TEXTBOOK OF HUMAN GENETICS

Second Edition

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Ashley Montagu

REVISED BY
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Preface to the First Edition

Few groups of students are so varied in their preparation as those who enter a course in human genetics. This is true whether the course is offered in a medical school, dental school, school of nursing, or the liberal arts division of a college or university. Many have had some exposure to genetics, usually a course in general genetics. Some may have had several courses in genetics. A large number, however, have had no genetics instruction except perhaps for some introductory remarks in a high school or college general biology course.

This book was written with this heterogeneity in mind, as a result primarily of many years in which one of us (M.L.) attempted to cope with it in teaching with the textbooks available. Students new to genetics often complained that the best of these was too difficult. The students with more background soon found the easier textbooks boring. Some of the more interesting books from the medical point of view could not be used because they virtually avoid the arithmetic and mathematical aspects of the subject. This short-changes the student in an area that is most important for understanding the genetics of man, particularly since we are a species in which as a rule the family unit is small.

We have attempted therefore to produce a textbook which would satisfy both kinds of students, those with little background in the subject and those with a good deal. For the benefit of the unsophisticated student an attempt is made to explain the fundamental theory in some detail. Special effort is devoted to making clear the fundamentals of such important concepts for human genetics as the expectations in small family units, levels of significance, and the expectations under random and assortative mating. We feel that if these aspects of the field are explained in sufficient detail they can be understood by any college level student who has had any algebra at all.

At the same time we have tried to provide some fundamental insight into areas of the field which are close to the current research frontiers and areas, such

as the gamma-globulin story, which have often been considered too complex for an undergraduate textbook. The hope is that these discussions—and the references in them—will interest the student who is already thoroughly grounded in the fundamentals of the subject and will assist him in entering into the current literature.

In both phases of the book, the method is to present principles and cite examples to illustrate them. It must be clearly understood that in most instances no attempt has been made to be exhaustive, that is, to find all the possible examples or to make complete surveys of the literature. However, in a few exceptional instances, such as enzyme deficiency disorders or the abnormal hemoglobins, some attempt is made at completeness, to provide a picture of the state of the art, as it were.

A book of this type could not be written without the assistance, co-operation, and painstaking effort of many persons. It is impossible, unfortunately, to name them all. We owe particular gratitude to all the original workers whose research forms the basis of this book. Some are acknowledged in the references and in the legends of the illustrations, but we recognize that many others have made invaluable contributions that we have not cited. Furthermore, even those who are cited have contributed much more than can be gleaned from the bibliography.

We owe special thanks to the scientists and students, among them Michael Balkin, Harold F. Falls, Kurt Hirschhorn, Victor A. McKusick, Marian Rivas, Richard E. Rosenfield, Arthur G. Steinberg, Alexander S. Wiener, and several anonymous readers who have gone over various chapters and made numerous criticisms, corrections, and suggestions, not all of which we were able (or wise enough) to follow. Also invaluable has been the knowledge we have absorbed at the regular meetings of the University Seminar on Genetics and Evolution of Man at Columbia University, led at different times by Professors Leslie C. Dunn, Theodosius Dobzhansky, and Howard Levene.

One of us (M.L.) feels very indebted to the Genetic Biology section of the National Science Foundation for the support of his research that enabled him to develop many of the concepts presented here, particularly work described in chapter 12.

We are also very grateful to those who assisted in producing this work, among them are our very efficient typists Dolores Brennan, Sharon Matney, Phillis Gott, Barbara Davis, Blazena Soskice, and Jeanne Hickey, and the excellent and patient staff of the Oxford University Press, particularly Leona Capeless, William Halpin, Jeffrey House, and many members of the design and manufacturing departments.

M.L.
A.M.

January 1971

Preface to the Second Edition

It is a striking commentary on the remarkable speed of advances, indeed *fundamental* advances, in the field of human genetics that several sections in the first edition of this book became out-of-date between the time its writing was completed and the date of its publication. This made all the more gratifying the reception the book received at the hands of reviewers and a broad spectrum of teachers of human genetics courses, both graduate and undergraduate, in this country and abroad. Their comments, including many made privately to the authors and to the publishers' representatives, indicated that a real need had existed for a human genetics text which attempted to explain in some detail the principles of the field, with special emphasis on the areas, such as some of the complex loci and the mathematical aspects of genetics, that students find particularly difficult and which are so often neglected in other textbooks. For these reasons I felt an obligation to revise the text as soon as it became practicable.

The major changes include a new chapter on identification of the human chromosomes. In addition there have been major revisions of the chapter on linkage (Chapter 14 in this edition), to describe the newer techniques, such as somatic cell hybridization, aberrancy mapping, and nucleic acid hybridization, that provide evidence of the synteny of gene loci; of the chapters dealing largely with biochemical genetics (Chapters 5 and 15), including the rapid strides in the study of enzyme variations; the chapter on genetic counselling (Chapter 20), with special emphasis on new data on amniocentesis and on empiric risk factors; and the chapter dealing with special problems of allelism (now Chapter 16), with an up-to-date review of the major histocompatibility locus of man, close upon the discussion of the Gm locus. Developments in the last-named area, immunogenetics, are coming so thick and fast that the subject will undoubtedly demand a chapter all to itself in the next edition. A number of chapters, notably 4, 5, 14, and 18, contain new material that reflects the increasing influence of molecular biology on human genetics.

The basic organization of the first edition has been retained, except that the three chapters concerned with multiple loci (14–16), whether apparent or postulated, are now contiguous. The first three chapters review the chromosomal background of human genetics and the known chromosomal aberrations. They are followed by a group of chapters (4–8) concerned primarily with the genetics of the single locus—as it follows Mendel's first law and as it may be modified by the special problems introduced by gene action and by the small size of the typical human sibship. Chapter 9 carries this discussion forward to modifications related to sex–X-linkage, Y-linkage, and sex-influenced heredity. The next four chapters (10–13) take up some of the special methods, from population genetics and from twin studies, that have been so important to human geneticists, who cannot do controlled breeding experiments. Chapters 14–16 then deal with the genetics of multiple loci, followed by three chapters related to the origin and maintenance of human variation and a final chapter on counselling.

As in the case of the first edition, this work would have been impossible without the splendid cooperation and assistance of so many persons that it is impossible to give proper credit to all of them. I am particularly grateful to the many colleagues named in the figure legends who have taken the time from an already busy schedule to provide me with illustrative material from their research. Drs. Richard Rosenfield and Alexander Wiener have been helpful in reading and criticizing selected portions of the manuscript. I have been assisted also by discussions of the contents with my three daughters, Eve, Sara, and Margie, of whom I am justifiably proud; Sara was particularly helpful as she gave the proofs a painstaking reading. Finally, the editors who have gone over the manuscript, Leona Capeless and Brenda Jones, deserve my gratitude not only for their usual efficient assistance but, along with Jeffrey House, for their ever pleasant manner and encouragement.

M. L.

New York
January 1977

Contents

PART ONE
The Chromosomal Background

I · Mitosis and Meiosis

Of the many pervasive generalizations that advanced biological science in the nineteenth century, none has been more influential than the cell theory which established that the living stuff, the protoplasm, of an organism does not exist as a homogeneous mass, but is instead distributed in the discrete units we call cells (Fig. 1–1).

Most of the Protista are, in a sense, exceptions to this rule because the entire organism consists of a single cell, but these exceptions are so in only a philosophical sense. Even viruses, which are not cells, conform to the rule, for they do not manifest the properties of life until they are inside a cell. To be alive they must become essentially organelles, albeit parasitic ones, of the host cell.

Each of us begins life as a single cell, which biologists call a ZYGOTE, formed by the union of two cells, an egg or *ovum* (plural, *ova*) produced by the mother and a sperm or *spermatozoön* (plural, *spermatozoa*) produced by the father.

The human ovum (Fig. 1–2) is a spherical cell about 140 microns (about 1/175 of an inch) in diameter which weighs about one-millionth of a gram. Although this is relatively large as cells go, it would take about 20,000,000 ova to weigh an ounce. The single cell can barely be seen by the naked eye; the actual size of the human ovum is about one-fourth of the diameter of the period at the end of this sentence. The spermatozoön, being microscopic, is even smaller. Note the contrasts in Figure 1–2. Its head and neck combined—the part that enters the egg in fertilization in most organisms—is only about 10 microns long and less than 5 microns wide. It would take about five billion sperm to weigh one gram. From these tiny beginnings develops an adult human being weighing about fifty *trillion* times as much as the egg and sperm combined! Even the newborn baby represents more than a two trillionfold increase in weight over the short space of nine months.

This tremendous growth takes place largely from the production of new cells.

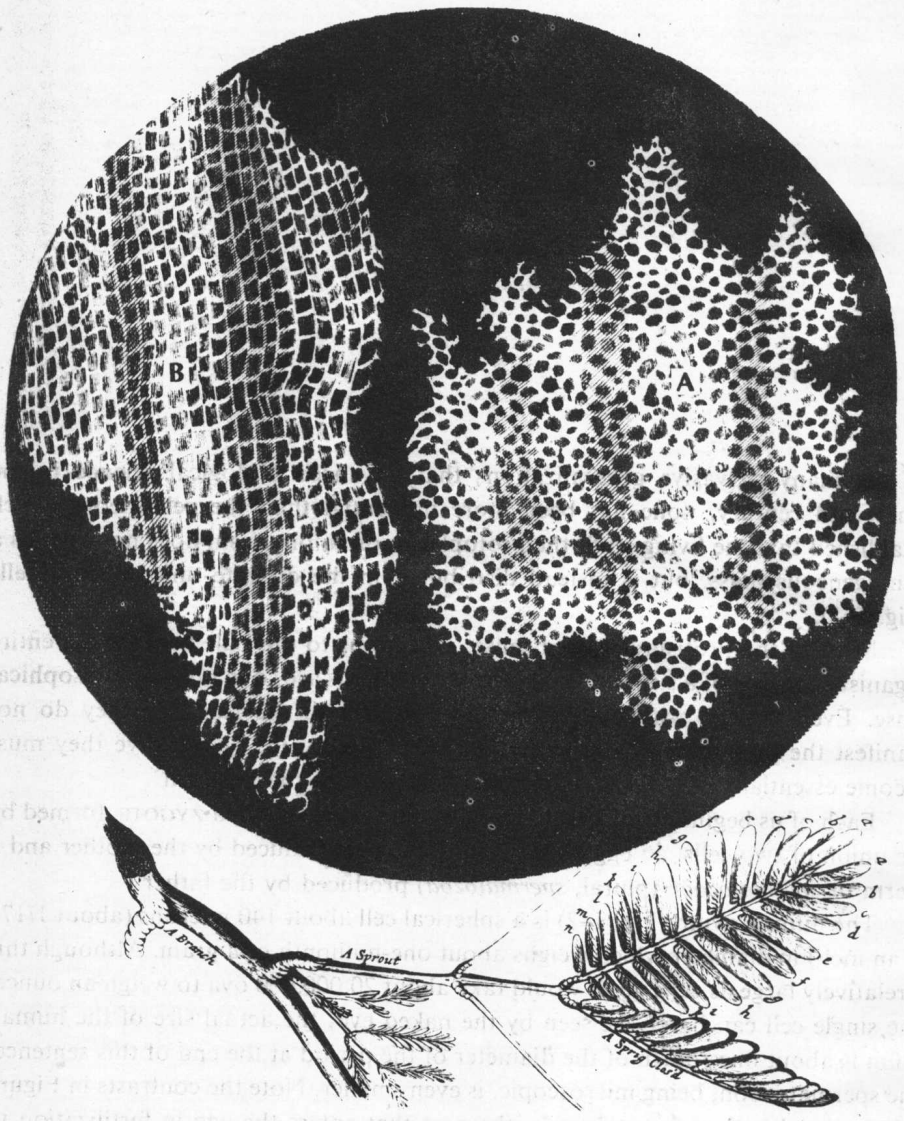

FIG. 1–1. Robert Hooke (1636–1703) gave the name "cells" to the cavities in cork, (A) cross section, (B) longitudinal section, which he pictured in his book *Micrographia* (1665). In addition to being a mathematics professor and architect, Hooke improved the compound microscope, and he was therefore able to see these basic units of biological structure. He did not see or recognize the protoplasmic content of the cells, however, even when he looked at living tissue. (Courtesy of the New York Public Library Photographic Service.)

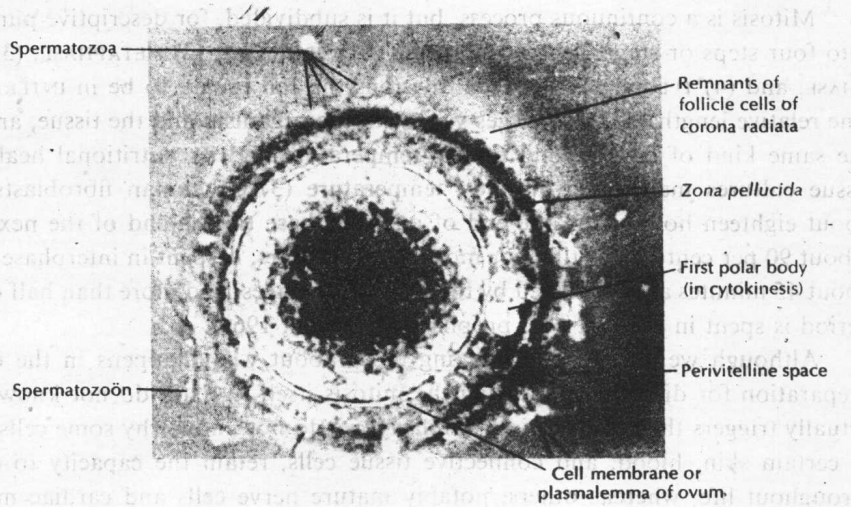

FIG. 1–2. The human egg cell ready to be fertilized, and some of the structures which may surround it soon after it has been released from the ovary. The *zona pellucida* consists of non-living matter secreted in the ovary between the cell membrane and the follicle cells of the corona radiata; it corresponds to the "vitelline membrane" of insects, amphibians, and birds, and the jelly coat surrounding sea urchin eggs. Originally closely adherent to the cell membrane, it later separates away, leaving the fluid-filled *perivitelline space*, into which the first and second polar bodies are extruded. (Phase-contrast photomicrograph of living cell, × 132, from Shettles, 1960. Courtesy of L. B. Shettles and Hafner Publishing Co.)

The human adult who started life as a single cell has about 10^{14}, or one hundred *quadrillion*, cells.

How are all these new cells produced? The evidence is strong that there is only one way of producing new cells: the division of old cells. It is even more remarkable that in almost all the living world there is basically only one way for living cells to divide: the process called MITOSIS (plural, *mitoses*). (Even cancers involve mitoses, disorderly and abnormal, but mitoses nonetheless.) Further along, we shall describe the process of cell division by meiosis, but it will not be difficult to see that this represents only a slight modification of mitosis. In any case, the majority of the cells of the human body are produced by mitoses of preceding cells. Starting with the cleavage divisions of the one-celled embryo, about forty-four generations of mitosis are needed to produce the newborn baby, and four more to reach the adult number of cells. These are only average figures, of course. Some lines of cells undergo many more generations of division in order to replace worn-out cells, while other lines attain maturity in a few divisions and do not divide again.

Mitosis is a continuous process, but it is subdivided, for descriptive purposes, into four steps or stages, named, in order: (1) PROPHASE, (2) METAPHASE, (3) ANAPHASE, and (4) TELOPHASE. Between divisions the cell is said to be in INTERPHASE. The relative lengths of these stages vary with the organism and the tissue, and, for the same kind of cell, depend on the temperature and its nutritional health. In tissue cultures maintained at body temperature (37°C) human fibroblasts take about eighteen hours from the end of one telophase till the end of the next one. About 90 per cent of this time, or more than 17 hours, is spent in interphase. Only about 45 minutes are consumed by the other four stages, and more than half of this period is spent in the first one, prophase (Swanson, 1964).

Although we are steadily learning more about what happens in the cell in preparation for division and during the mitosis itself, we still do not know what actually triggers the cell to divide. Similarly, we do not know why some cells, such as certain skin, blood, and connective tissue cells, retain the capacity to divide throughout life, whereas others, notably mature nerve cells and cardiac muscle, lose this capacity once they are formed. Many cytologists, the scientists who study the structure and division of single cells, are convinced that only when we have learned these secrets will we be able to solve the mystery of why cells sometimes start to divide in a disorderly way and produce cancers.

Until prophase begins it is usually not apparent that a cell is about to divide. Generally, but not invariably, the cell has enlarged relative to its neighbors, but there is no exact critical size to give a clue that division will begin. In animal cells the first clear sign of an impending division usually comes with the activity of a small cytoplasmic organelle, the centriole or centrosome, which lies near the nucleus and stains darkly with basic dyes (Fig. 1–3). At the beginning of prophase this is seen to have divided, and each has "rays" radiating from it (Fig. 1–4A and B). The combination of a centriole and its rays has been called an *aster* or *astral body*. Considerable evidence exists that each centriole, as soon as it is fully formed, begins to produce another one, often referred to as its daughter centriole; this is why each centriole (shown in Figs. 1–3 and 1–4H) appears to consist of two parts. Many authors use the term "centrosome" to denote the combined centrioles and rays (the usage in Fig. 1–4), while other authors consider "centrosome" synonymous with "centriole." At an early point in prophase the two fully formed centrioles separate, and they move around the nuclear membrane until there is about 180° of arc between them (Fig. 1–4, especially B and I).

Cytoplasmic molecules orient themselves as microtubular fibrils between the centrioles (Fig. 1–6) so that the combination of centrosomes and the new fibrils assumes the shape of an old-fashioned weaver's spindle and is named accordingly. The areas of the spindle near the centrosomes are called poles, and the broadened

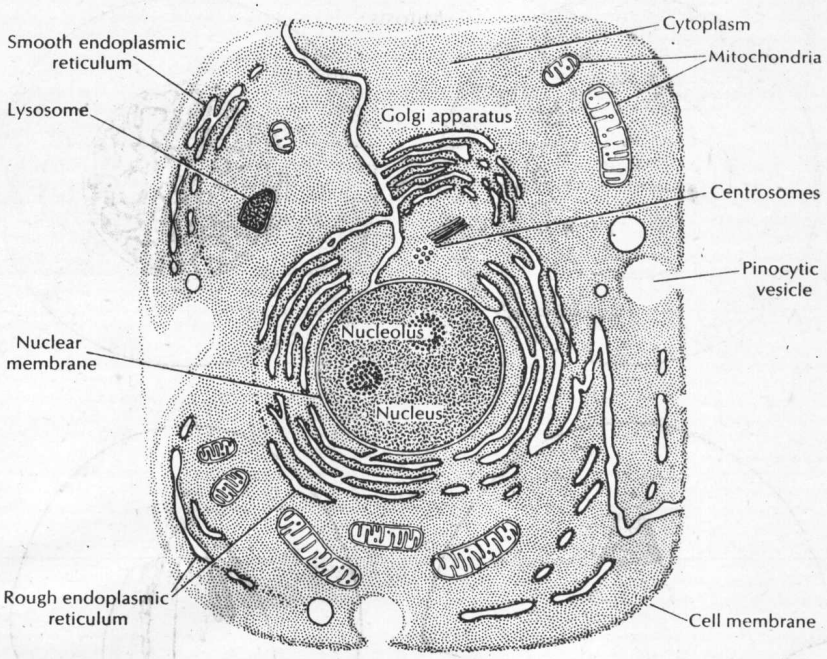

FIG. 1–3. Diagram of a typical cell. The ribosomes are the dots lining the rough endoplasmic reticulum, the sites of protein synthesis. The mitochondria are the power plants providing the cell with energy. Lysosomes are bodies containing digestive enzymes that break down larger molecules into smaller constituents. The centrosomes, one shown in longitudinal section and one in cross section, separate to form the poles of the spindle apparatus. Pinocytic vesicles represent areas of the cell membrane that invaginate to incorporate external materials into the cytoplasm. The function of the Golgi body is related to secretion. (Modified from Montagu, 1963. Courtesy of World Publishing Co.)

area midway between the poles is called the equator of the spindle (Figs. 1–4D-H, 1–5, and 1–6A).*

Meanwhile the most remarkable event of mitosis takes place: what appear to be irregular chromatin granules in the interphase nucleus (Fig. 1–4A) are gradually replaced by continuous thread-like structures (Fig. 1–4B). These give the process its name, from *mitos*, the Greek word for thread. Since they stain darkly with

* In plants all the elements of a spindle are visible except the centrioles. It is uncertain whether this means that centrioles are not essential to the formation of the spindle—as they appear to be in animals (Mazia, 1961)—or whether they are present but cannot be demonstrated by present methods.