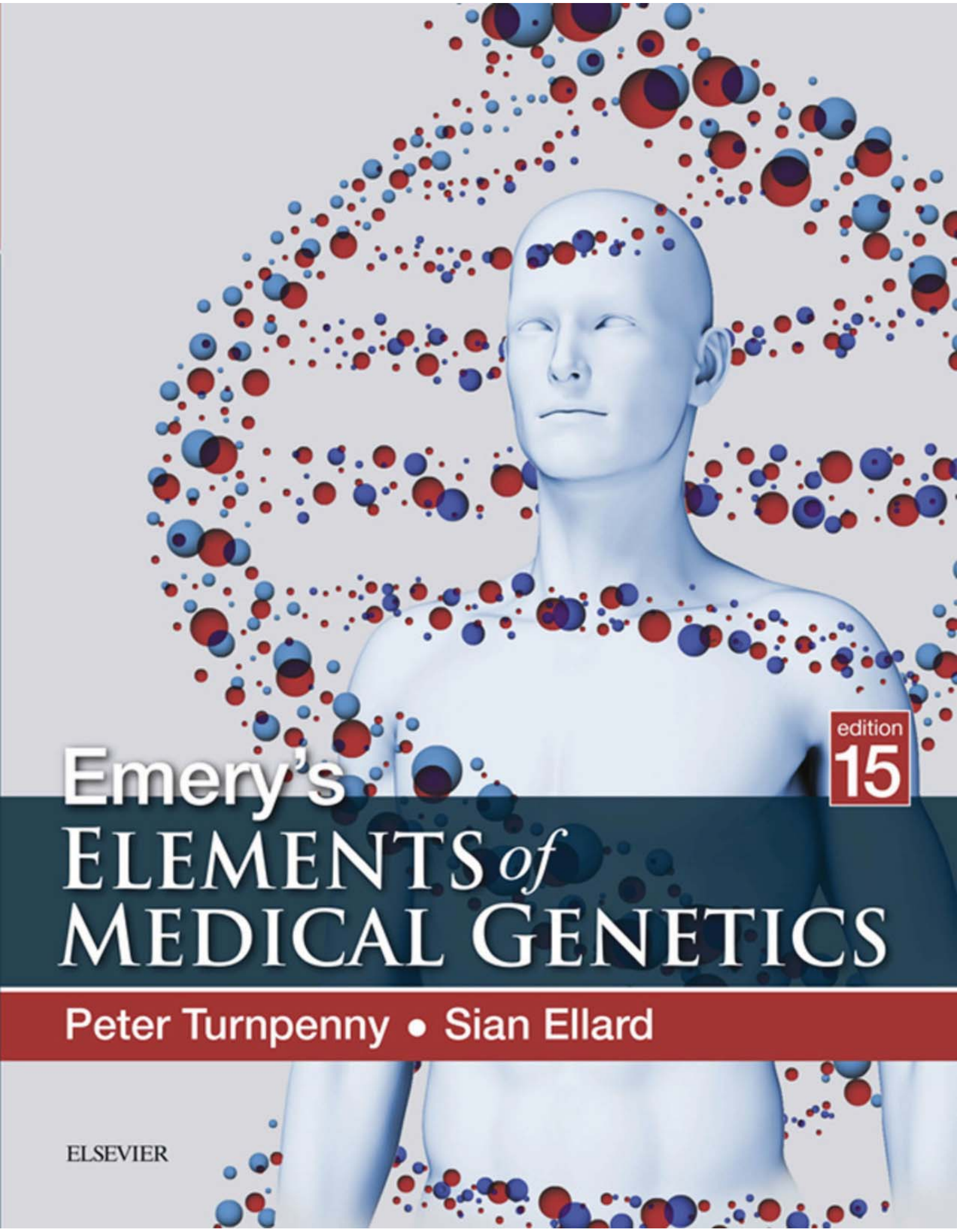
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ELEMENTS of
MEDICAL GENETICS
Peter Turnpenny • Sian Ellard
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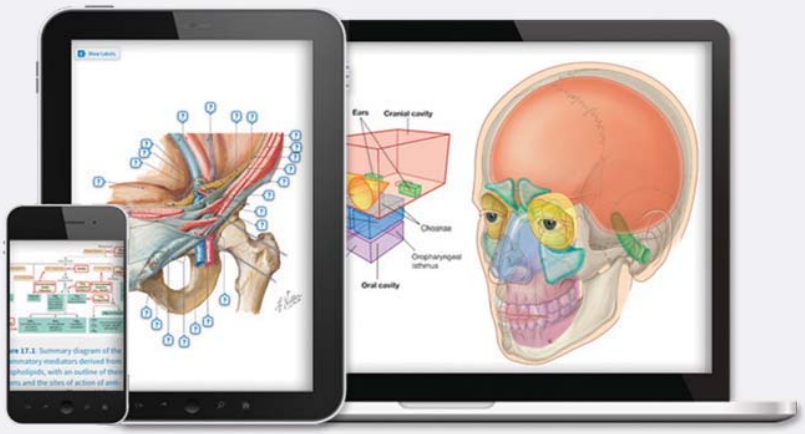

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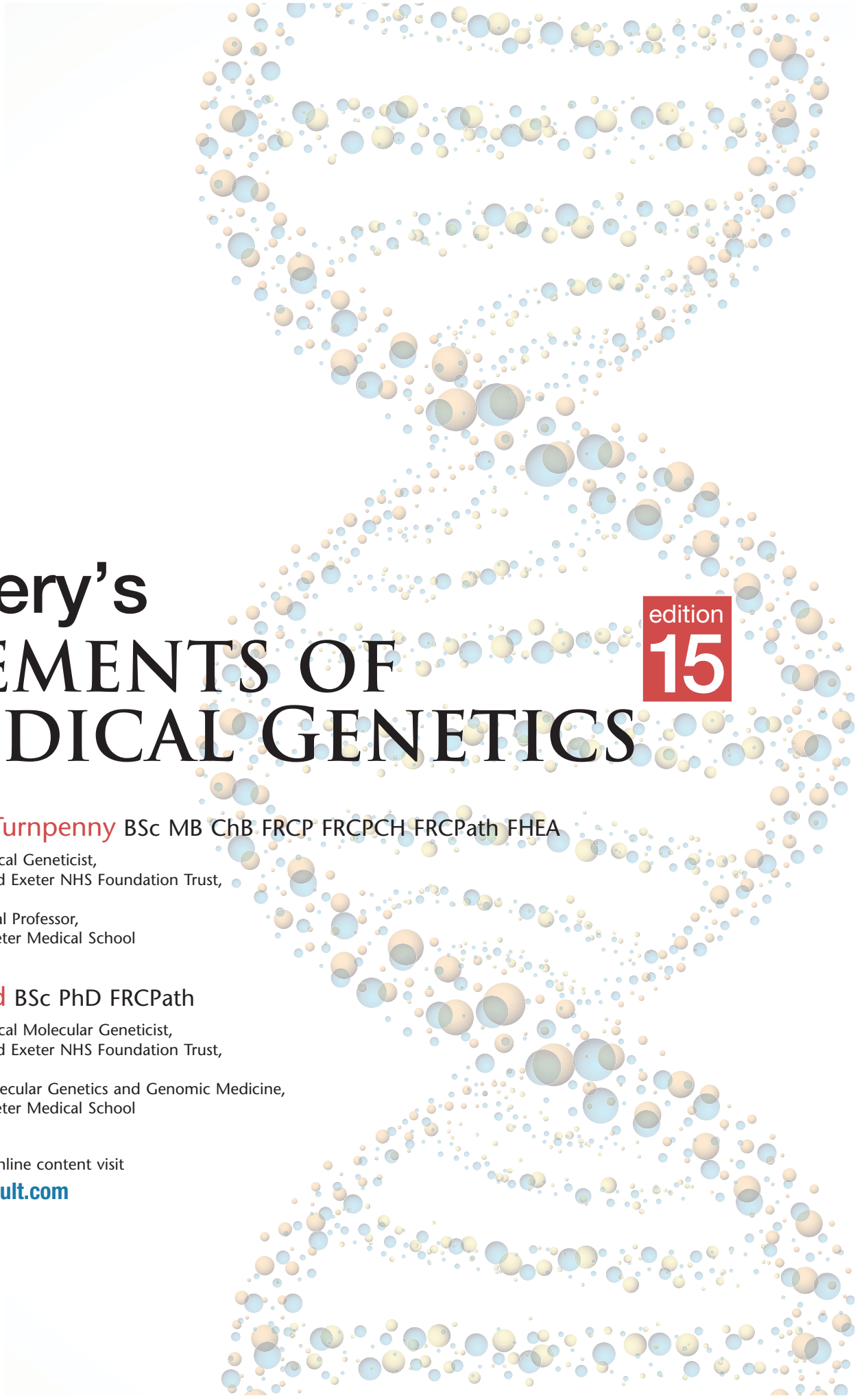

Emery's Elements of Medical Genetics

edition 15

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Preface

"Reading maketh a full man; conference a ready man; and writing an exact man."

Francis Bacon (1561–1626)

It is more than five years since we last updated *Emery's Elements* and the task of producing a new edition has seemed bigger and more daunting than ever. For the last edition we mentioned the incoming technology of *next generation sequencing* and the impact it was beginning to have on solving long-standing diagnostic conundrums, especially in a research environment. Already, just a few years later, we owe so much to the scientists and bioinformaticians who make the technology work for patients and families affected by genetic disease. Gene discovery for rare disease has risen exponentially as a result, and we now routinely request 'panel' tests for different phenotypes—whether for conditions of the RAS-MAPK pathway or inherited eye disease—anything from 20 to 200 genes. So, next generation sequencing is now very much a clinical and service tool as well, yielding a higher rate of diagnoses, and often at a price that is not much more than the cost of testing one gene in the past.

Whole exome or whole genome sequencing has given birth to a huge field of ethical debate within and beyond the professions concerning 'what to do' with *secondary* or *incidental findings* that have health implications. Europe and North America are not always aligned in their views and practice in these difficult areas, so the issues will continue to be discussed and contested at length.

To these developments can be added the rapidly developing applications of non-invasive prenatal testing and screening, as well as nuclear cell transfer with mitochondrial donation to treat some families devastated by mitochondrial disease. Advances in the use of genetic technologies for assisted reproduction always provoke debate and controversy with entrenched, polarized views frequently pitted against each other in the media. As we write this, the most recent advance to feature in this way is the use of *gene editing*, or *CRISPR*, technology in the treatment of genetic disease. Together with other novel approaches, there is more expectation than ever before that families affected by genetic disease will in due course benefit from treatment strategies judiciously applied.

We have made some major changes to this edition in our efforts to bring it up to date. We have re-ordered the chapters to a format that we believe is more logical and appropriate, referred repeatedly to the use of new technologies, and added much new clinical material to broaden its appeal as a basic text. As before, we hope this will prove useful to undergraduates and postgraduates alike, and help them swim rather than sink when tackling the mysteries of medical genetics.

Peter Turnpenny and Sian Ellard
Exeter, United Kingdom

Acknowledgments

As always, we feel privileged to be working in an area of healthcare science and service that continues to be exciting and captivating as the technologies and knowledge move forward so inexorably. We work within teams and networks of very talented colleagues who are similarly inspired and, even though unaware, they contribute to this volume through their knowledge, professional companionship and encouragement. For this edition we particularly thank Dr Anna Murray (University of Exeter Medical School) who helped with the merger of chapters into the new 'Common disease, Polygenic and Multifactorial Genetics'. This edition includes a large number of new clinical images, for which we must once again thank our patients who have been so willing to share themselves in this way. We are grateful to Elsevier, especially Alexandra Mortimer, for her guidance and patience, particularly as several deadlines came and went!

Dedication

To Alan Emery, a friend, mentor, and constant source of inspiration and encouragement.

Alan E. H. Emery (c. 1983), Emeritus Professor of Human Genetics & Honorary Fellow, University of Edinburgh, who first established the *Elements of Medical Genetics* in 1968.

"The book was first conceived and published by the University of California Press in 1968 as *Heredity, Disease, and Man: Genetics in Medicine*. However, when appointed Professor of Human Genetics at Edinburgh in 1968 I decided I should prefer the book to be published by Churchill Livingstone under the title *Elements of Medical Genetics*, and made more accessible to UK students with a cheaper paperback edition. This was all achieved and has retained this format ever since. The current 15th edition illustrates very clearly how the subject has advanced so much over the intervening years."

Alan Emery

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 have benefited hugely, but success will be measured by ongoing progress in translating discoveries into both treatment and prevention of disease, and we are privileged to be witnessing such developments at the beginning of what promises to be a dramatic and exciting era. But it is always inspiring to look 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, it is also essential to check the rear and side mirrors regularly.

Gregor Mendel and the Laws of Inheritance

Early Beginnings

Developments in genetics during the 20th 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. As we write this in 2016, the published sequence of the entire human genome (2004) already feels like a piece of history, chromosomes can be rapidly analyzed to an extraordinary level of sophistication by microarray techniques, and next generation sequencing is transforming gene discovery and genetic testing in a clinical setting. The number of phenotypes with a known molecular basis is almost 5500 and the number of genes with a phenotype causing mutation is almost 3400.

Genetics is relevant and important to 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, longevity, and a host of physiological variations and tolerances. Clearly, a fundamental grounding in genetics should be part of any undergraduate medical curriculum.

We start with an overview of some of the most notable milestones in the history of genetics and medical genetics, followed by reviewing the overall impact of genetic factors in causing disease. Finally, we mention some new developments of major importance.

It is not known precisely when *Homo sapiens* first appeared on this planet, but current estimates, based on the finding of fossilized human bones in Ethiopia, suggest man was roaming East Africa approximately 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, not without a little prejudice, that important human characteristics were determined by semen, using menstrual blood as a culture 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 17th 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 scientific revolution of the 18th and 19th centuries saw a revival of interest in heredity by scientists and physicians, among whom two 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. Also worthy of mention is the English physician Edward Meryon (1809–1880), who in 1851 was the first to provide a systematic clinicopathological study of three boys with the muscular disorder

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

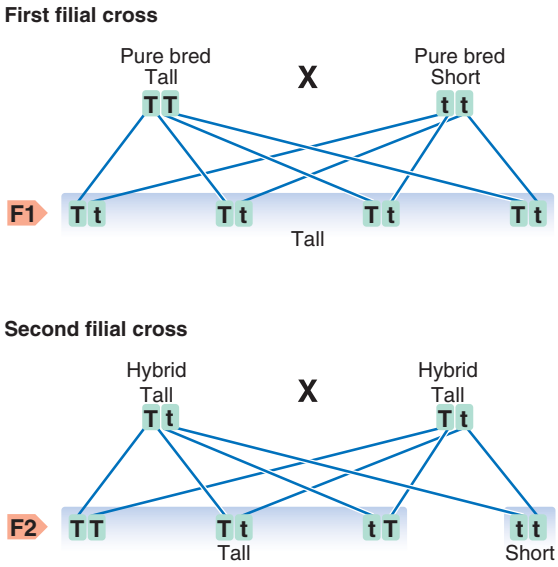

FIGURE 1.2 An illustration of one of Mendel's breeding experiments and how he correctly interpreted the results.

later eponymously attributed to the Frenchman, Guillaume Duchenne (1806–1875), who described a larger series in 1868.

The modern scientific era really begins with 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 recognition of Mendel's foundational work, the term **mendelian** is now part of scientific vocabulary, applied both to the different patterns of inheritance 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 case, 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.

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 7 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.

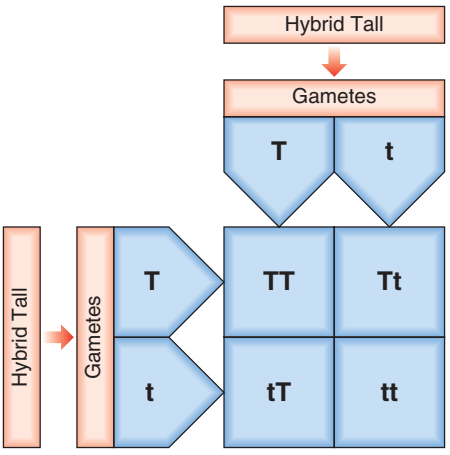

FIGURE 1.3 A Punnett square showing the different ways in which genes can segregate and combine in the second filial cross from Figure 1.2. Construction of a Punnett square provides a simple method for showing the possible gamete combinations in different matings.

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 nondisjunction at the first meiotic division (p. 30).

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. 89). 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 19th 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. Key to the number 48 was a paper in 1921 from Theophilus Painter, an American cytologist who had been a student of Boveri. In fact, Painter 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 17. Some chromosome aberrations, such as translocations, can run in families (p. 35), 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

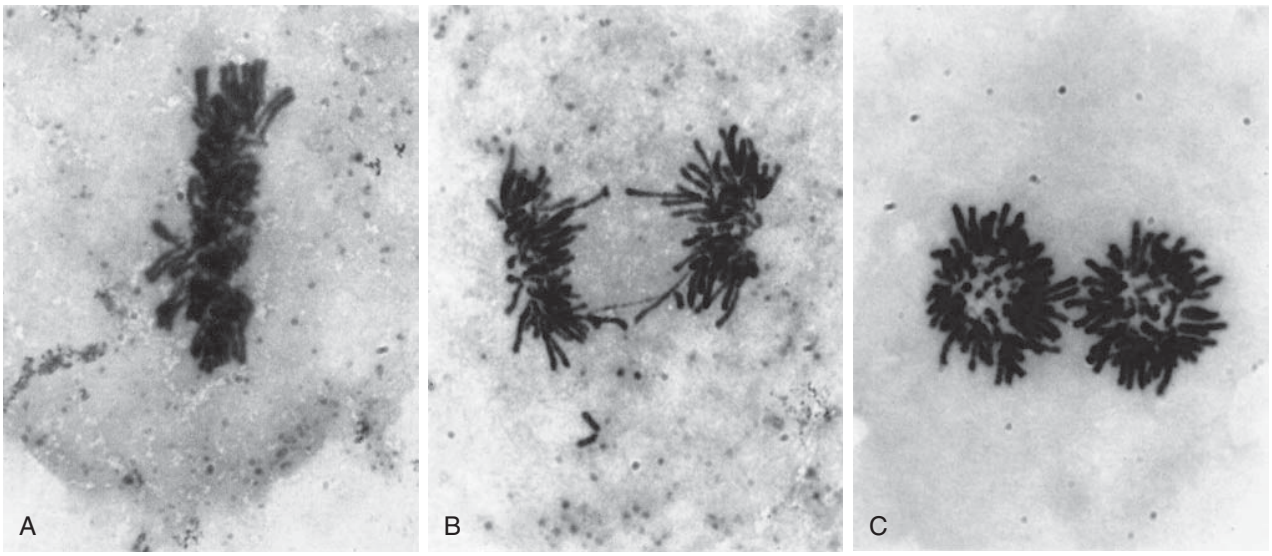

FIGURE 1.4 Chromosomes dividing into two daughter cells at different stages of cell division. **A,** Metaphase; **B,** anaphase; **C,** telophase. The behavior of chromosomes in cell division (mitosis) is described at length in Chapter 3. *(Photographs courtesy Dr. K. Ocraft, City Hospital, Nottingham.)*

Streptococcus, realized 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 *Streptococcus pneumoniae*. Even then, many in the scientific community were sceptical; 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, the elegant double helix, that would explain the very essence of biological reproduction. Crucial to their discovery were the x-ray crystallography images captured by the often-overlooked graduate technician Raymond Gosling, working under the supervision of Maurice Wilkins and Rosalind Franklin in John Randall's laboratory 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. 15), 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 that 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, contributing enormously to 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 9). The sequencing of the 180 million base pairs of the *Drosophila melanogaster* genome was completed in late 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; color blindness is still occasionally referred to as **daltonism.**

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. 258). 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, though his work was largely ignored until the mid-20th century when electrophoresis and chromatography revolutionized biochemistry. Several hundred such disorders have now been identified, giving rise to the field of **biochemical genetics** (see Chapter 18).

During the course of the 20th 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 be recessive. 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 the catalog was published, it contained more than 8500 entries. The growth of 'McKusick's Catalog' was exponential and became the electronic *Online Mendelian Inheritance in Man* (OMIM) (see Appendix) in 1987. By August 2016, OMIM contained more than 23,600 entries.

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 Down syndrome. Other similar discoveries followed rapidly—Klinefelter and Turner syndromes—also in 1959. The identification of chromosome abnormalities was further aided by the development of banding techniques in 1970 (p. 26). These enabled reliable identification of individual chromosomes and helped confirm that loss or gain of even a very small segment of a

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

chromosome can have devastating effects on human development (see Chapter 17).

Later it was shown that several rare conditions featuring learning difficulties and abnormal physical features are due to loss of such a tiny amount of chromosome material that no abnormality can be detected using even the most high-powered light microscope. These conditions are referred to as microdeletion syndromes (p. 245) and can be diagnosed using a technique known as **FISH (fluorescent *in situ* hybridization)**, which combines conventional chromosome analysis (**cytogenetics**) with newer DNA diagnostic technology (**molecular genetics**) (see Chapter 5). Today, the technique of microarray **CGH (comparative genomic hybridization)** has revolutionized clinical investigation through the detection of subtle genomic imbalances (p. 54) and, where it is available, become the first-line test of choice.

Multifactorial Disorders

Francis Galton, a cousin of Charles Darwin, had a long-standing interest in human characteristics such as stature, physique, and intelligence. Much of his research was based on the study of identical twins, in whom it was realized that differences in these parameters must be largely the result of environmental influences. Galton introduced to genetics the concept of the **regression coefficient** as a means of estimating the degree of resemblance between various relatives. This concept was later extended to incorporate Mendel's discovery of genes, to try to explain how parameters such as height and skin color could be determined by the interaction of many genes, each exerting a small additive effect. This is in contrast to single-gene characteristics in which the action of one gene is exerted independently, in a nonadditive fashion.

This model of **quantitative inheritance** is now widely accepted and has been adapted to explain the pattern of inheritance observed for many relatively common conditions (see Chapter 10). These include congenital malformations such as cleft lip and palate, and late-onset conditions such as hypertension, diabetes mellitus, and Alzheimer disease. The prevailing view is that genes at several loci interact to generate a susceptibility to the effects of adverse environmental trigger factors. Recent research has confirmed that many genes are involved in most of these adult-onset disorders, although progress in identifying specific susceptibility loci has been disappointingly slow. It has also emerged that in some conditions, such as type I diabetes mellitus, different genes can exert major or minor effects in determining susceptibility (p. 130). Overall, **multifactorial** or **polygenic** conditions are now known to make a major contribution to chronic illness in adult life (see Chapter 10).

Acquired Somatic Genetic Disease

Not all genetic errors are present from conception. Many billions of cell divisions (**mitoses**) occur in the course of an average human lifetime. During each mitosis, there is an opportunity for both single-gene mutations to occur, because of DNA copy errors, and for numerical chromosome abnormalities to arise as a result of errors in chromosome separation. Accumulating somatic mutations and chromosome abnormalities are now known to play a major role in causing cancer (see Chapter 14), and they probably also explain the rising incidence with age of many other serious illnesses, as well as the aging process itself. It is therefore necessary to appreciate that not all disease with a genetic basis is hereditary.

Before considering the impact of hereditary disease, it is helpful to introduce a few definitions.

Incidence

Incidence refers to the rate at which new cases occur. Thus, if the birth incidence of a particular condition equals 1 in 1000, then on average 1 in every 1000 newborn infants is affected.

Prevalence

This refers to the proportion of a population affected at any one time. The prevalence of a genetic disease is usually less than its birth incidence, either because life expectancy is reduced or because the condition shows a delayed age of onset.

Frequency

Frequency is a general term that lacks scientific specificity, although the word is often taken as being synonymous with incidence when calculating gene 'frequencies' (see Chapter 7).

Congenital

Congenital means that a condition is present at birth. Thus, cleft palate represents an example of a congenital **malformation**. Not all genetic disorders are congenital in terms of age of onset (e.g., Huntington disease), nor are all congenital abnormalities genetic in origin (e.g., fetal disruptions, as discussed in Chapter 16).

DNA Sequencing

The ability to search for mutations in human DNA to identify the causes of genetic disease clearly depended on being able to sequence DNA, which initially was very laborious. The first really practical method was developed by Walter Gilbert, with sequencing based on a cleavage at specific bases after chemical modification of DNA. But it was Frederick Sanger's (Figure 1.6) ingenious technique (1975), based on dideoxynucleotide chain termination, that proved efficient, reliable and popular, not least because of low radioactivity. These techniques formed the basis for embarking on the Human Genome Project, though

FIGURE 1.6 Frederick Sanger, who invented the most widely used method of DNA sequencing, and won two Nobel Prizes.

the first genome to be sequenced was that of a bacteriophage in 1977. Both men were awarded the Nobel Prize in 1980 for this achievement, which was Sanger's second—he was awarded the Chemistry Prize in 1958 for determining the amino acid sequence of insulin (he remains the only British scientist to have won two Nobel Prizes). '**Sanger sequencing**' remains vital to human molecular genetics, and the term is as prominent in the language of genetics as 'mendelian inheritance' and 'McKusick's Catalog'.

The Impact of Genetic Disease

During the 20th century, improvements in all areas of medicine, most notably public health and therapeutics, resulted in changing patterns of disease, with increasing recognition of the role of genetic factors at all ages. For some parameters, such as perinatal mortality, the actual numbers of cases with exclusively genetic causes have probably remained constant but their **relative** contribution to overall figures has increased as other causes, such as infection, have declined. For other conditions, such as the chronic diseases of adult life, the overall contribution of genetics has almost certainly increased as greater life expectancy has provided more opportunity for adverse genetic and environmental interaction to manifest itself, for example in Alzheimer disease, macular degeneration, cardiomyopathy, and diabetes mellitus. Today there is much debate about the relative contributions of genetic and environmental factors in the increasing prevalence of obesity in the developed world.

Consider the impact of genetic factors in disease at different ages from the following observations.

Spontaneous Miscarriages

A chromosome abnormality is present in 40% to 50% of all recognized first-trimester pregnancy loss. Approximately 1 in 4 of all pregnancies results in spontaneous miscarriage, so at least 10% of all recognized conceptions are chromosomally abnormal (p. 236). This value would be much higher if unrecognized pregnancies could also be included, and it is likely that a significant proportion of miscarriages with normal chromosomes do in fact have catastrophic submicroscopic genetic errors.

Newborn Infants

Up to 3% of neonates have at least one major congenital abnormality, of which at least 50% are caused exclusively or partially by genetic factors (see Chapter 16), with the incidences of chromosome abnormalities and single-gene disorders in neonates being roughly 1 in 200 and 1 in 100, respectively.

Childhood

By school age roughly 12-14% of children show problems of developmental origin. Genetic disorders account for at least 50% of all childhood blindness, at least 50% of all childhood deafness, and at least 50% of all cases of severe learning difficulty. In developed countries, genetic disorders and congenital malformations together also account for 30% of all childhood hospital admissions and 40% to 50% of all childhood deaths.

Adult Life

Approximately 1% of all malignancies are primarily caused by single-gene inheritance, and between 5% and 10% of common cancers such as those of the breast, colon, and ovary have a strong hereditary component. By the age of 25 years, 5% of the population will have a disorder in which genetic factors play an important role. Taking into account the genetic contribution to cancer and cardiovascular diseases, such as coronary artery occlusion and hypertension, it has been estimated that more than 50% of the older adult population in developed countries will have a genetically determined medical problem.

Major New Developments

The study of genetics and its role in causing human disease is now widely acknowledged as being among the most exciting and influential areas of medical research. Since 1962 when Francis Crick, James Watson, and Maurice Wilkins gained acclaim for their elucidation of the structure of DNA, the Nobel Prize for Medicine and/or Physiology has been won on 24 occasions, and the Chemistry Prize on six occasions, by scientists working in human and molecular genetics or related fields (Table 1.1). These pioneering studies have spawned a thriving molecular technology industry with applications as diverse as the development of genetically modified disease-resistant crops, the use of genetically engineered animals to produce therapeutic drugs, and the possible introduction of DNA-based vaccines for conditions such as malaria, not to mention the growing availability of affordable direct-to-consumer testing for disease susceptibility. Pharmaceutical companies are investing heavily in the DNA-based **pharmacogenomics**—drug therapy tailored to personal genetic makeup.

The Human Genome Project (HGP)

In 1988 a group of visionary scientists in the United States persuaded Congress to fund a coordinated international program to sequence the entire human genome. The program would run from 1990 to 2005 and US$3 billion were initially allocated to the project. Some 5% of the budget was allocated to study the ethical and social implications of the new

Table 1.1 Genetic Discoveries That Have Led to the Award of the Nobel Prize for Medicine or Physiology and/or Chemistry, 1962–2012

Year	Prize Winners	Discovery
1962	Francis Crick James Watson Maurice Wilkins	The molecular structure of DNA
1965	François Jacob Jacques Monod André Lwoff	Genetic regulation
1966	Peyton Rous	Oncogenic viruses
1968	Robert Holley Gobind Khorana Marshall Nireberg	Deciphering of the genetic code
1972	Christian B. Anfisen Stanford Moore William H. Stein	Ribonuclease
1975	David Baltimore Renato Dulbecco Howard Temin	Interaction between tumor viruses and nuclear DNA
1978	Werner Arber Daniel Nathans Hamilton Smith	Restriction endonucleases
1980	Baruj Benacerraf Jean Dausset George Snell	Genetic control of immunologic responses (Medicine)
	Paul Berg Walter Gilbert Frederick Sanger	Biochemistry of nucleic acids (Chemistry)
1983	Barbara McClintock	Mobile genes (transposons)
1985	Michael Brown Joseph Goldstein	Cell receptors in familial hypercholesterolemia
1987	Susumu Tonegawa	Genetic aspects of antibodies
1989	Michael Bishop Harold Varmus	Study of oncogenes (Medicine)
	Sidney Altman Thomas R. Cech	Catalytic properties of RNA (Chemistry)
1993	Richard Roberts Phillip Sharp	'Split genes' (Medicine)
	Kary B. Mullis Michael Smith	DNA-based chemistry, including the invention of PCR (Chemistry)
1995	Edward Lewis Christiane Nüsslein-Volhard Eric Wieschaus	Homeotic and other developmental genes
1997	Stanley Prusiner	Prions
1999	Günter Blobel	Protein transport signaling
2000	Arvid Carlsson Paul Greengard Eric Kandel	Signal transduction in the nervous system
2001	Leland Hartwell Timothy Hunt Paul Nurse	Regulators of the cell cycle
2002	Sydney Brenner Robert Horritz John Sulston	Genetic regulation in development and programmed cell death (apoptosis)
2006	Andrew Fire Craig Mello	RNA interference (Medicine)
	Roger D. Kornberg	Eukaryotic transcription (Chemistry)
2007	Mario Capecchi Martin Evans Oliver Smithies	Gene modification by the use of embryonic stem cells
2009	Elizabeth Blackburn Carol Greider Jack Szostak	The role of telomerase in protecting chromosome telomeres (Medicine)
	Venkatraman Ramakrishnan Thomas A. Steitz Ada E. Yonath	Structure and function of the ribosome (Chemistry)
2010	Robert G. Edwards	In vitro fertilization
2012	John B. Gurdon Shinya Yamanaka	Mature cells reprogrammed to become pluripotent cells (Medicine)
	Robert J. Lefkowitz Brian K. Kobilka	G-protein coupled receptors (Chemistry)

knowledge in recognition of the enormous potential to influence public health policies, screening programs, and personal choice. The project was likened to the Apollo moon mission in terms of its complexity, although in practical terms the long-term benefits are likely to be much more tangible. The draft DNA sequence of 3 billion base pairs was completed successfully in 2000 and the complete sequence published ahead of schedule in October 2004. Before the closing stages of the project, it was thought that there might be approximately 100,000 coding genes that provide the blueprint for human life. It has come as a surprise to many that the number is much lower, and has been continually revised downwards with current estimates at around 20,000. However, we have learned that many genes have the capacity to perform multiple functions, thus challenging traditional concepts of disease classification. The HGP has now been succeeded by the **Human Variome Project**, aimed at compiling and sharing the enormous variation in human DNA sequence worldwide, all of which is potentially possible since **whole exome sequencing** (WES) and **whole genome sequencing** (WGS) are taking place on an industrial scale in numerous population studies and, for the direct benefit of patients, projects such as Deciphering Developmental Disorders (DDD) based at the Sanger Centre, Cambridge, and 100 000 Genomes in the UK, and their equivalent elsewhere. Indeed, WES in particular has facilitated a huge surge in disease gene discovery since the last published edition of this book. This has led to the exciting growth area of **Bioinformatics,** the science where biology, computer science, and information technology merge into a single discipline that encompasses gene maps, DNA sequences, comparative and functional genomics, and a lot more. Familiarity with interlinking databases is essential for the molecular geneticist, and increasingly so for keen clinicians with an interest in genetics, who will find OMIM a good place to start.

The Prospects for Treatment

Most genetic disease is resistant to conventional treatment so that the prospect of successfully modifying the genetic code in a patient's cells is extremely attractive. Despite major investment and extensive research, success in humans has so far been

limited to a few very rare immunologic disorders. For more common conditions, such as cystic fibrosis, major problems have been encountered, such as targeting the correct cell populations, overcoming the body's natural defense barriers, and identifying suitably nonimmunogenic vectors. However, the availability of mouse models for genetic disorders, such as cystic fibrosis (p. 286), Huntington disease (p. 273), and Duchenne muscular dystrophy (p. 281), has greatly enhanced research opportunities, particularly in unraveling the cell biology of these conditions. In recent years there has been increasing optimism for novel drug therapies and stem cell treatment (p. 210), besides the prospects for gene therapy itself (p. 207).

The Societal Impact of Advances in Genetics

Each new advance in genetic technology has generated fresh ethical concerns about how the science will be applied and utilized in medicine, at the center of which is the recognition that a person's genetic make-up is fundamental to both their identity and possible disease susceptibility. These issues are explored in detail in Chapter 22. The most contentious field is prenatal genetics and reproductive choice, though national legal frameworks and cultural practices vary widely worldwide. The controversy surrounding the early ability to perform prenatal karyotyping for Down syndrome in the mid-1960s is mirrored today in the technology that will make it possible to perform detailed genetic screening of the unborn baby on cell-free fetal DNA in the maternal circulation, or on embryos created through *in vitro* fertilization. Great debate has taken place, and will continue, concerning the disclosure of unexpected but significant 'incidental findings' from WES or WGS carried out for specific clinical purposes, and the possibility of all newborns having their genome sequenced and screened is both technically feasible and has been seriously mooted at governmental level. Many of the questions raised do not have easy or straightforward answers, which means that there will be a great need for appropriately trained clinicians and counselors to meet the public demands for the foreseeable future.

FURTHER READING

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Databases

Online Mendelian Inheritance in Man:
http://www.ncbi.nlm.nih.gov/omim
For Literature:
http://www.ncbi.nlm.nih.gov/PubMed/
http://scholar.google.com/
Genome:
http://www.ncbi.nlm.nih.gov/omim/GenBank
http://www.hgmd.cf.ac.uk (human, Cardiff)
http://www.ensembl.org (human, comparative, European, Cambridge)
http://genome.ucsc.edu (American browser)
http://www.humanvariomeproject.org/

ELEMENTS

1. A characteristic manifest in a hybrid (heterozygote) is dominant. A recessive characteristic is expressed only in an individual with two copies of the mutated gene (i.e., a homozygote).
2. Mendel proposed that each individual has two genes for each characteristic: one is inherited from each parent and one is transmitted to each child. Genes at different loci act and segregate independently.
3. Chromosome separation at cell division facilitates gene segregation.
4. Genetic disorders are present in at least 2% of all neonates, accounting for at least 50% of childhood blindness, deafness, learning difficulties and deaths.
5. From the rediscovery of Mendel's genetic research on peas, to the full sequencing of the human genome, almost exactly 100 years elapsed.
6. Molecular genetics and cell biology are at the forefront of medical research, combined with the discipline of bioinformatics, and hold the promise of novel forms of treatment for genetic diseases.

SECTION A
The Scientific Basis of Human Genetics

Chapter 2

The Cellular and Molecular Basis of Inheritance

There is nothing, Sir, too little for so little a creature as man.
It is by studying little things that we attain the great art of having as little misery and as much happiness as possible.
SAMUEL JOHNSON

The hereditary material is present in the nucleus of the cell, whereas protein synthesis takes place in the cytoplasm. What is the chain of events that leads from the gene to the final product?

This chapter covers basic cellular biology outlining the structure of DNA, the process of DNA replication, the types of DNA sequences, gene structure, the genetic code, the processes of transcription and translation, the various types of mutations, mutagenic agents, and DNA repair.

The Cell

Within each cell of the body, visible with the light microscope, is the **cytoplasm** and a darkly staining body, the **nucleus**, the latter containing the hereditary material in the form of **chromosomes** (Figure 2.1). The phospholipid bilayer of the plasma membrane protects the interior of the cell but remains selectively permeable and has integral proteins involved in recognition and signaling between cells. The nucleus has a darkly staining area, the **nucleolus**. The nucleus is surrounded by a membrane, the **nuclear envelope**, which separates it from the cytoplasm but still allows communication through **nuclear pores**.

The cytoplasm contains the **cytosol**, which is semifluid in consistency, containing both soluble elements and cytoskeletal structural elements. In addition, in the cytoplasm there is a complex arrangement of very fine, highly convoluted, interconnecting channels, the endoplasmic reticulum. The **endoplasmic reticulum**, in association with the **ribosomes**, is involved in the biosynthesis of proteins and lipids. Also situated within the cytoplasm are other even more minute cellular organelles that can be visualized only with an electron microscope. These include the Golgi apparatus, which is responsible for the secretion of cellular products, the **mitochondria**, which are involved in energy production through the oxidative phosphorylation metabolic **pathways**, and the **peroxisomes** (p. 268) and **lysosomes,** both of which are involved in the degradation and disposal of cellular waste material and toxic molecules.

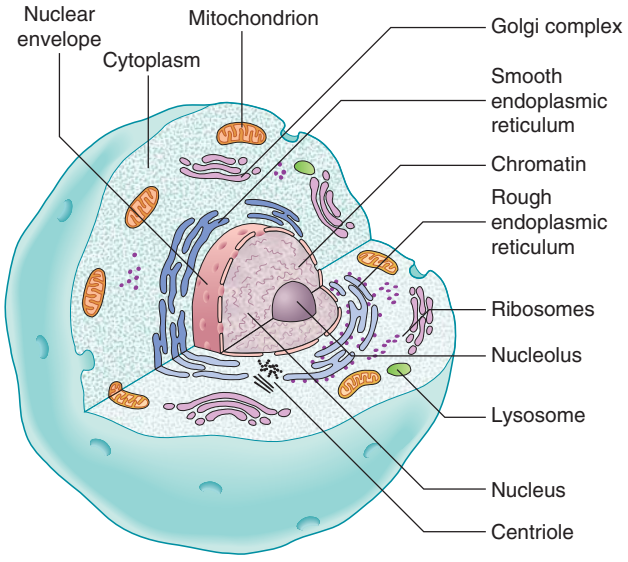

FIGURE 2.1 Diagrammatic representation of an animal cell.

DNA: The Hereditary Material

Composition

Nucleic acid is composed of a long polymer of individual molecules called **nucleotides**. Each nucleotide is composed of a nitrogenous base, a sugar molecule, and a phosphate molecule. The nitrogenous bases fall into two types, **purines** and **pyrimidines**. The purines include adenine and guanine; the pyrimidines include cytosine, thymine, and uracil.

There are two different types of nucleic acid, **ribonucleic acid (RNA)**, which contains the five-carbon sugar ribose, and **deoxyribonucleic acid (DNA)**, in which the hydroxyl group at the 2 position of the ribose sugar is replaced by a hydrogen (i.e., an oxygen molecule is lost, hence 'deoxy'). DNA and RNA both contain the purine bases adenine and guanine and the pyrimidine cytosine, but thymine occurs only in DNA and uracil is found only in RNA.

RNA is present in the cytoplasm and in particularly high concentrations in the nucleolus of the nucleus. DNA, on the other hand, is found mainly in the chromosomes.

Structure

For genes to be composed of DNA, it is necessary that the latter should have a structure sufficiently versatile to account for the great variety of different genes and yet, at the same time, be