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GENETICS in MEDICINE

第6版（修订版）

NUSSBAUM · McINNES · WILLARD

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Robert L. Nussbaum, MD
Chief, Genetic Diseases Research Branch
Acting Chief, Inherited Disease Research Branch
National Human Genome Research Institute
Executive Faculty
Johns Hopkins/NHGRI Joint Genetic Counseling Graduate Program
National Institutes of Health
Bethesda, Maryland
Roderick R. McInnes, MD, PhD, FRS(C)
Scientific Director, Institute of Genetics
Canadian Institutes of Health Research
Anne and Max Tanenbaum Chair in Molecular Medicine
Professor of Pediatrics and Molecular and Medical Genetics
University of Toronto and The Hospital for Sick Children
Toronto, Ontario, Canada
Huntington F. Willard, PhD
Director
The Institute for Genome Science and Policy
Vice Chancellor for Genome Sciences
Duke University
Durham, North Carolina
With Clinical Case Studies prepared by
Cornelius F. Boerkoel III, MD, PhD
Assistant Professor
Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, Texas

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Preface

In their preface to the first edition of *Genetics in Medicine*, published 35 years ago, James and Margaret Thompson wrote

> Genetics is fundamental to the basic sciences of preclinical medical education, and has important applications to clinical medicine, public health and medical research. With recognition of the role of genetics in medicine has come the problem of providing a place for it in the undergraduate curriculum, a problem which is as yet only partly solved in most medical schools. This book has been written to introduce the medical student to the principles of genetics as they apply to medicine, and to give him (her) a background for his own reading of the extensive and rapidly growing literature in the field. If his (her) senior colleagues also find it useful, we shall be doubly satisfied.

What was true then is even more so now as our knowledge of genetics and of the genome is rapidly becoming an integral part of public health and the practice of medicine. This new edition of *Genetics in Medicine*, the sixth in the series, has the same goal as did the previous five: to provide an accurate exposition of the fundamental principles of human genetics, with an emphasis on the genes and molecular mechanisms operating in human diseases. The concepts presented within the text are illustrated with examples drawn from medicine. A new, additional feature of this edition of *Genetics in Medicine* is a set of cases designed to demonstrate and reinforce general principles of disease inheritance, pathogenesis, diagnosis, management, and counseling. The book is not intended to be a compendium of genetic diseases nor is it an encyclopedic treatise on human genetics in general. Rather, the authors hope that the sixth edition of *Genetics in Medicine* will provide students with a framework for understanding the field of medical genetics while giving them a basis on which to establish a program of continuing education in this area. Any medical or genetic counseling student, advanced undergraduate, graduate student in genetics, resident in any field of clinical medicine, practicing physician, or allied medical professional in nursing or physical therapy should find this book to be a thorough but not exhaustive (or exhausting!) presentation of the fundamentals of human genetics as applied to health and disease.

ROBERT L. NUSSBAUM, MD
RODERICK R. MCINNES, MD, PhD
HUNTINGTON F. WILLARD, PhD

Acknowledgments

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Our deepest thanks go to our colleague and friend Dr. Margaret Thompson, not only for her help in reviewing new material but also for her trust and guidance during. the revision process. Finally, we thank our families for their patience and understanding during the many hours of writing and revising that went into the sixth edition of *Genetics in Medicine*.

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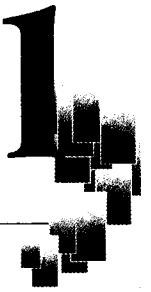

Introduction

THE ROLE OF GENETICS IN MEDICINE

Genetics as a Medical Specialty

This is an especially exciting time in medical and human genetics. Medical genetics has achieved a recognized role as *the* specialty of medicine that deals with the diagnosis, treatment, and management of hereditary disorders. The idea that medical genetics is concerned only with the inheritance of trivial, superficial, and rare characteristics has given way to an understanding of the fundamental role of the **gene** in basic life processes. Medical and human geneticists are at the forefront of investigations into human variability and human heredity while also participating in and benefiting from rapid progress in molecular biology, biochemistry, and cell biology. In particular, the last decade of the 20th century and the beginning of the 21st century have seen the completion of the **Human Genome Project**, an international effort to determine the complete content of the human genome, defined simply as the sum total of the genetic information of our species, encoded within each nucleated cell of the body. In partnership with all the other disciplines of modern biology, the Human Genome Project is revolutionizing human and medical genetics by providing fundamental insights into many diseases and promoting the development of far better diagnostic tools, preventive measures, and therapeutic methods in the near future. The Human Genome Project has made available the complete sequence of all human DNA; knowledge of the complete sequence will, in turn, allow the identification of all human genes and, ultimately, make it possible to determine how variation in these genes contributes to health and disease.

Relevance of Genetics to All Medical Practice

Although medical genetics has become a recognized specialty, it has also become abundantly clear that human genetics provides important unifying concepts that illuminate and unify all medical practice. To give patients and their families the full benefit of expanding genetic knowledge, all physicians and their colleagues in the health professions need to understand the underlying principles of human genetics. The existence of alternative forms of a gene (**alleles**) in the population; the occurrence of similar **phenotypes** developing from mutation and variation at different loci; the importance of gene-gene and gene-environmental interactions in disease; the role of somatic mutation in cancer and aging; the feasibility of prenatal diagnosis, presymptomatic testing, and population screening; and the promise of powerful gene therapies are concepts that now permeate all medical practice and will become only more important in the future. Thus, genetic principles and approaches are not restricted to any one medical subspecialty.

One aspect of medical genetics practice relevant to all of medicine deserves special emphasis: it focuses not only on the patient but also on the entire family. A comprehensive family history is an important first step in the analysis of any disorder, whether or not the disorder is known to be genetic. As pointed out by Childs, "to fail to take a good family history is bad medicine. . . ." A family history is important because it can be critical in diagnosis, may show that a disorder is hereditary, can provide information about the natural history of a disease and variation in its expression, and can clarify the pattern of inheritance. The diagnosis of a hereditary condition allows the risk in other family members to be estimated, so that proper management, prevention, and counseling can be offered to the patient *and* the family.

Disciplines within Human and Medical Genetics

Genetics is a diverse subject concerned with variation and heredity in all living organisms. Within this broad field, **human genetics** is the science of variation and heredity in human beings, whereas **medical**

genetics deals with the subset of human genetic variation that is of significance in the practice of medicine and in medical research.

Within human and medical genetics, there are many fields of interest, as indicated by the various directions in which genetics has developed. Major recognized areas of specialization are the study of chromosomes (**cytogenetics**); the study of the structure and function of individual genes (**molecular and biochemical genetics**); the study of the genome, its organization, and functions (**genomics**); the study of genetic variation in human populations and the factors that determine allele frequencies (**population genetics**); the study of the genetic control of development (**developmental genetics**); and the application of genetics to diagnosis and patient care (**clinical genetics**). The literal meaning of *clinical* is *bedside* (*klinikos*, Greek for "bedside"), and a clinical geneticist is an appropriately qualified physician-geneticist directly involved in the diagnosis of genetic diseases and the care of patients with such diseases. **Genetic counseling**, which combines the provision of risk information while providing psychological and educational support, has matured into a new health profession with a whole cadre of genetic professionals dedicated to the care of patients and their families.

In addition to direct patient contact, medical geneticists provide care to individuals, through the provision of laboratory diagnosis, and to the population at large, through screening programs designed to identify persons at risk of developing or transmitting a genetic disorder. The diagnosis of genetic disease in patients, carrier testing, prenatal diagnosis, and the identification of individuals at risk of developing disease later in life are rapidly expanding specialties in clinical laboratories. Population screening for genetic disease is also becoming increasingly widespread.

CLASSIFICATION OF GENETIC DISORDERS

In clinical practice, the chief significance of genetics is in elucidating the role of genetic variation and mutation in the etiology of a large number of disorders. Virtually any disease is the result of the combined action of genes and environment, but the relative role of the genetic component may be large or small.

Among disorders caused wholly or partly by genetic factors, three main types are recognized:

1. Single-gene disorders
2. Chromosome disorders
3. Multifactorial disorders

Single-gene defects are caused by individual mutant genes. The mutation may be present on only one chromosome of a pair (matched with a normal allele on the homologous chromosome) or on both chromosomes of the pair. In a few cases, the mutation is in the mitochondrial rather than the nuclear genome. In any case, the cause is a critical error in the genetic information carried by a single gene. Single-gene disorders usually exhibit obvious and characteristic pedigree patterns. Most such defects are rare, with a frequency that may be as high as 1 in 500 but is usually much less. Although individually rare, as a group single-gene disorders are responsible for a significant proportion of disease and death. Taking the population as a whole, single-gene disorders affect 2 percent of the population sometime over an entire life span. In a population study of more than 1 million live births, the incidence of serious single-gene disorders in the pediatric population was estimated to be 0.36 percent; among hospitalized children, 6 to 8 percent probably have single-gene disorders.

In **chromosome disorders**, the defect is due not to a single mistake in the genetic blueprint but to an excess or a deficiency of the genes contained in whole chromosomes or chromosome segments. For example, the presence of an extra copy of one chromosome, chromosome 21, produces a specific disorder, Down syndrome, even though no individual gene on the chromosome is abnormal. As a group, chromosome disorders are quite common, affecting about 7 per 1000 liveborn infants and accounting for about half of all spontaneous first-trimester abortions.

Multifactorial inheritance is responsible for a number of developmental disorders resulting in congenital malformations and for many common disorders of adult life. There appears to be no single error in the genetic information in many of these conditions. Rather, the disease is the result of a combination of small variations in genes that together can produce or predispose to a serious defect, often in concert with environmental factors. Multifactorial disorders tend to recur in families but do not show the characteristic pedigree patterns of single-gene traits. Estimates of the impact of multifactorial disease range from 5 percent in the pediatric population to more than 60 percent in the entire population.

ONWARD

During the 40-year professional life of today's medical and genetic counseling students, extensive changes are likely to take place in appreciating—and acting on—the role of genetics in medicine. It is hard to imagine that any period could encompass changes greater than those seen over the past 50 years, during which the field has gone from first recognizing the

identity of DNA as the active agent of inheritance, to uncovering the molecular structure of DNA and chromosomes, to determining the complete code of the human genome. And yet, judging from the quickening pace of discovery within only the past decade, it is virtually certain that we are just at the beginning of a revolution in integrating knowledge of genetics and the genome into public health and the practice of medicine.

An introduction to the language and concepts of human and medical genetics and an appreciation of the genetic and genomic perspective on health and disease will form a framework for lifelong learning that is part of any health professional's career.

General References

Baker DL, Schuette JL, Uhlmann WR (1998) A Guide to Genetic Counseling. John Wiley & Sons, New York.

Childs B (1993) Genetics in medical education. Am J Hum Genet 52:225–227.

King RA, Rotter JI, Motulsky AG (2002) The Genetic Basis of Common Diseases, 2nd ed. Oxford University Press, Oxford.

McKusick VA. Online Mendelian inheritance in man: catalogs of autosomal dominant, autosomal recessive, and X-linked phenotypes at *http://www3.ncbi.nlm.nih.gov*.

Rimoin DL, Connor JM, Pyeritz RE (2001) Emery and Rimoin's Principles and Practice of Medical Genetics, 4th ed. WB Saunders, Philadelphia.

Scriver CR, Beaudet AL, Sly WS, Valle D (eds) (2000) The Metabolic and Molecular Bases of Inherited Disease, 8th ed. McGraw-Hill, New York.

Vogel F, Motulsky AG (1997) Human Genetics: Problems and Approaches, 3rd ed. Springer-Verlag, New York.

Specific References

Collins FS, Green ED, Guttmacher AE, Guyer MS, et al (2003) A vision for the future of genomics research. Nature 422:835–847.

Guttmacher AE, Collins FS (2002) Genomic medicine—a primer. N Engl J Med 347:1512–1520.

Weinshilboum RM (2002) The genomic revolution and medicine. Mayo Clin Proc 77:745–746.

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Chromosomal Basis of Heredity

Appreciation of the importance of genetics to medicine requires an understanding of the nature of the hereditary material, how it is packaged into the human genome, and how it is transmitted from cell to cell during cell division and from generation to generation during reproduction. The human genome consists of large amounts of the chemical deoxyribonucleic acid (**DNA**) that contains within its structure the genetic information needed to specify all aspects of embryogenesis, development, growth, metabolism, and reproduction—essentially all aspects of what makes a human being a functional organism. The human genome contains, by current estimates, about 30,000 **genes**, which at this point we define simply as units of genetic information. Genes are encoded in the DNA that makes up a number of rod-shaped organelles called **chromosomes** in the nucleus of each cell. The influence of genes and genetics on states of health and disease is widespread, and its roots are the information encoded in the DNA found in the human genome.

Within each cell, the genome is packaged as **chromatin**, in which genomic DNA is complexed with several classes of chromosomal proteins. Some of the proteins found in chromatin perform structural roles, whereas others serve to regulate the expression of individual genes. Except during cell division, chromatin is distributed throughout the nucleus and is relatively homogeneous in appearance under the microscope. When a cell divides, however, its nuclear material condenses to appear as microscopically visible chromosomes. Chromosomes are thus visible as discrete structures only in dividing cells, but they nevertheless retain their integrity between cell divisions.

Each species has a characteristic chromosome complement (**karyotype**) in terms of the number and the morphology of its chromosomes. The genes are in linear order along the chromosomes, each gene having a precise position or **locus**. The **gene map** is the map of the chromosomal location of the genes and is also characteristic of each species and the individuals within a species.

The study of chromosomes, their structure, and their inheritance is called **cytogenetics**. The science of modern human cytogenetics dates from 1956, when Tjio and Levan developed effective techniques for chromosome analysis and established that the normal human chromosome number is 46. Since that time, much has been learned about human chromosomes, their normal structure, their molecular composition, the locations of the genes that they contain, and their numerous and varied abnormalities.

Chromosome analysis has become an important diagnostic procedure in clinical medicine. As described more fully in subsequent chapters, some of these applications include the following:

Clinical Diagnosis. Numerous medical disorders, including some that are quite common, such as Down syndrome, are associated with microscopically visible changes in chromosome number or structure and require chromosome analysis for diagnosis and genetic counseling (see Chapters 9 and 10).

Gene Mapping. A major goal of medical genetics today is the mapping of specific genes to chromosomes as part of the Human Genome Project. This topic is referred to repeatedly but is discussed in detail in Chapter 8.

Cancer Cytogenetics. Chromosomal changes in somatic cells are involved in the initiation and progression of many types of cancer (see Chapter 16).

Prenatal Diagnosis. Chromosome analysis is an essential procedure in prenatal diagnosis (see Chapter 18).

The ability to interpret a chromosome report and some knowledge of the methodology, the scope, and the limitations of chromosome studies are essential skills for physicians and others working

with patients with birth defects, mental retardation, disorders of sexual development, and many types of cancer.

THE HUMAN CHROMOSOMES

With the exception of cells in the germline, all cells that contribute to one's body are called **somatic cells** (*soma*, body). The 46 chromosomes of human somatic cells constitute 23 pairs. Of those 23 pairs, 22 are alike in males and females and are called **autosomes**, numbered in decreasing order from the largest (chromosome 1) to the smallest (chromosomes 21 and 22). The remaining pair comprises the **sex chromosomes**: XX in females and XY in males. Each chromosome carries a different subset of genes that are arranged linearly along its DNA. Members of a pair of chromosomes (described as **homologous chromosomes** or **homologs**) carry matching genetic information; that is, they have the same genes in the same sequence. At any specific locus, however, they may have either identical or slightly different forms of the same gene, called **alleles**. One member of each pair of chromosomes is inherited from the father, the other from the mother. Normally, the members of a pair of autosomes are microscopically indistinguishable from each other. In females, the sex chromosomes, the two **X chromosomes**, are likewise largely indistinguishable. In males, however, the sex chromosomes differ. One is an X, identical to the Xs of the female, inherited by a male from his mother and transmitted to his daughters; the other, the **Y chromosome**, is inherited from his father and transmitted to his sons. In Chapter 10, we look at some exceptions to the simple and almost universal rule that human females are XX and human males are XY.

There are two kinds of cell division: mitosis and meiosis. **Mitosis** is ordinary somatic cell division, by which the body grows, differentiates, and effects tissue regeneration. Mitotic division normally results in two daughter cells, each with chromosomes and genes identical to those of the parent cell. There may be dozens or even hundreds of successive mitoses in a lineage of somatic cells. In contrast, **meiosis** occurs only in cells of the germline. Meiosis results in the formation of reproductive cells (**gametes**), each of which has only 23 chromosomes: one of each kind of autosome and either an X or a Y. Thus, whereas somatic cells have the **diploid** (*diploos*, double) or the 2n chromosome complement (i.e., 46 chromosomes), gametes have the **haploid** (*haploos*, single) or the n complement (i.e., 23 chromosomes). Abnormalities of chromosome number or structure, which are usually clinically significant, can arise in either somatic cells or cells of the germline by errors in cell division.

THE LIFE CYCLE OF A SOMATIC CELL

A human being begins life as a fertilized ovum (**zygote**), a diploid cell from which all the cells of the body (estimated at about 100 trillion in number) are derived, by a series of dozens or even hundreds of mitoses. Mitosis is obviously crucial for growth and differentiation, but it takes up only a small part of the life cycle of a cell. What goes on in **interphase**, the period between two successive mitoses?

As Figure 2–1 shows, mitosis is the shortest of the four stages of the cell cycle. Immediately after mitosis, the cell enters a phase, called G_1, in which there is no DNA synthesis. Some cells spend a very long time, days or even years, in G_1; others pass through this stage in hours. Although the molecular mechanisms controlling cell-cycle progression are incompletely understood, the cell cycle is governed by a series of **checkpoints** that determine the timing of each step in mitosis. In addition, checkpoints monitor and control the accuracy of DNA synthesis, as well as the assembly and attachment of an elaborate network of microtubules that facilitate chromosome movement. If damage to the genome is detected, these mitotic checkpoints halt cell-cycle progression until repairs are made or, if the damage is excessive, until the cell is instructed to die by programmed cell death (a process called **apoptosis**).

G_1 is followed by the **S phase**, the stage of DNA synthesis. During this stage, each chromosome, which in G_1 has been a single DNA molecule (whose exact structure we examine in Chapter 3), replicates to become a bipartite chromosome consisting of two **sister chromatids** (see Fig. 2–1), each of which contains an identical copy of the original linear DNA molecule. The ends of each chromosome (or

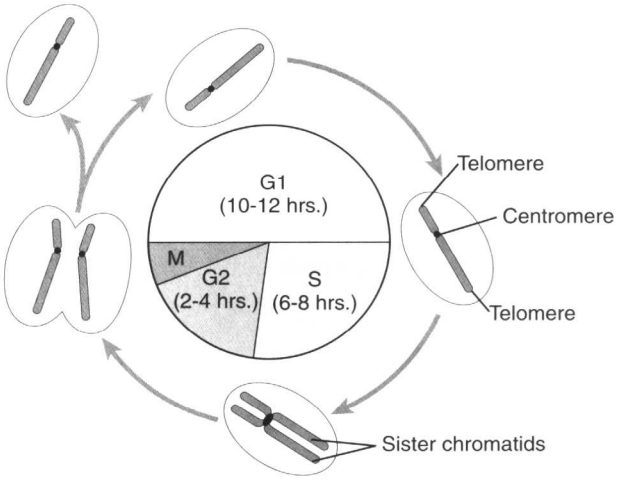

Figure 2–1. A typical mitotic cell cycle, described in the text. The telomeres, the centromere, and sister chromatids are indicated.

chromatid) are marked by **telomeres**, which consist of specialized DNA sequences that ensure the integrity of the chromosome during cell division. The two sister chromatids are held together physically at the **centromere**, a region of DNA that associates with a number of specific proteins to form the **kinetochore**. This complex structure serves to attach each chromosome to the microtubules of the mitotic spindle and to govern chromosome movement during mitosis. DNA synthesis during S phase is not synchronous throughout all chromosomes or even within a single chromosome; rather, along each chromosome, it begins at hundreds to thousands of sites, called **origins of DNA replication**. Individual chromosome segments have their own characteristic time of replication during the 6- to 8-hour S phase.

By the end of S phase, the DNA content of the cell has doubled, and the cell enters a brief next stage, called G_2. Throughout the whole cell cycle, ribonucleic acids and proteins are produced and the cell gradually enlarges, eventually doubling its total mass before the next mitosis. G_2 is ended by mitosis, which begins when individual chromosomes begin to condense and become visible under the microscope as thin, extended threads, a process that is considered in greater detail in the following section and in Chapter 3.

The G_1, S, and G_2 phases together constitute interphase. In typical dividing human cells, the three phases take a total of 16 to 24 hours, whereas mitosis lasts only 1 to 2 hours (see Fig. 2–1). There is great variation, however, in the length of the cell cycle, which ranges from a few hours in rapidly dividing cells, such as those of the dermis of the skin or the intestinal mucosa, to months in other cell types. In fact, some cell types, such as neurons and red blood cells, do not divide at all once they are fully differentiated; rather, they are permanently arrested during G_1 in a phase known as G_0. Other cells, such as liver cells, may enter G_0 but, following organ damage, eventually return to G_1 and continue through the cell cycle.

Mitosis

During the mitotic phase of the cell cycle, an elaborate apparatus is brought into play to ensure that each of the two daughter cells receives a complete set of genetic information. This result is achieved by a mechanism that distributes one chromatid of each chromosome to each daughter cell and is illustrated schematically in Figure 2–2. The process of distributing a copy of each chromosome to each daughter cell is called **chromosome segregation**. The importance of this process for normal cell growth is illustrated by the observation that many tumors are invariably characterized by a state of genetic imbalance that results from mitotic errors in distributing chromosomes to daughter cells.

The process of mitosis is continuous, but five stages are distinguished: prophase, prometaphase, metaphase, anaphase, and telophase.

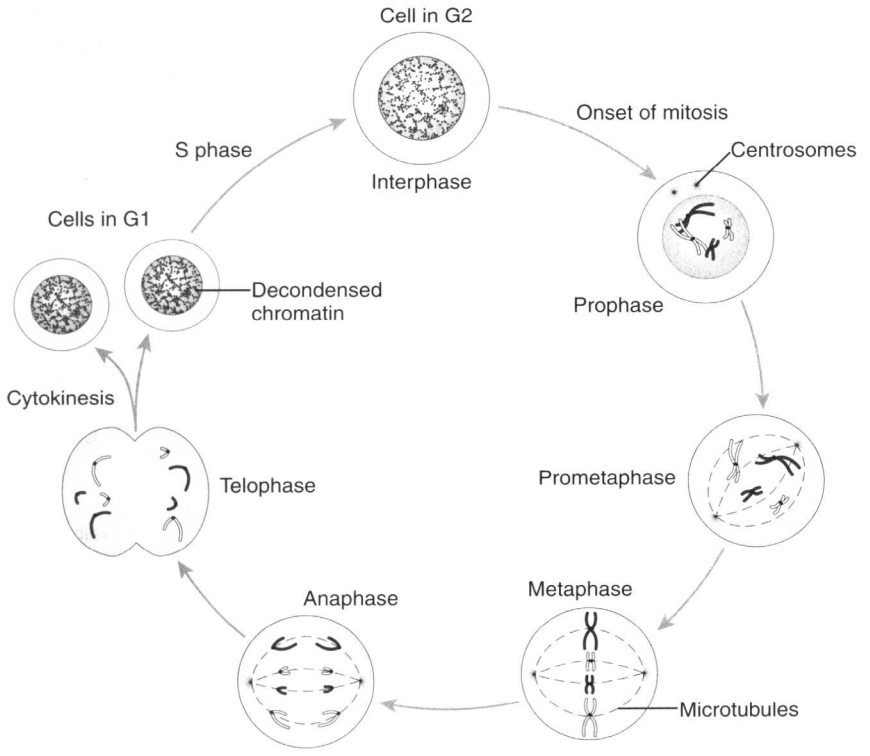

Figure 2–2. Mitosis. Diagrammatic representation, showing only two chromosome pairs. For further details, see text.

Prophase. This stage initiates mitosis and is marked by gradual condensation of the chromosomes, disintegration and eventual disappearance of the nucleolus, and the beginning of the formation of the **mitotic spindle**. A pair of microtubule organizing centers, also called **centrosomes**, form foci from which microtubules radiate. The centrosomes gradually move to take up positions at the poles of the cell.

Prometaphase. The cell enters prometaphase when the nuclear membrane breaks up, allowing the chromosomes to disperse within the cell and to attach, via their kinetochores, to microtubules of the mitotic spindle. The chromosomes begin to move toward a point midway between the spindle poles, a process called **congression**. The chromosomes continue to condense throughout this stage.

Metaphase. At metaphase, the chromosomes reach maximal condensation. They become arranged at the equatorial plane of the cell, balanced by the equal forces exerted on the kinetochore of each chromosome by microtubules emanating from the two spindle poles. The chromosomes of a dividing human cell are most readily analyzed at the metaphase or the prometaphase stage of mitosis (see later discussion and Chapter 9).

Anaphase. Anaphase begins abruptly when the chromosomes separate at the centromere. The sister chromatids of each chromosome now become independent **daughter chromosomes**, which move to opposite poles of the cell (see Fig. 2–2).

Telophase. In telophase, the chromosomes begin to decondense from their highly contracted state, a nuclear membrane begins to reform around each of the two daughter nuclei, and each nucleus gradually resumes its interphase appearance.

To complete the process of cell division, the cytoplasm cleaves by a process known as **cytokinesis**, which begins as the chromosomes approach the spindle poles. Eventually there are two complete daughter cells, each with a nucleus containing all the genetic information of the original cell.

There is an important difference between a cell entering mitosis and one that has just completed the process. The parent cell's chromosomes in G_2 each have a pair of chromatids, but the chromosomes of the daughter cell each consist of only one copy of the genetic material. This copy will not be duplicated until the daughter cell in its turn reaches the S phase of the next cell cycle (see Fig. 2–1). The entire process of mitosis thus ensures the orderly duplication and distribution of the genome through successive cell divisions.

The Human Karyotype

The condensed chromosomes of a dividing human cell are most readily analyzed at metaphase or prometaphase. At these stages, the chromosomes are visible under the microscope as a **chromosome spread**, and each chromosome can be seen to consist of its sister chromatids, joined at the centromere.

Most chromosomes can be distinguished not only by their length, but also by the location of the centromere. The centromere is apparent as a **primary constriction**, a recognizable cytogenetic landmark, dividing the chromosome into two **arms**, a short arm designated **p** (for *petit*) and a long arm designated **q**. The staining methods originally available for human cytogenetic analysis, however, did not allow all 24 types of chromosome (22 autosomes, X, and Y) to be individually identified. Instead, the chromosomes could be classified only into seven groups, named by the letters A to G, on the basis of their overall length and the position of the centromere. These designations are no longer in general use but are seen in the literature. With techniques now in common use, all the chromosomes can be individually identified.

Figure 2–3 shows a prometaphase cell in which the chromosomes have been stained by the Giemsa-staining (**G-banding**) method, the technique most

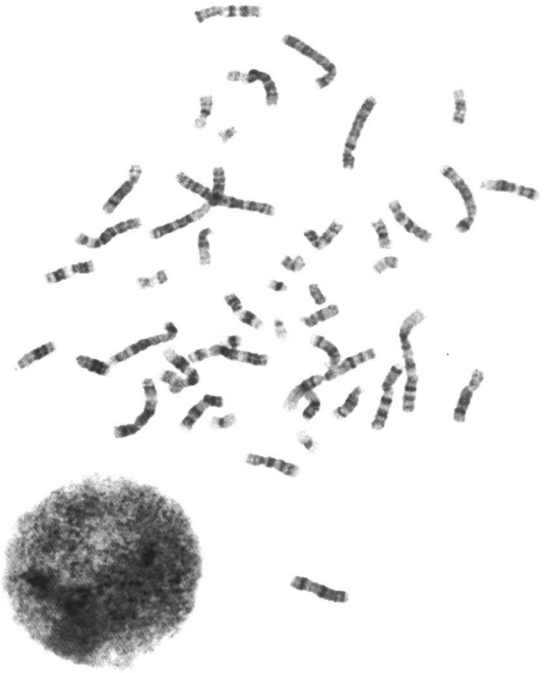

Figure 2–3. A chromosome spread prepared from a lymphocyte culture which has been stained by the Giemsa-banding (G-banding) technique. The darkly stained nucleus adjacent to the chromosomes is from a different cell in interphase, when chromosomal material is diffuse throughout the nucleus. (Photomicrograph courtesy of Stuart Schwartz, University Hospitals of Cleveland.)

widely used in clinical cytogenetics laboratories. The chromosomes are treated first with trypsin to digest the chromosomal proteins and then with Giemsa stain. Each chromosome pair stains in a characteristic pattern of light and dark bands (G bands). Using this method and other so-called banding techniques, all of the chromosomes can be individually distinguished. Further, the nature of any structural or numerical abnormalities can be readily determined, as we examine in greater detail in Chapters 9 and 10.

Although experts can often analyze metaphase chromosomes directly under the microscope, a common procedure is to cut out the chromosomes from a photomicrograph and arrange them in pairs in a standard classification, as shown in Figure 2–4. The completed picture is called a **karyotype**. The word *karyotype* is also used to refer to the standard chromosome set of an individual ("a normal male karyotype") or of a species ("the human karyotype") and, as a verb, to refer to the process of preparing such a standard figure ("to karyotype").

Unlike the chromosomes seen in stained preparations under the microscope or in photographs, the chromosomes of living cells are fluid and dynamic structures. During mitosis, for example, the chromatin of each interphase chromosome condenses substantially (Fig. 2–5). At prophase, when chromosomes become visible under the light microscope, chromosome 1 has condensed to an overall length of about 50 μm. When maximally condensed at metaphase, DNA in chromosomes is about 1/10,000 of its fully extended state. When chromosomes are prepared to reveal bands (see Figs. 2–3 and 2–4), as many as 1000 or more bands can be recognized in stained preparations of all the chromosomes, and each cytogenetic band therefore contains as many as 50 or more genes. After metaphase, as cells complete mitosis, chromosomes decondense and return to their relaxed state as chromatin in the interphase nucleus, ready to begin the cycle again (see Fig. 2–5).

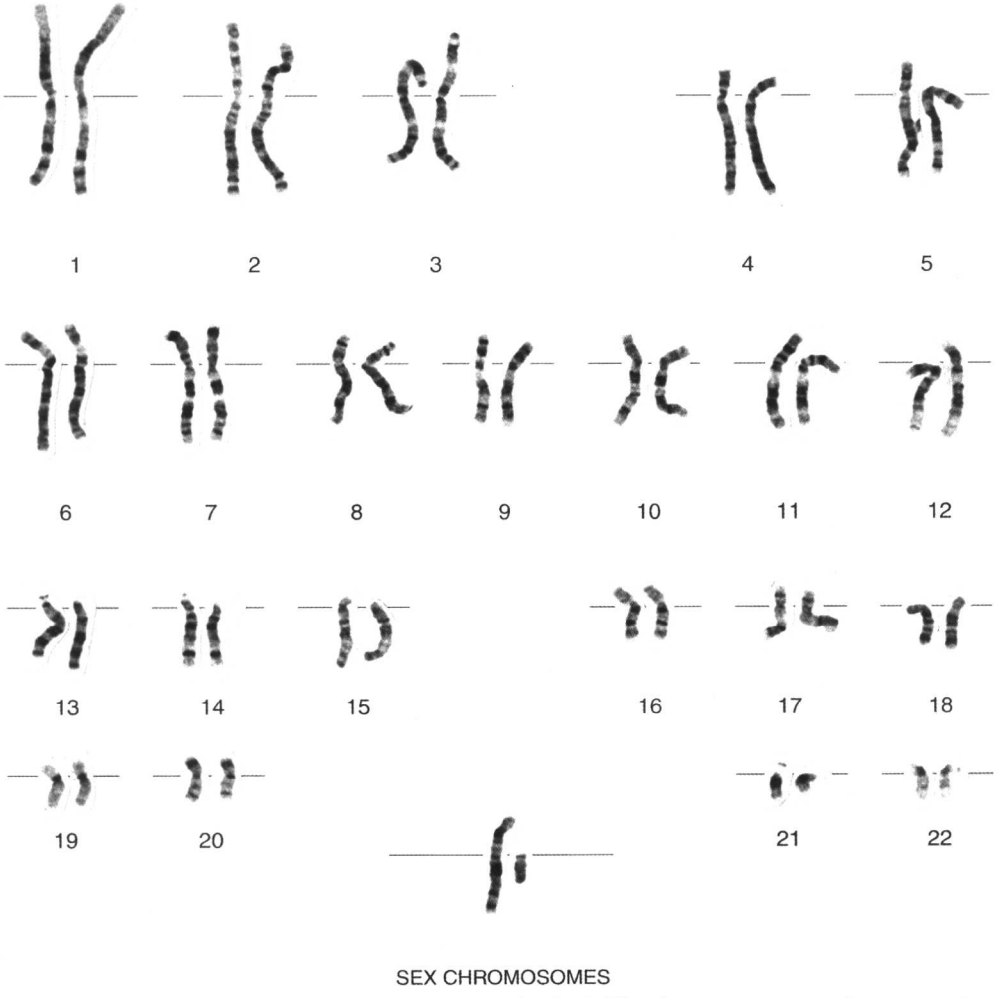

Figure 2–4. A human male karyotype with Giemsa banding (G banding). The chromosomes are at the prometaphase stage of mitosis and are arranged in a standard classification, numbered 1 to 22 in order of length, with the X and Y chromosomes shown separately. (Photomicrograph courtesy of Stuart Schwartz, University Hospitals of Cleveland.)

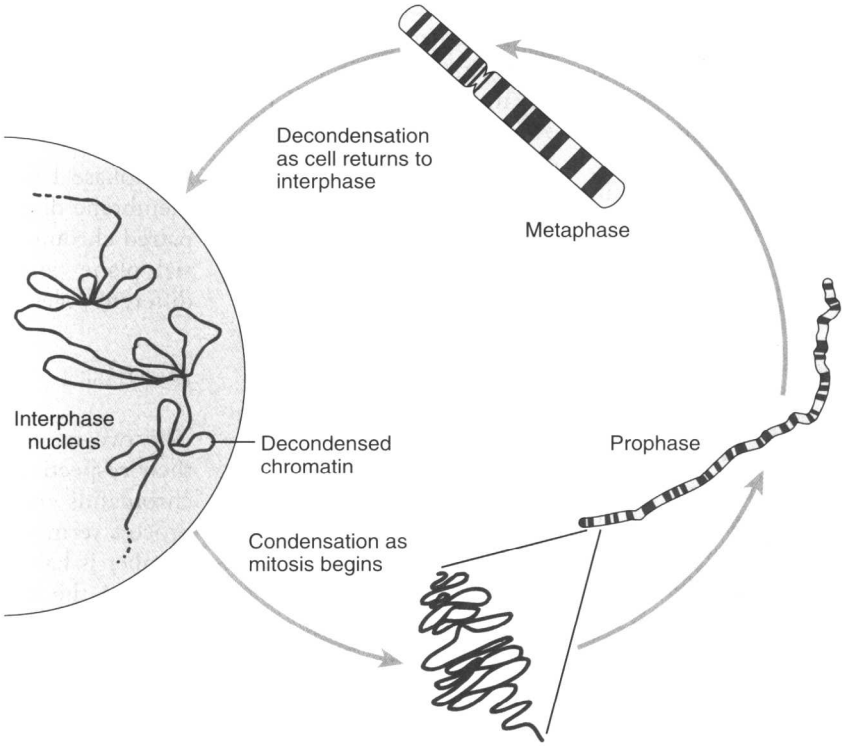

Figure 2–5. Cycle of condensation and decondensation as a chromosome proceeds through the cell cycle.

MEIOSIS

Meiosis is the type of cell division by which the diploid cells of the germline give rise to haploid gametes. Meiosis consists of one round of DNA synthesis followed by two rounds of chromosome segregation and cell division (Fig. 2–6). The cells in the germline that undergo meiosis, primary spermatocytes or primary oocytes, are derived from the zygote by a long series of mitoses before the onset of meiosis.

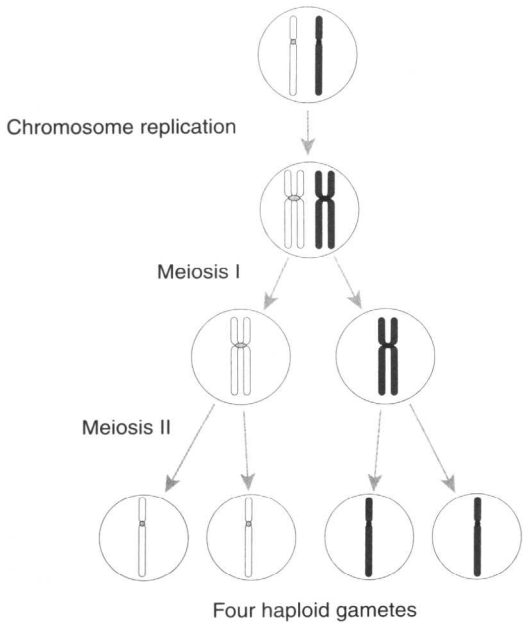

Figure 2–6. A simplified representation of the essential steps in meiosis, consisting of one round of DNA replication, followed by two rounds of chromosome segregation, meiosis I and meiosis II.

Male and female gametes have different histories, but the sequence of events is the same, although their timing is very different. The two successive meiotic divisions are called meiosis I and meiosis II. Meiosis I is also known as the **reduction division** because it is the division in which the chromosome number is reduced from diploid to haploid by the pairing of homologs in prophase and by their segregation to different cells at anaphase of meiosis I. The X and Y chromosomes are not homologs in a strict sense but do have homologous segments at the ends of their short and long arms, and they pair in both regions.

Meiosis I is also notable because it is the stage at which genetic **recombination** (also called **meiotic crossing over**) occurs. In this process, homologous segments of DNA are exchanged between nonsister chromatids of a pair of homologous chromosomes, thus ensuring that none of the gametes produced by meiosis is identical to another. The concept of recombination is fundamental to the process of mapping genes responsible for inherited disorders, as we discuss at length in Chapter 8. Because recombination involves the physical intertwining of the two homologs until the appropriate point during meiosis I, it is also critical for ensuring proper chromosome segregation during meiosis. Failure to recombine properly can lead to chromosome missegregation in