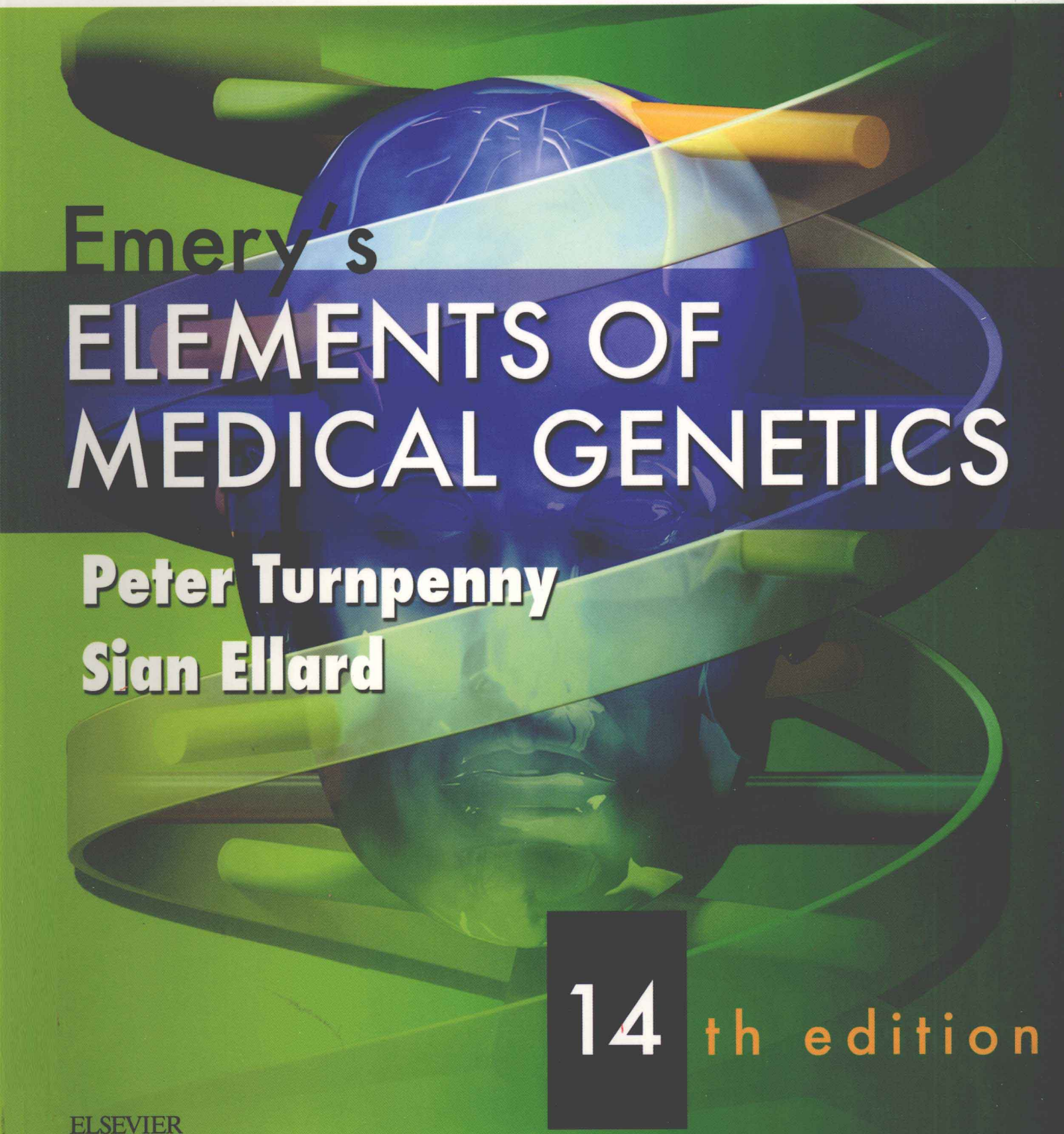

Emery's ELEMENTS OF MEDICAL GENETICS

Peter Turnpenny
Sian Ellard

14th edition

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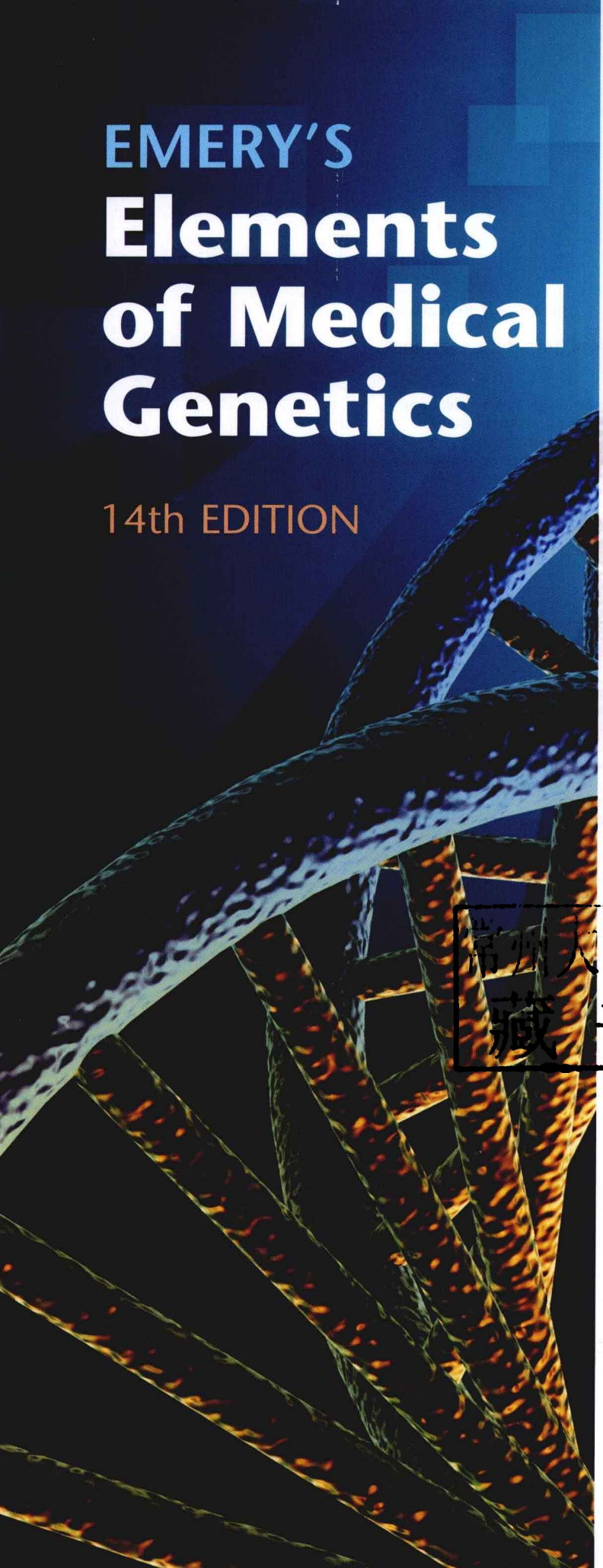
14th EDITION



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To our fathers—
sources of encouragement and support
who would have been proud of this work

Preface

Alan E.H. Emery
Emeritus Professor of Human Genetics & Honorary Fellow
University of Edinburgh

"A man ought to read just as inclination leads him; for what he reads as a task will do him little good."

Dr. Samuel Johnson

Advances and breakthroughs in genetic science are continually in the news, attracting great interest because of the potential, not only for diagnosing and eventually treating disease, but also for what we learn about humankind through these advances. In addition, almost every new breakthrough raises a fresh ethical, social, and moral debate about the uses to which genetic science will be put, particularly in reproductive medicine and issues relating to identity and privacy. Increasingly, today's medical graduates, and mature postgraduates, must be equipped to integrate genetic knowledge and science appropriately into all areas of medicine, for the task cannot be left solely to clinical geneticists, who remain small in number; indeed, in many countries there is either no structured training program in clinical genetics or the specialty is not recognized at all.

Since the publication of the thirteenth edition of *Emery's Elements of Medical Genetics* there has been a huge surge forward in our knowledge and understanding of the human genome as the technology of *microarray comparative genomic hybridization* has been extensively applied, both in research and clinical service settings. We know so much more about the normal variability of the human genome as the extent of *copy number variants* (of DNA) has become clearer, though we are still trying to unravel the possible significance of these in relation to health and disease. And as we write this there is great excitement about the next technological revolution that is underway, namely *next generation sequencing*. Already there are dramatic examples of gene discovery in mendelian conditions through analysis of the whole *exome* of very small numbers of patients with clear phenotypes. There is also more realistic anticipation than before that breakthroughs will be made in the treatment of genetic disease, which will take a variety of different forms. Whilst discovery and knowledge proceed apace, however, the foundation for those who aspire to be good clinical practitioners in this field lies in a thorough grasp of the basics of medical genetics, which must include the ability to counsel patients and families with sensitivity and explain difficult concepts in simple language.

In this fourteenth edition of *Emery's Elements of Medical Genetics* we have tried to simplify some of the language and reduce redundant text where possible, to make way for some new, updated material. Several chapters have undergone significant revisions, and the range of illustrations has increased. We have listened to those colleagues (a small number!) who identified one or two errors in the last edition and also suggested ideas for improvement. Once again, we have sought to provide a balance between a basic, comprehensive text and one that is as up to date as possible, still aiming at medical undergraduates and those across both medical and non-medical disciplines who simply want to "taste and see." The basic layout of the book has not changed because it seems to work well, and for that we remain in debt to our predecessors in this project, namely Alan Emery, Bob Mueller, and Ian Young.

Peter D. Turnpenny and Sian Ellard
Exeter, United Kingdom
November 2010

Acknowledgments

As with the previous two editions, we are very grateful to those of our patients who were asked for consent to publish their photographs for the first time; again, not one refused, which was enormously helpful. In preparation of this edition we thank colleagues who cast a critical but very constructive eye over particular chapters, which led to some very necessary changes to the text. These were Dr. Paul Kerr (Consultant Hematologist, Royal Devon and Exeter Hospital, Exeter) and Dr. Claire Bethune (Consultant Immunologist, Derriford Hospital, Plymouth). Dr. Rachel Freathy (Sir Henry Wellcome Postdoctoral Fellow, Peninsula Medical School, Exeter) provided new insights and assisted with revision of the chapters describing polygenic inheritance and common disorders. We thank those at Elsevier who communicated very fully and promptly throughout the revision, and were patient with delays on our part. We again thank those at our respective homes who had to put up with a season of early mornings and late nights, without which the revision would not have been possible.

EMERY'S Elements of Medical Genetics

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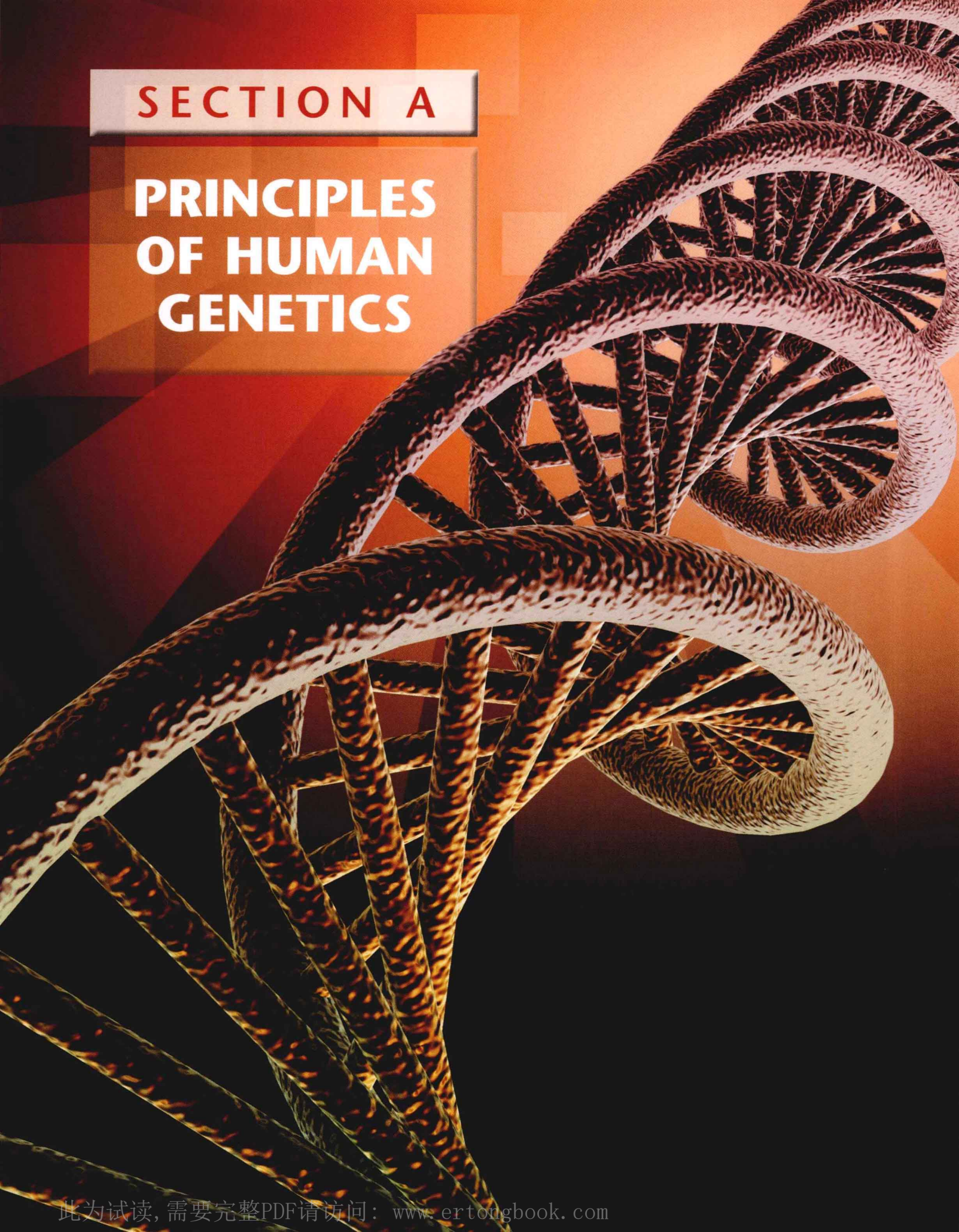
SECTION A

PRINCIPLES OF HUMAN GENETICS



CHAPTER 1

The History and Impact of Genetics in Medicine

It's just a little trick, but there is a long story connected with it which it would take too long to tell.

GREGOR MENDEL, IN CONVERSATION WITH C. W. EICHLING

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

WATSON & CRICK (APRIL 1953)

Presenting historical truth is at least as challenging as the pursuit of scientific truth and our view of human endeavors down the ages is heavily biased in favor of winners—those who have conquered on military, political, or, indeed, scientific battlefields. The history of genetics in relation to medicine is one of breathtaking discovery from which patients and families already benefit hugely, but in the future success will be measured by ongoing progress in translating discoveries into both treatment and prevention of disease. As this takes place, we should not neglect looking back with awe at what our forebears achieved with scarce resources and sheer determination, sometimes aided by serendipity, in order to lay the foundations of this dynamic science. A holistic approach to science can be compared with driving a car: without your eyes on the road ahead, you will crash and make no progress; however, the competent driver will glance in the rear and side mirrors regularly to maintain control.

Gregor Mendel and the Laws of Inheritance

Early Beginnings

Developments in genetics during the twentieth century have been truly spectacular. In 1900 Mendel's principles were awaiting rediscovery, chromosomes were barely visible, and the science of molecular genetics did not exist. By contrast, at the time of writing this text in 2010, chromosomes can be rapidly analyzed to an extraordinary level of sophistication by microarray techniques and the sequence of the entire human genome has been published. Some 13,000 human genes with known sequence are listed and nearly 6500 genetic diseases or **phenotypes** have been described, of which the molecular genetic basis is known in approximately 2650.

Few would deny that genetics is of major importance in almost every medical discipline. Recent discoveries impinge not just on rare genetic diseases and syndromes, but also on many of the common disorders of adult life that may be predisposed by genetic variation, such as cardiovascular disease, psychiatric illness, and cancer, not to mention influences on obesity, athletic performance, musical ability, and longevity. Consequently a fundamental grounding in genetics should be an integral component of any undergraduate medical curriculum.

To put these exciting developments into context, we start with an overview of some of the most notable milestones in the history of medical genetics. The importance of understanding its role in medicine is then illustrated by reviewing the overall impact of genetic factors in causing disease. Finally, new developments of major importance are discussed.

It is not known precisely when *Homo sapiens* first appeared on this planet, but according to current scientific consensus based on the finding of fossilized human bones in Ethiopia, man was roaming East Africa about 200,000 years ago. It is reasonable to suppose that our early ancestors were as curious as ourselves about matters of inheritance and, just as today, they would have experienced the birth of babies with all manner of physical defects. Engravings in Chaldea in Babylonia (modern-day Iraq) dating back at least 6000 years show pedigrees documenting the transmission of certain characteristics of the horse's mane. However, any early attempts to unravel the mysteries of genetics would have been severely hampered by a total lack of knowledge and understanding of basic processes such as conception and reproduction.

Early Greek philosophers and physicians such as Aristotle and Hippocrates concluded, with typical masculine modesty, that important human characteristics were determined by semen, using menstrual blood as a culture

FIGURE 1.1 Gregor Mendel. (Reproduced with permission from BMJ Books.)

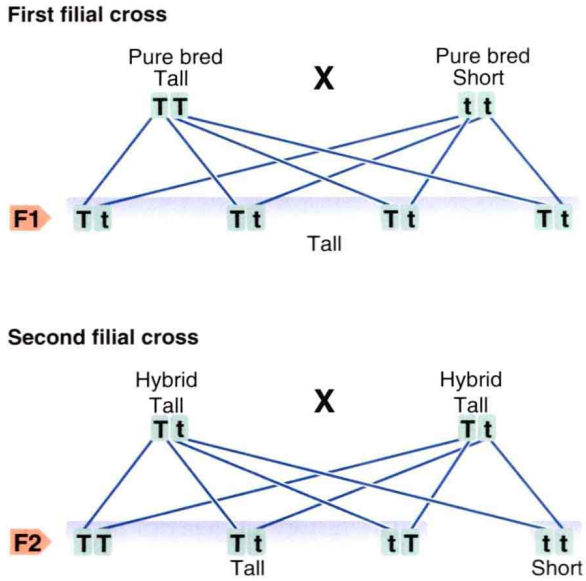


FIGURE 1.2 An illustration of one of Mendel's breeding experiments and how he correctly interpreted the results.

medium and the uterus as an incubator. Semen was thought to be produced by the whole body; hence bald-headed fathers would beget bald-headed sons. These ideas prevailed until the seventeenth century, when Dutch scientists such as Leeuwenhoek and de Graaf recognized the existence of sperm and ova, thus explaining how the female could also transmit characteristics to her offspring.

The blossoming of the scientific revolution in the 18th and 19th centuries saw a revival of interest in heredity by both scientists and physicians, among whom two particular names stand out. Pierre de Maupertuis, a French naturalist, studied hereditary traits such as extra digits (polydactyly) and lack of pigmentation (albinism), and showed from pedigree studies that these two conditions were inherited in different ways. Joseph Adams (1756–1818), a British doctor, also recognized that different mechanisms of inheritance existed and published *A Treatise on the Supposed Hereditary Properties of Diseases*, which was intended as a basis for genetic counseling.

Our present understanding of human genetics owes much to the work of the Austrian monk Gregor Mendel (1822–1884; Figure 1.1) who, in 1865, presented the results of his breeding experiments on garden peas to the Natural History Society of Brünn in Bohemia (now Brno in the Czech Republic). Shortly after, Mendel's observations were published by that association in the Transactions of the Society, where they remained largely unnoticed until 1900, some 16 years after his death, when their importance was first recognized. In essence, Mendel's work can be considered as the discovery of genes and how they are inherited. The term **gene** was first coined in 1909 by a Danish botanist, Johannsen, and was derived from the term 'pangen' introduced by De Vries. This term was itself a derivative of the word 'pangenesis,' coined by Darwin in 1868. In acknowledgement of Mendel's enormous contribution, the term **mendelian** is now part of scientific vocabulary, applied both to the different patterns of inheritance shown by single-gene characteristics and to disorders found to be the result of defects in a single gene.

In his breeding experiments, Mendel studied contrasting characters in the garden pea, using for each experiment varieties that differed in only one characteristic. For example, he noted that when strains bred for a feature such as tallness were crossed with plants bred to be short all of the offspring in the first filial or F1 generation were tall. If plants in this F1 generation were interbred, this led to both tall and short plants in a ratio of 3:1 (Figure 1.2). Characteristics that were manifest in the F1 hybrids were referred to as **dominant**, whereas those that reappeared in the F2 generation were described as being **recessive**. On reanalysis it has been suggested that Mendel's results were 'too good to be true' in that the segregation ratios he derived were suspiciously closer to the value of 3:1 than the laws of statistics would predict. One possible explanation is that he may have published only those results that best agreed with his preconceived single-gene hypothesis. Whatever the truth of the matter, events have shown that Mendel's interpretation of his results was entirely correct.

Mendel's proposal was that the plant characteristics being studied were each controlled by a pair of factors, one of which was inherited from each parent. The pure-bred plants, with two identical genes, used in the initial cross would now be referred to as **homozygous**. The hybrid F1 plants, each of which has one gene for tallness and one for shortness, would be referred to as **heterozygous**. The genes responsible for these contrasting characteristics are referred to as **allelomorphs**, or **alleles** for short.

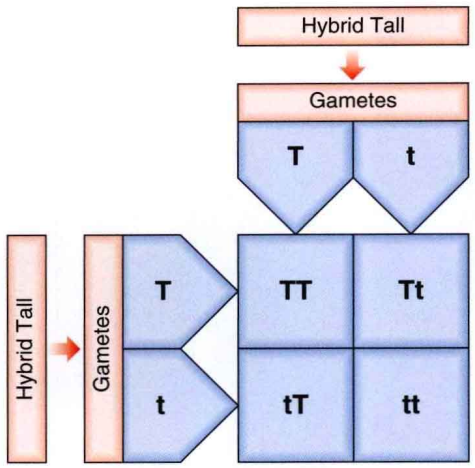


FIGURE 1.3 A Punnett square showing the different ways in which genes can segregate and combine in the second filial cross from Figure 1.2. Construction of a Punnett square provides a simple method for showing the possible gamete combinations in different matings.

An alternative method for determining **genotypes** in offspring involves the construction of what is known as a Punnett square (Figure 1.3). This is used further in Chapter 8 when considering how genes segregate in large populations.

On the basis of Mendel's plant experiments, three main principles were established. These are known as the laws of uniformity, segregation, and independent assortment.

The Law of Uniformity

The *law of uniformity* refers to the fact that when two homozygotes with different alleles are crossed, all of the offspring in the F1 generation are identical and heterozygous. In other words, the characteristics do not blend, as had been believed previously, and can reappear in later generations.

The Law of Segregation

The *law of segregation* refers to the observation that each person possesses two genes for a particular characteristic, only one of which can be transmitted at any one time. Rare exceptions to this rule can occur when two allelic genes fail to separate because of chromosome non-disjunction at the first meiotic division (p. 43).

The Law of Independent Assortment

The *law of independent assortment* refers to the fact that members of different gene pairs segregate to offspring independently of one another. In reality, this is not always true, as genes that are close together on the same chromosome tend to be inherited together, because they are 'linked' (p. 136). There are a number of other ways by which the laws of mendelian inheritance are breached but, overall, they remain foundational to our understanding of the science.

The Chromosomal Basis of Inheritance

As interest in mendelian inheritance grew, there was much speculation as to how it actually occurred. At that time it was also known that each cell contains a nucleus within which there are several threadlike structures known as **chromosomes**, so called because of their affinity for certain stains (*chroma* = color, *soma* = body). These chromosomes had been observed since the second half of the nineteenth century after development of cytologic staining techniques. Human mitotic figures were observed from the late 1880s, and it was in 1902 that Walter Sutton, an American medical student, and Theodour Boveri, a German biologist, independently proposed that chromosomes could be the bearers of heredity (Figure 1.4). Subsequently, Thomas Morgan transformed Sutton's chromosome theory into the theory of the gene, and Alfons Janssens observed the formation of chiasmata between homologous chromosomes at meiosis. During the late 1920s and 1930s, Cyril Darlington helped to clarify chromosome mechanics by the use of tulips collected on expeditions to Persia. It was during the 1920s that the term **genome** entered the scientific vocabulary, being the fusion of *genom* (German for 'gene') and *ome* from 'chromosome'.

When the connection between mendelian inheritance and chromosomes was first made, it was thought that the normal chromosome number in humans might be 48, although various papers had come up with a range of figures. The number 48 was settled on largely as a result of a paper in 1921 from Theophilus Painter, an American cytologist who had been a student of Boveri. In fact, Painter himself had some preparations clearly showing 46 chromosomes, even though he finally settled on 48. These discrepancies were probably from the poor quality of the material at that time; even into the early 1950s, cytologists were counting 48 chromosomes. It was not until 1956 that the correct number of 46 was established by Tjio and Levan, 3 years after the correct structure of DNA had been proposed. Within a few years, it was shown that some disorders in humans could be caused by loss or gain of a whole chromosome as well as by an abnormality in a single gene. Chromosome disorders are discussed at length in Chapter 18. Some chromosome aberrations, such as translocations, can run in families (p. 44), and are sometimes said to be segregating in a mendelian fashion.

DNA as the Basis of Inheritance

Whilst James Watson and Francis Crick are justifiably credited with discovering the structure of DNA in 1953, they were attracted to working on it only because of its key role as the genetic material, as established in the 1940s. Formerly many believed that hereditary characteristics were transmitted by proteins, until it was appreciated that their molecular structure was far too cumbersome. Nucleic acids were actually discovered in 1849. In 1928 Fred Griffith, working on two strains of *Streptococcus*, realized

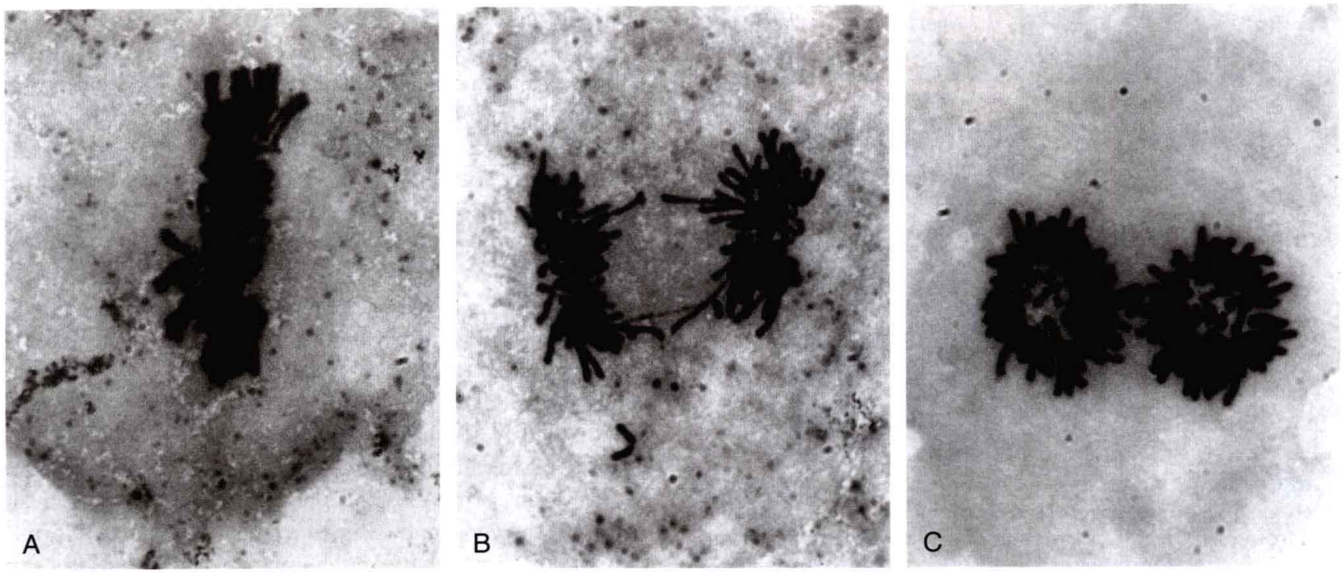


FIGURE 1.4 Chromosomes dividing into two daughter cells at different stages of cell division. **A,** Metaphase; **B,** anaphase; **C,** telophase. The behavior of chromosomes in cell division (mitosis) is described at length in Chapter 3. (Photographs courtesy Dr. K. Ocraft, City Hospital, Nottingham.)

that characteristics of one strain could be conferred on the other by something that he called the **transforming principle**. In 1944, at the Rockefeller Institute in New York, Oswald Avery, Maclyn McCarty, and Colin MacLeod identified DNA as the genetic material while working on the pneumococcus (*Streptococcus pneumoniae*). Even then, many in the scientific community were skeptical; DNA was only a simple molecule with lots of repetition of four nucleic acids—very boring! The genius of Watson and Crick, at Cambridge, was to hit on a structure for DNA that would explain the very essence of biological reproduction, and their elegant double helix has stood the test of time. Crucial to their discovery was the x-ray crystallography work of Maurice Wilkins and Rosalind Franklin at King's College, London.

This was merely the beginning, for it was necessary to discover the process whereby DNA, in discrete units called genes, issues instructions for the precise assembly of proteins, the building blocks of tissues. The sequence of bases in DNA, and the sequence of amino acids in protein, the **genetic code**, was unravelled in some elegant biochemical experiments in the 1960s and it became possible to predict the base change in DNA that led to the amino-acid change in the protein. Further experiments, involving Francis Crick, Paul Zamecnik, and Mahlon Hoagland, identified the molecule transfer RNA (tRNA) (p. 20), which directs genetic instructions via amino acids to intracellular ribosomes, where protein chains are produced. Confirmation of these discoveries came with DNA sequencing methods and the advent of recombinant DNA techniques. Interestingly, however, the first genetic trait to be characterized at the molecular level had already been identified in 1957 by laborious sequencing of the purified proteins. This was sickle-cell anemia, in which the mutation affects the amino-acid sequence of the blood protein hemoglobin.

The Fruit Fly

Before returning to historical developments in human genetics, it is worth a brief diversion to consider the merits of an unlikely creature, which has proved to be of great value in genetic research. The fruit fly, *Drosophila*, possesses several distinct advantages for the study of genetics:

1. It can be bred easily in a laboratory.
2. It reproduces rapidly and prolifically at a rate of 20 to 25 generations per annum.
3. It has a number of easily recognized characteristics, such as *curly wings* and a *yellow body*, which follow mendelian inheritance.
4. *Drosophila melanogaster*, the species studied most frequently, has only four pairs of chromosomes, each of which has a distinct appearance so that they can be identified easily.
5. The chromosomes in the salivary glands of *Drosophila* larvae are among the largest known in nature, being at least 100 times bigger than those in other body cells.

In view of these unique properties, fruit flies were used extensively in early breeding experiments. Today their study is still proving of great value in fields such as developmental biology, where knowledge of gene homology throughout the animal kingdom has enabled scientists to identify families of genes that are important in human embryogenesis (see Chapter 6). When considering major scientific achievements in the history of genetics, it is notable that sequencing of the 180 million base pairs of the

Drosophila melanogaster genome was completed toward the end of 1999.

The Origins of Medical Genetics

In addition to the previously mentioned Pierre de Maupertuis and Joseph Adams, whose curiosity was aroused by polydactyly and albinism, there were other pioneers. John Dalton, of atomic theory fame, observed that some conditions, notably color blindness and hemophilia, show what is now referred to as sex- or X-linked inheritance, and to this day color blindness is still occasionally referred to as **daltonism**. Inevitably, these founders of human and medical genetics could only speculate on the nature of hereditary mechanisms.

In 1900 Mendel's work resurfaced. His papers were quoted almost simultaneously by three European botanists—De Vries (Holland), Correns (Germany), and Von Tschermak (Austria)—and this marked the real beginning of medical genetics, providing an enormous impetus for the study of inherited disease. Credit for the first recognition of a single-gene trait is shared by William Bateson and Archibald Garrod, who together proposed that alkaptonuria was a rare recessive disorder. In this relatively benign condition, urine turns dark on standing or on exposure to alkali because of the patient's inability to metabolize homogentisic acid (p. 171). Young children show skin discoloration in the napkin (diaper) area and affected adults may develop arthritis in large joints. Realizing that this was an inherited disorder involving a chemical process, Garrod coined the term **inborn error of metabolism** in 1908. However, his work was largely ignored until the mid-twentieth century, when the advent of electrophoresis and chromatography revolutionized biochemistry. Several hundred such disorders have now been identified, giving rise to the field of study known as **biochemical genetics** (see Chapter 11). The history of alkaptonuria neatly straddles almost the entire twentieth century, starting with Garrod's original observations of recessive inheritance in 1902 and culminating in cloning of the relevant gene on chromosome 3 in 1996.

During the course of the twentieth century, it gradually became clear that hereditary factors were implicated in many conditions and that different genetic mechanisms were involved. Traditionally, hereditary conditions have been considered under the headings of **single gene**, **chromosomal,** and **multifactorial**. Increasingly, it is becoming clear that the interplay of different genes (**polygenic inheritance**) is important in disease, and that a further category—**acquired somatic genetic disease**—should also be included.

Single-Gene Disorders

In addition to alkaptonuria, Garrod suggested that albinism and cystinuria could also show recessive inheritance. Soon other examples followed, leading to an explosion in knowledge and disease delineation. By 1966 almost 1500 single-gene disorders or traits had been identified, prompting the publication by an American physician, Victor McKusick (Figure 1.5), of a catalog of all known single-gene conditions. By 1998, when the 12th edition of this catalog was published, it contained more than 8500 entries (Figure 1.6). The growth of 'McKusick's Catalog' has been exponential and is now available electronically as *Online Mendelian Inheritance in Man* (OMIM) (see Appendix). By 2010 OMIM contained a total of almost 20,000 entries.

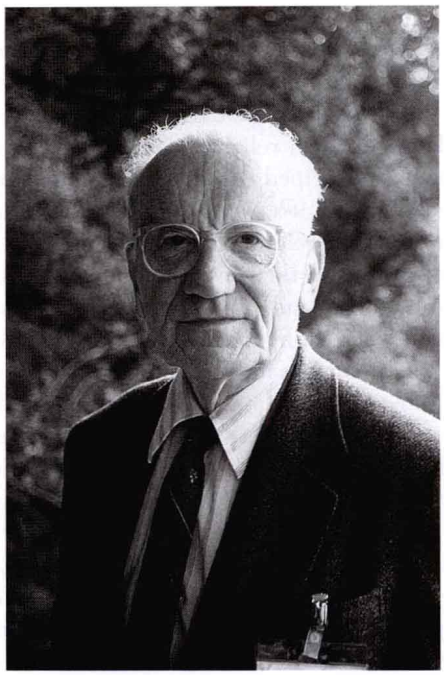


FIGURE 1.5 Victor McKusick in 1994, whose studies and catalogs have been so important to medical genetics.

Chromosome Abnormalities

Improved techniques for studying chromosomes led to the demonstration in 1959 that the presence of an additional number 21 chromosome (*trisomy 21*) results in

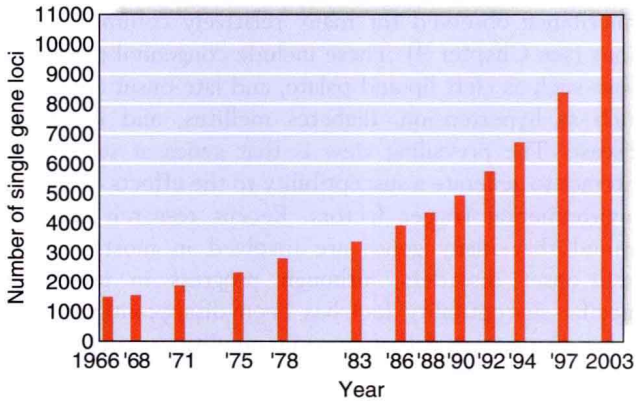


FIGURE 1.6 Histogram showing the rapid increase in recognition of conditions and characteristics (traits) showing single-gene inheritance. (Adapted from McKusick, 1998, and OMIM—see Appendix.)