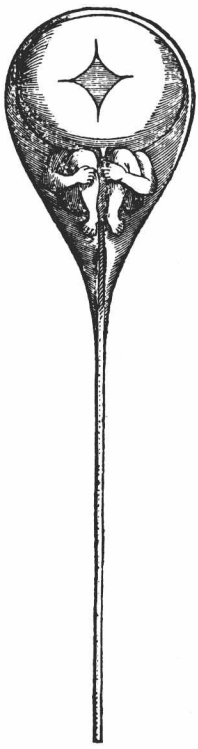

FIGURE 1-3. *Homunculus, "little man in a sperm cell."* (Drawing by N. Hartsoecker, *Journal des Scavans,* Feb. 7, 1695.)

posed in the early 1800s that minute particles, one from each body part, united in sexual reproduction to form a new individual. In some instances, he reasoned, particles from the male parent might dominate those from the female, and in other cases the reverse might be true. Thus the notion of particulate inheritance came into consideration. Maupertuis was actually closer to the truth, in general terms, than anyone realized for more than a century.

Charles Darwin suggested in the nineteenth century essentially the same basic mechanism in his theory of pangenesis, the central idea of which had first been put forward by Hippocrates (400 B.C.). Under this concept, each part of the body produced minute particles ("gemmules") that were contained in the blood of the entire body but eventually concentrated in the reproductive organs. Thus an individual would represent a "blending" of both parents. Moreover, acquired characters would be inherited because as parts of the body changed, so did the pangenes they produced. A champion weight lifter, therefore, should produce children with strong arm muscles; such transmission of acquired traits we know does not occur.

Pangenesis was disproved later in the same century by the German biologist Weismann. In a well-known experiment he cut off the tails of mice for 22 generations, yet each new lot of offspring consisted only of animals with tails. If the source of pangenes for tails was removed, how, he reasoned, could the next generation have tails? Yet, in spite of these early problems with the idea of particulate inheritance, its basic concept is the central core of our modern understanding.

Most attempts to explain observed breeding results failed because investigators generally tried to encompass simultaneously *all* variations, whether heritable or not. Nor was the progress of scientific thought or the development of suitable equipment and techniques ready to help point the way. It was the Augustinian monk Gregor Mendel who laid the groundwork for our modern concept of the particulate theory. He did so by attacking the problem in logical fashion, concentrating on one or a few observable, contrasting traits in a controlled breeding program. Both by his method and by his suggestion of causal "factors" (which we now call *genes*), Mendel came closer to a real understanding of heredity than had anyone in the preceding 5,000 years or more, yet he only opened the door for others. An understanding of the cellular mechanisms was still to be developed.

Characteristics of Useful Experimental Organisms

Even though Mendel's approach was probably more the result of luck than of thoughtful planning, it was superb in its simplicity and logic. First, Mendel was fortunate to have in the garden pea (*Pisum sativum*) what we recognize today as a good subject for genetic study. There are six important considerations for choosing a plant or animal for genetic experiments:

1. Variation. The organism chosen should show a number of detectable differences. Nothing could be learned of the inheritance of skin color in man, for example, if all human beings were alike in this respect. In general, the larger the number of discontinuous traits and the more clearly marked they are, the greater the usefulness of the species for genetic study.

2. Recombination. Genetic analysis of a species is greatly expedited if it has some effective means of combining, in one individual, traits of two parents. Such *recombination* permits comparison of one expression of a character with another expression of the same trait (e.g., tall versus dwarf *size,* brown versus blue *eye color*) through several generations. In many organisms recombination occurs as the result of *sexual reproduction,* in which two sex cells (**gametes**), generally from two different parents, combine as a fertilized egg (**zygote**). The sexual process is characteristic of higher animals and plants, and occurs in many lower forms as well. In bacteria and viruses there occur such processes as conjugation and transduction which also bring about recombination. Life cycles of several genetically important organisms are reviewed in Appendix B.

On the other hand, many organisms reproduce *asexually* or *vegetatively* and cannot furnish recombinational information. Basically, asexual reproduction may involve specialized cells (often called **spores**), daughter cells (in unicellular forms), parts of a single parent (cuttings, grafts, fragmentation, etc.), or **parthenogenesis,** in which an individual develops from an unfertilized egg, as in the male honeybee. By and large, a means of recombination is required for genetic study.

3. Controlled Matings. Systematic study of an organism's genetics is far easier if we can make controlled matings, choosing parental lines with particular purposes in mind, and keep careful records of offspring through several generations. The mouse, the fruit fly (Fig. 1-4), corn, and the red bread mold (*Neurospora*), for instance, make better genetic subjects in this respect than does man. In human genetics we are dependent largely on pedigree analysis, or studies of traits as they have appeared in a given family line for several past generations. Although such analyses are certainly useful, the human geneticist must rely largely on lines of progeny that *have been* established and cannot devise desired crosses of his own.

4. Short Life Cycle. Acquisition of genetic knowledge is facilitated if the organism chosen requires only a short time between generations. Mice, which are sexually mature at five or six weeks of age and have a gestation period of about 19 to 31 days, are much more useful, for instance, than elephants, which mature in eight to 16 years and have a gestation period of nearly two years. Likewise, the fruit fly, *Drosophila,* is much used in investigations because it may provide as many as five or six generations in a season. But first place for short life cycle goes to bacteria and to bacteriophages (or simply phages, viruses that infect bacteria), which, under optimum conditions, have a generation time of only 20 minutes! Both bacteria and phages also offer a number of other advantages for genetic study, as we shall subsequently see.

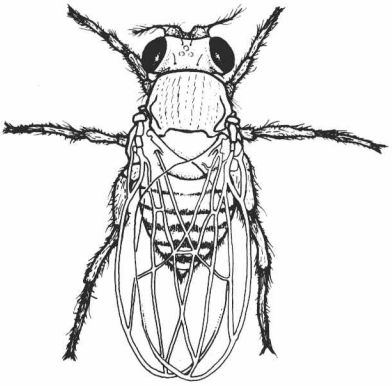

FIGURE 1-4. *The fruit fly,* Drosophila melanogaster, *an animal highly useful in genetic research.*

5. Large Number of Offspring. Genetic studies are greatly speeded if the organism chosen produces fairly sizable lots of progeny per mating. Cattle, with generally one calf per breeding, do not provide nearly as much information in a given time as many lower forms of life where offspring may number many thousands.

6. Convenience of Handling. For practical reasons, an experimental species should be of a type that can be raised and maintained conveniently and relatively inexpensively. Whales are obviously less useful in this context than are bacteria.

Methods of Genetic Study

Mendel's pea studies illustrate an approach useful both in classical, descriptive genetics and in modern molecular studies. This is the *planned breeding experiment,* in which parents exhibiting contrasting expressions of the same trait or traits are mated or crossed and careful records of results kept through several generations. We shall examine a number of such experiments in the next and succeeding chapters.

In addition to experimental breeding, we have already noted *pedigree analysis* in cases where controlled breeding programs are impossible. Pedigrees of three different conditions are shown in Figures 1-5 to 1-7; Figure 1-5 illustrates a pedigree of polydactyly, the occurrence of extra fingers, shaded symbols indicating this condition and unshaded ones representing individuals with the usual five fingers. As is customary in pedigree diagrams, squares represent males, circles females. Here we have a marriage between a polydactylous man and woman (generation I). They have three children, a polydactylous girl, a polydactylous son, and a "normal" son (generation II). The first and third individuals of generation II each marry "normal" persons; their children are shown in generation III. Note in this case that affected individuals appear

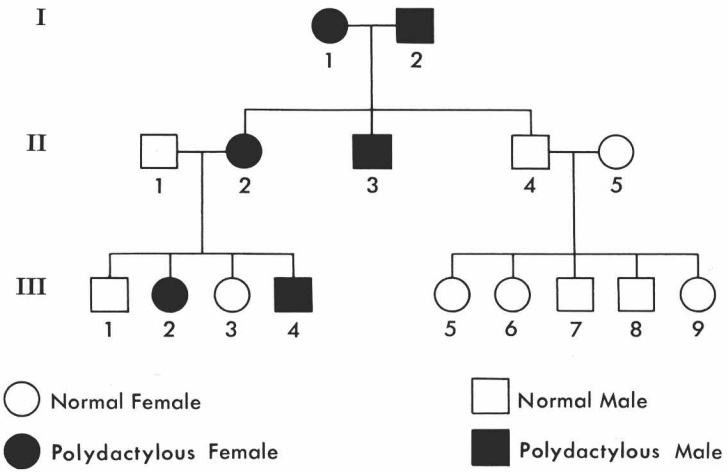

FIGURE 1-5. *Pedigree of polydactyly, occurrence of extra fingers, in human beings.*

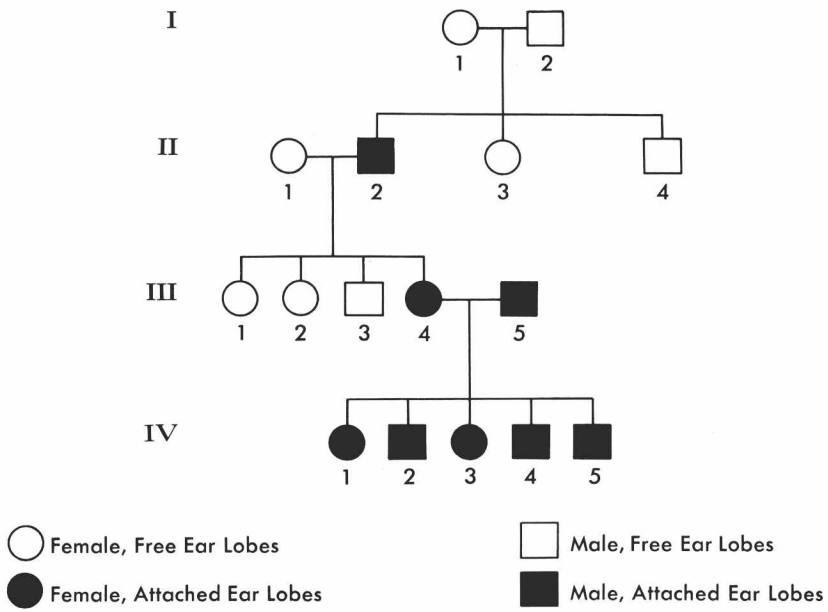

FIGURE 1-6. *Pedigree of ear-lobe shape in human beings.*

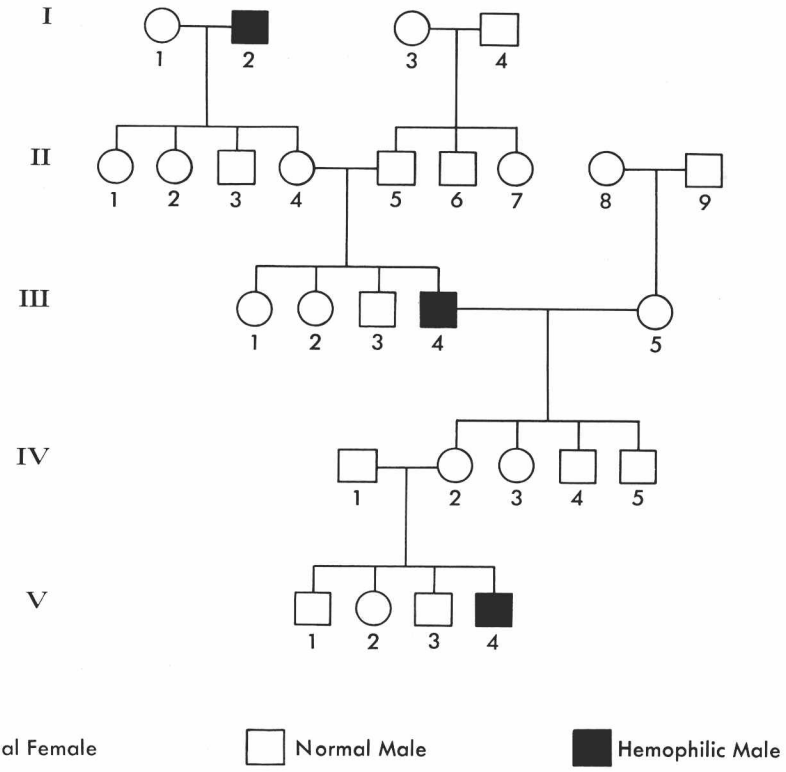

FIGURE 1-7. *Pedigree of hemophilia in man.*

only when at least one parent is polydactylous; marriages between five-fingered persons appear to produce only "normal" offspring.

A different kind of situation is illustrated in Figure 1-6. Here the condition with which we are concerned is the shape of the ear lobe, which may be either "free" or "attached" (Fig. 1-1). In this pedigree, the shaded symbols represent persons with attached ear lobes. Here we see that an individual may display this condition without its having appeared in either parent, whereas if both parents have attached ear lobes, all the children have the same condition. Does this mean that heredity is not operating in this case? Not at all. But certainly the genetic situation here is not the same as in the previous illustration of polydactyly.

As another example of pedigree, note the case shown in Figure 1-7. Here the shaded symbols represent hemophilia, in which an impairment of the clotting mechanism causes severe bleeding from even minor skin breaks with consequent danger to life. In this instance the trait appears to be confined to the

males but transmitted from an affected male through his daughters to some of his grandsons. This pattern, repeated in many pedigrees of hemophilia, certainly suggests a genetic basis, but one that is quite different from either of the first two.

Finally, *statistical analyses* of several kinds are used (1) to predict the probability of certain results in untried crosses and (2) to provide degrees of confidence in a theory regarding the specific genetic mechanism operating in a given case. Geneticists employ primarily several statistics of probability, which may be applied either to the results of an experimental breeding program or to a particular pedigree.

Fields of Study Useful in Genetics

After an initial and appropriate preoccupation with descriptive genetics, scientists turned naturally to problems of the mechanics of the processes they observed. The "what" of the earliest twentieth century rapidly gave way to a concern with "how." Parallels between inheritance patterns and the structure and behavior of cells were noted by a number of pioneer investigators. Thus *cytology* rapidly became an important adjunct to genetics. In fact, a pair of papers by Sutton as early as 1902 and 1903 clearly pointed the way to a physical basis for the burgeoning science of heredity. Sutton concluded his 1902 paper with a bold prediction: "I may finally call attention to the probability that (the behavior of chromosomes) may constitute the physical basis of the Mendelian law of heredity." Truly the door was thereby opened to an objective examination of the physical mechanisms of the genetic processes.

As the science of genetics developed rapidly during the first quarter of this century, a considerable body of knowledge was built up for such organisms as the fruit fly (*Drosophila*), corn (*Zea*), the laboratory mouse (*Mus*), and the tomato (*Lycopersicon*) concerning *what* traits are inherited and how different expressions of these are related to each other. Genetic *maps,* based on breeding experiments, were constructed for these and other species showing which genes were located on which chromosomes and the distances between *linked* genes. (We shall examine such maps and the methods used to acquire information needed to construct them in Chapter 6.) Geneticists next began to turn from concern with inheritance patterns of such traits as eye color in fruit flies to problems of *how* the observable trait is produced. Especially in the period since the beginning of World War II, a central question has been the *structure* of the gene and the mode of its operation. As the search for answers has proceeded ever more deeply into molecular levels, an increasingly important part in genetic study has been played by chemistry and physics. Contributions of these sciences have enabled geneticists to gain a clear concept of the molecular nature of the gene and its operation.

Practical Applications of Genetics

Genetics appeals to many of us not only because we are part of an ongoing genetic stream, but also because it has had such an exciting history in which theory has evolved out of observation and led, in turn, to experimental proof of fundamental operating mechanisms. Of course, any science may make the same claim, but the history of man's knowledge and understanding of genetics is to other sciences as a time-lapse movie of a growth process is to a normal-speed film. A fraction of a century ago the scientific community at large knew nothing of genetic mechanisms. Now, however, we can, with considerable accuracy, construct molecular models of genes, atom by atom. In fact, one relatively simple gene has recently been synthesized in the laboratory of Khorana and his associates (Agarwal et al., 1970). But besides being a fascinating intellectual discipline intimately related to ourselves, genetics has many important practical applications. Some of these are fairly familiar; others may be less so.

The history of improvement of food crops and domestic animals by selective breeding is too well known to warrant detailed description here (Figs. 1-8, 1-9). Increases in yield of crops such as corn and rice, improvement in flavor and size, as well as the production of seedless varieties of fruits, and advances in meat production of cattle and swine have markedly benefited mankind. As the population of the world continues to increase, this practical utilization of genetics is likely to assume even greater significance. Appropriately, the 1970 Nobel Peace Prize was awarded to a scientist, Norman Borlaug, for more than a quarter century of successful work in breeding high-yield, stiff-stemmed varieties of Mexican wheat. These new varieties, incorporating genes from American, Japanese, Australian, and Colombian stocks, not only have much-improved yield, but also wide geographic, photoperiodic, and climatic adaptability. They are successfully grown in such varied parts of the world as Mexico, Turkey, Afghanistan, Pakistan, and India. In the five-year period ending in 1970, introduction of the new varieties into India resulted in raising the wheat crop from 12 to 21 million tons, a rate of increase greater than that of India's population. Borlaug's efforts are also buying precious time in the race to control population growth. Similarly, the effort to breed disease-resistant plants must be never-ending. The 1970 epidemic of southern corn blight in the United States is a case in point.

Applications of genetics in the general field of medicine are numerous and growing. Many diseases and abnormalities are now known to have genetic bases. Hemophilia, some types of diabetes, an anemia known as hemolytic icterus, some forms of deafness and of blindness, several hemoglobin abnormalities, and Rh incompatibility are a few conditions that fall into this category. Recognition of their inherited nature is important in anticipating their possible future occurrence in a given family, so that appropriate preventive steps may be taken.

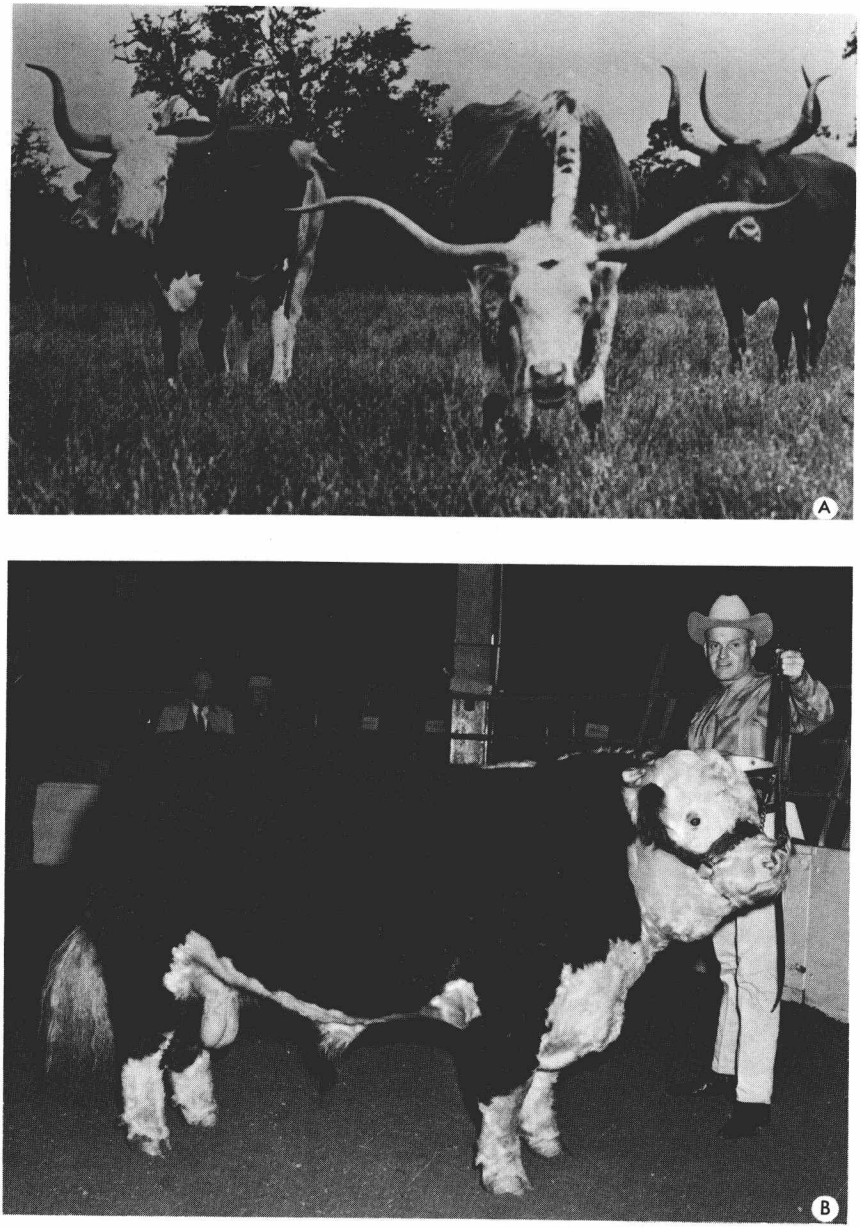

FIGURE 1-8. *Effects of breeding programs in cattle.* (*A*) *Texas Longhorn.* (USDA photo). (*B*) *Hereford, bred for meat production.* (Photo courtesy National Hereford Association.)