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SECOND EDITION

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PREFACE

The purposes of this book are to provide basic theoretical information about genetics, the study of heredity, and to present some of the experiments and reasoning through which this information has been achieved.

Although genetics is a modern science, it has grown even more rapidly in recent years and its branches now extend to almost all fields of biology. In fact, the diverse specializations of genetics enable it to occupy at present a unique central position among the biological sciences in that it ties together different disciplines that involve form, function, and change. This unifying "core" quality of genetics stems from the many levels in which genetic phenomena operate, from the molecules of cells, through developmental stages of individuals, to populations of organisms. Compartmentalization at each of these levels is common and even unavoidable since research work proceeds separately in each area of genetics. To picture genetics, however, only in terms of its many separate constituent parts leads easily to an unbalanced and fragmented view that does not do justice to the unity of the science as a whole.

Where does the unity of genetics lie? Initially the recognition of heredity began with the simple observation made among different organisms that "like begets like." In the course of history, however, the simplicity of this observation was replaced by many complex questions: From what source does this wonderful correspondence between generations arise? How is the knowledge transmitted that determines biological development? What factors account for similarities between generations and what for differences? What is inherited and what is not? What hereditary factors do members of a species have in common and in what factors do they differ? Why and how do new species of organisms arise? How can we control heredity?

A theme shared by all these questions is a concern with the materials and modes of inheritance. Since genetics is the science that seeks to answer these questions, it can be broadly defined as the study of biological material transmitted between generations of organisms. More exactly, this science encompasses studies of the kind of material transmitted, the manner in which this is accomplished, and the effect of this material on an individual organism and on generations of organisms. If we call this hereditary material *genetic material,* we can mark out the following areas of study.

1. What and where is genetic material?
2. How is it formed, transmitted, and changed?
3. How is it organized and how does it function?
4. What happens to it among groups of organisms as time passes?

The fundamental unifying theme of genetics is thus a material one which can be studied at many different levels of existence. The order of these questions and levels does not at all imply a rank of importance, since each aspect is only one facet of genetics, although some problems may assume more interest at particular historical times. It is with this over-all view in mind that the book is organized.

Within this framework a historical approach to genetics has been presented in many places for a number of reasons. First, in the swift progress of modern genetics, many aspects of our present understanding will rapidly be changed by future discoveries. Rather than be the study of a static set of axioms, a true presentation of genetics should include a sense of its continuity and progress. Second, such an approach provides many opportunities for the development of ideas from the simple to the complex and thereby facilitates learning. Third, the people who have contributed to a science and the relationship between their contributions are an important and interesting aspect of the science and help to encourage student interest.

For teaching purposes, the instructor can select sections of the text according to his training and inclination, but it is suggested that material be used from each of the basic subdivisions of the book with special emphasis on chapters included in the sections on transmission and arrangement of genetic material. A thorough understanding of basic genetic methodology and recombinational principles is extremely important in enabling students to forge ahead intelligently in areas of their own interest. One suggested program for a single-semester genetics course meeting three times weekly is to include Chapters 1 through 7, 9 through 12, 16 and 17, and selected sections of Chapter 8 (e.g., chi-square) and of Chapters 19 through 31. A one-semester course that is oriented toward evolutionary problems can follow a similar program but include material in Chapters 14 and 15, Chapters 32 through 36, and omit material in Chapters 19 and 20, and 24 through 30.

M. W. S.

ACKNOWLEDGMENTS

In the face of the large volume of genetic literature and the many important developments and changes that are continually taking place in genetics, it would be an illusion for an author to maintain, or for a reader to believe, that a textbook in this field can be written *without errors or misinterpretations*. For the first edition of this book I was therefore fortunate in having extensive sections of the manuscript reviewed by L. Van Valen and C. J. Wills. Various chapters were read and criticized by the late Th. Dobzhansky, N. E. Melechen, H. D. Stalker, and the late R. Rolfe. Exercise problems were offered to me by S. W. Brown, M. M. Green, H. D. Stalker, and the late J. A. Jenkins.

The present edition was undertaken about five years after the first was completed and incorporates a large number of changes and additions. Through the mediation of the Biology Editor for the publisher, Charles E. Stewart, Jr., extensive portions of this material were reviewed by J. Antonovics, J. Boynton, N. W. Gillham, G. B. Johnson, J. H. Postlethwait, E. Simon, and F. W. Stahl. I am also grateful to H. N. Arst, Jr., M. Ashburner, D. J. Cove, A. Derby, G. A. Dover, R. T. O. Kemp, D. W. MacDonald, P. Oliver, H. E. Schaffer, J. M. Thoday, H. L. K. Whitehouse, and A. S. Wiener, who criticized individual chapters, and to many colleagues and students who were kind enough to point out errors and ambiguities in *the first edition*.

Credits for the original sources of illustrations are given in the figure legends, and the full citations are usually in the references at the end of each chapter. The references also include sources used for the text material as well as selected further articles or books that may be relevant. Citations for authors mentioned in the problems are usually not included in the references, but will mostly be found in the *Answer Manual for Genetics, Second Edition*, published separately by the Macmillan Company. I take responsibility for errors that remain, and I would be grateful if they are brought to my attention in a constructive fashion.

Again, I owe special thanks to my wife, Zelda, for *considerable typing and many* corrections. A large amount of additional typing for this edition was carefully done by Mrs. Robyn Salvato. Kenneth Johnson and Patricia Comens helped greatly with indexing.

CONTENTS

PART

I

IDENTIFICATION OF GENETIC MATERIAL

Nothing from nothing ever yet was born.

LUCRETIUS
On the Nature of Things

1
HISTORY OF THE PROBLEM

The modern science of genetics originated when Gregor Mendel discovered that hereditary characteristics are determined by elementary units transmitted between generations in uniform predictable fashion. Each such unit, which can be called a genetic unit, or *gene*, is a substance that must satisfy at least two essential requirements: (1) that it is inherited between generations in such fashion that each descendant has a physical copy of this material, and (2) that it provide information to its carriers in respect to structure, function, and other biological attributes. Perhaps as a consequence of this double aspect of the gene, there have been two important historical approaches toward genetic phenomena: one toward identifying its physical substance, the genetic material, and the other toward discovering the manner and ways by which its manifestations, the biological characters, are inherited. Until the twentieth century these lines of investigation were usually separate, because so little was known about both transmitted substances and transmitted characters.

THE CONTINUITY OF LIFE

The first aspect of the problem, to determine the exact form of genetic material, was not an easy task. For a long period of time it was common to think that biological materials did not necessarily have to be transmitted between generations. At least until the middle of the eighteenth century, practically all biologists believed that many organisms, especially small "primitive" ones, could arise spontaneously from various combinations of decaying matter. The spontaneous appearance of flies from refuse, the observation by Leeuwenhoek (1632–1723) of small infusoria "arising" from apparently clear infusions of hay, and many other observations seemed to support the idea that life could arise without the direct transfer of matter from immediate ancestors.

It took a series of experiments begun by two Italian biologists, Redi (1621–1697) and Spallanzani (1729–1799), to seriously question this doctrine of "spontaneous generation." By excluding adult flies from laying eggs on meat, Redi showed that fly larvae would not develop. Spallanzani found that if one boiled sealed flasks of organic matter long enough, the usual tiny "animalcules" observed by Leeuwenhoek would no longer appear spontaneously. Since Spallanzani's sealed boiled flasks now contained heated or "tainted" air, the question remained of whether unheated air would, nevertheless, generate new organisms.

The seventeenth and eighteenth centuries also marked the beginnings of systematic studies or the classification of biological organisms into separate and distinct species. According to Linnaeus (1707–1778), the founder of systematics, there was a "fixity of species," so that organisms of one species could only give rise to organisms of the same type. As the science of classification grew, this view became generally accepted among biologists. At the same time, however, the spontaneous origin of living creatures from organic matter implied a nonfixity of species and this proved quite difficult to reconcile with the Linnaean concept.

Controversy on this subject raged until the nineteenth century, when the idea of spontaneous generation was finally put to rest by Pasteur (1822–1895) and by Tyndall (1820–1893), who showed that the putrefaction of organic matter only occurred under conditions that permitted solid particles to enter a nutrient culture. These solid particles were soon identified as the microbes whose multiplication leads to the fermentation of organic cultures. By common agreement these findings led to the view that, at least for the present, the birth of new organisms arises only through the continuity of life.

PREFORMATIONISM AND EPIGENESIS

The concept of a continuous transfer of living material left important questions to be answered in respect to the specific physical parts transferred by a parental organism and the manner in which this is accomplished. Originally Aristotle had proposed that an organism formed through sexual reproduction receives the "substance" of the female egg and a contribution of "form" by the male seminal fluid. The combined effect produced by these two factors in creating a new organism did not necessarily involve any material transfer between them but occurred through a mystical influence of the male semen, called by Harvey (1578–1657) the *aura seminalis.* Later, during the seventeenth and eighteenth centuries, after the discovery of eggs and sperm and of pollen and ova, the idea was advanced by many biologists that one of the sex cells, or gametes, either sperm or egg, contained within itself the entire organism in perfect miniature form (*preformationism*); for this miniature creature to unfold into its preformed adult proportions only proper nourishment was necessary. There were, of course, many difficulties in accepting this hypothesis, not the least being that such perfect miniature creatures, although imagined (Fig. 1-1), were never truly observed. Nevertheless the concept that an organism develops from a minuscule piece of transmitted matter, "preformed" though it may be, was an important step forward as compared to the idea of spontaneous generation.

When Wolff (1738–1794) showed that different adult structures of both plants and animals develop from uniform embryonic tissues that betray no inkling of their ultimate fate, preformationism was replaced by the more modern, although not necessarily novel, idea of *epigenesis.* The epigenetic view proposed that many new factors, such as tissues and organs, appeared during the development of an organism which were not present in its original formation. Wolff believed these organs arose completely *de novo* through mysterious vital forces, while his famous successor, von Baer (1792–1876), proposed the more accepted view

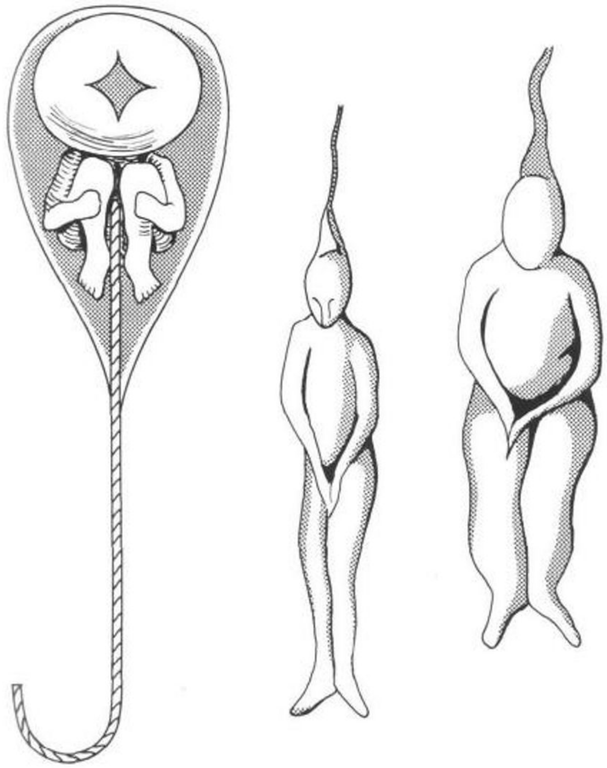


Figure 1–1
"Homunculi" presumed to be seen in human sperm. (After Singer, from Hartsoeker and Delenpatius.)

that they arose through a gradual transformation of increasingly specialized tissue.

PANGENESIS AND THE INHERITANCE OF ACQUIRED CHARACTERS

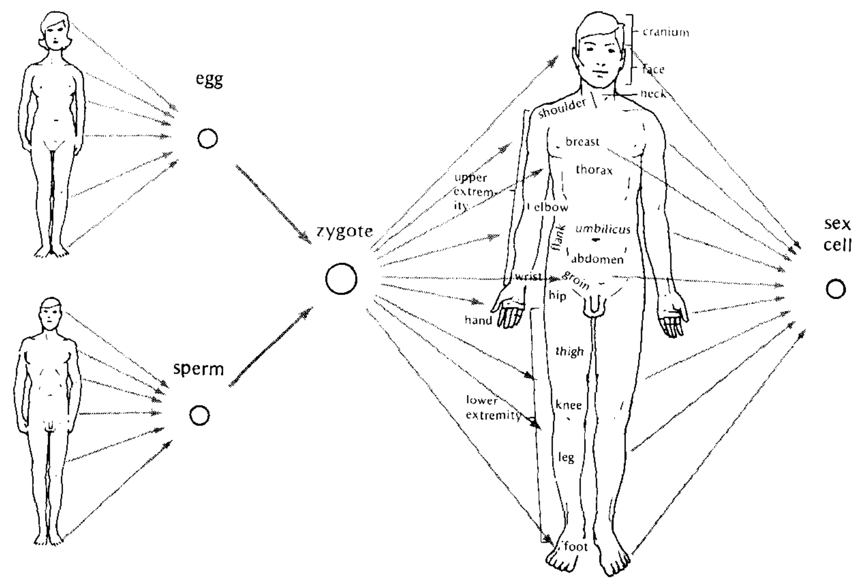
It is easy to see that with the acceptance of the theory of epigenesis the problem of finding the genetic material of an organism was put back to something invisible and, many believed, something mystical, within the original embryonic cell. Charles Darwin (1809–1882), the founder of modern evolutionary theory, and certainly no mystic, believed (as did many other biologists) that very small, exact, but invisible copies of each body organ and component (*gemmules*) were transported by the bloodstream to the sex organs and there assembled into the gametes. Upon fertilization gemmules of the opposite sex were added and all these miniature elements then separated out to different parts of the body during development to constitute a mixture of maternal and paternal organs and tissues (Fig. 1-2a).

To those who believed in evolution this doctrine of *pangenesis* provided an even further attraction by explaining how heritable changes could occur that might lead to the origin of new species. According to pangenesis, for example, the excess use or disuse of an organ would alter its gemmules and consequently lead to a changed inheritance in the descendants. This theory, named "the inheritance of acquired characters," had a long previous history and even has some few adherents today (Lysenko and his remaining followers in the Soviet Union).

Lamarck (1744–1829), the foremost eighteenth-century popularizer and exponent of this theory, tried to explain the extraordinary ability of these small hereditary agents to respond directly to the environment by assuming that each had a spiritual consciouslike property that could absorb and interpret messages from the outside. Despite the mysticism and many other difficulties involved in the theories of pangenesis and inheritance of acquired characters, many biologists felt it necessary to accept these theories as the only existent reasonable explanations of heredity.

By the end of the nineteenth century a number of important discoveries had been made which fortunately set the stage for a more precise material characterization of the source of heredity. Many details of cell structure and cell division were already known through the researches of a long line of biologists, among them notably Schleiden (1804–1881), Schwann (1810–1882), Nägeli (1817–1891), Virchow (1821–1902), Flemming (1843–1915), and Bütschli (1848–1920). The cell *nucleus*, named and described by Robert Brown (1773–1858) in 1833, was shown by O. Hertwig (1849–1922) to be directly involved in sea urchin fertilization through the union of the sperm and egg nuclei. Similarly Strasburger (1844–1912) had shown such union to occur for plants, and had invented the terms *nucleoplasm* and *cytoplasm* to refer to the protoplasmic material in the nucleus and its surrounding cell body, respectively. The dark-staining nuclear threads,

(a) Pangenesis theory



(b) Germplasm theory

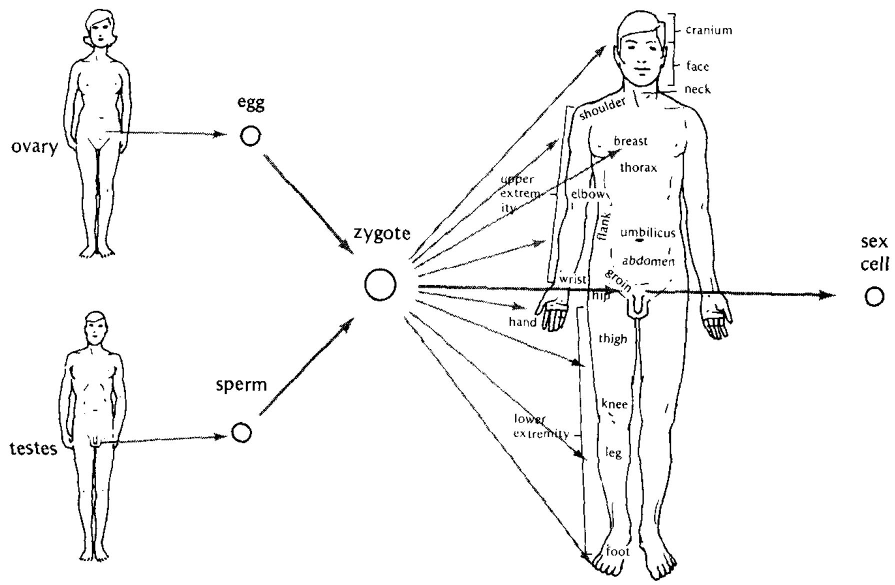


Figure 1–2

Comparison between (a) pangenesis and (b) germplasm theories in the formation of a human. In pangenesis all structures and organs throughout the body contribute copies of themselves to a sex cell. In the germplasm theory the plans for the entire body are contributed only by the sex organs.

named "chromatin," which had been shown first by Schneider (ca. 1873) and later by Flemming to divide longitudinally during cell division, also passed in equal portions to the two daughter cells according to van Beneden (1845–1910). The total number of these individual threads, or *chromosomes*, remained constant in all cells of an organism except during gamete formation. In gametes the number of chromosomes was reduced but was then later restored when the nuclei of the gametes fused during fertilization to form the first embryonic cell.

Thus the cellular link between parents and offspring that occurred through gametes was also accompanied by chromosomal links between each generation. The chromosomes of the offspring, however, were not merely quantitatively equal to the number of parental chromosomes but seemed to be qualitatively equal as well. That is, since the splitting of the parental chromosomes occurred longitudinally, any differences existing along the length of the chromosome were also passed on to offspring.

The close of the century had also fairly well established, through the efforts of Weismann (1834–1914), that pangenesis could not be verified. Weismann showed that even after 22 generations of mice had been denuded of their tails, newborn mice still managed to inherit the complete tail structure. The theory of pangenesis was therefore replaced by Weismann with the "germplasm" theory, which proposed that multicellular organisms give rise to two types of tissue: *somatoplasm* and *germplasm*. The somatoplasm consisted of tissues that were essential for the functioning of the organism but that lacked the property of entering into sexual reproduction. Changes that occurred in somatic tissues (e.g., mouse tails) were thus not passed on in heredity. Germplasm, on the other hand, was set aside for reproductive purposes, and any changes occurring within it could lead to changed inheritance. According to this view, there was a continuity of germplasm between all descendant generations which accounted for the many biological similarities that were inherited (Fig. 1–2b).

By the early twentieth century, most of the morphological features of the cell had been observed under the light microscope, as well as the general features involved in the cell-division processes of *mitosis* (somatic, or body-cell, division) and *meiosis* (germ-cell, or gamete, formation). Work by cytologists such as Boveri (1862–1915), Henking (ca. 1891), Montgomery (1873–1912), and others had shown that such cell divisions led to an accurate partitioning and separation of the nuclear chromosomes. In somatic mitosis, the number of chromosomes in each daughter cell remained identical to that of the parental cell. In meiosis, gametes were formed containing exactly half the parental number, which then combined with a gamete of the opposite sex to produce an individual with a full chromosomal complement.

It was only one step further to hypothesize that the constancy of chromosomes in a species and their precise partitioning in inheritance was a reflection of the similar constancy and inheritance pattern of more easily observable biological characters. That step was rapidly taken when a series of fundamental discoveries by the Austrian monk Gregor Mendel (1822–1884) was brought to light in 1900.

EXPERIMENTS WITH HYBRIDS

Mendel's important experiments will be discussed in detail in Chapters 6 and 7. For the present we can mention that they were an extension and development of the efforts of a long line of biologists who had been studying the effects of unifying (*hybridizing*) two differently appearing parental stocks. It had long been thought that heredity was a "blending" process and that offspring were essentially a "dilution" of the different parental characteristics. Blending inheritance thus helped to explain the observation that children were at times intermediate to both parents in respect to measurable characters such as size. On the other hand, there were also the frequent observations that children could resemble either one parent or the other, and that specific characteristics appeared