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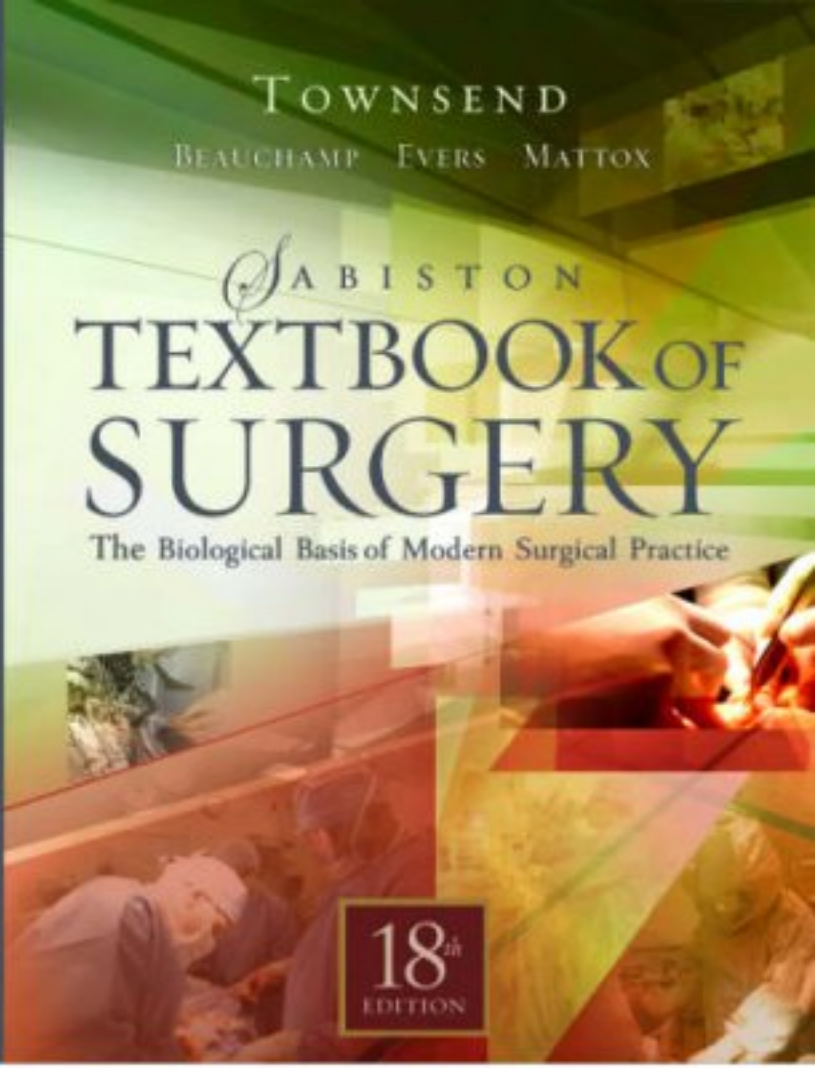

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FOREWORD

"To study the phenomena of disease without books is to sail an uncharted sea . . ."

SIR WILLIAM OSLER (1849–1919)

During the past 3 score and 7 years, this surgical text, edited successively by Christopher (5 editions), Davis (4 editions), Sabiston (6 editions), and now Townsend (3 editions), has charted the surgical seas for generations of surgeons throughout their careers as they progressed from students to practitioners and teachers. Dr. Townsend and his three associate editors have added to the innovations that they initiated in the 15th edition in recognition of the ever-increasing velocity of acquisition of knowledge, expansion of surgical practice, and application of new technology. This edition is organized into 13 sections—focused on basic principles of surgery, organ-specific general surgical care, and the surgical superspecialties—to recapitulate the content of the American Board of Surgery certifying examination. The editorial team has added more than 50 new members to the all-star cast of authors for the 77 chapters that provide global coverage of surgery.

Of all the surgical texts, this one most successfully integrates information from the laboratory to illuminate the rationale for surgical care. Each chapter begins with a chapter outline and contains other tables presenting checklists of key principles and practices. Abundant use is made of color in illustrative photographs and drawings and to emphasize important aspects of graphs and tables. A unique feature is the citation and brief summary of seminal articles, which are beyond the reach of short–time span search programs, designed to inform the reader how we arrived at the current state-of-the-art.

The new chapters about patient safety considerations, bedside procedures, and regenerative medicine provide the reader with charts of previously unexplored surgical seas. Dr. Townsend and his colleagues have further enhanced the value of this classic work by bringing it into the world of electronic education. Expert Consult will facilitate lifetime learning by giving access to the fully searchable complete book content online, along with updates, references linked to Medline, downloadable illustrations, and "bonus" articles from surgical periodicals, as well as review questions that can be used in preparing for examinations.

In sum total, this volume sets a new standard for surgical textbooks. The information contained in this, Dr. Townsend's 3rd and overall the 18th, edition of this venerable text ensures smooth sailing in the currently turbulent surgical seas.

BASIL A. PRUITT, JR., MD

PREFACE

Surgery continues to evolve as new technology, techniques, and knowledge are incorporated into the care of surgical patients. Safety is paramount in care of our surgical patients. We have included a new chapter in this edition of *Sabiston Textbook of Surgery* about our roles and responsibilities to ensure safety. Surgeons, traditional leaders in mass casualty situations, face new problems and challenges in the era of bioterrorism. Distant surgery, employing robotic and telementoring technology, has become a reality. Minimally invasive techniques are being employed in almost all invasive procedures. Increased understanding of molecular genetic abnormalities has expanded the application of preemptive surgical operations to prevent cancer.

The 18th edition of the *Sabiston Textbook of Surgery* reflects these exciting changes and new knowledge. We have incorporated 3 new chapters and more than 50 new authors to ensure that the most current information is presented. The goal of this new edition is to remain the most thorough, useful, readable, and understandable textbook presenting the principles and techniques of surgery. It is designed to be equally useful to students, trainees, and experts in the field. We are committed to maintaining this tradition of excellence begun in 1936. Surgery, after all, remains a discipline in which the knowledge and skill of a surgeon combine for the welfare of our patients.

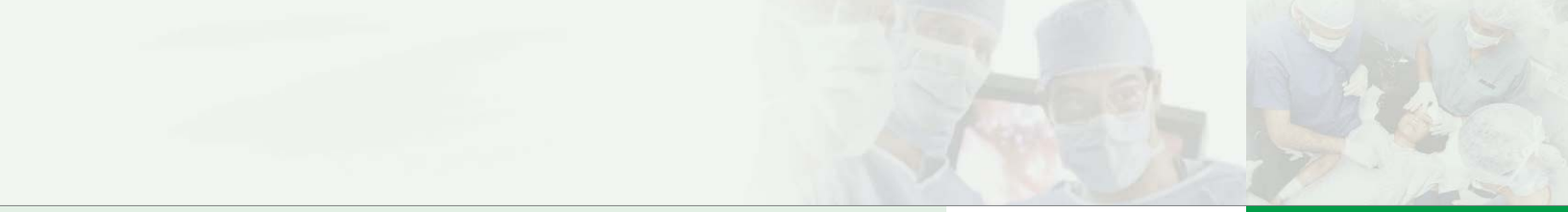
COURTNEY M. TOWNSEND, JR., MD

ACKNOWLEDGMENTS

We would like to recognize the invaluable contributions of editor Paul Waschka, publication coordinators Karen Martin, Steve Schuenke, and Eileen Figueroa, and administrator Barbara Petit. Their dedicated professionalism, tenacious efforts, and cheerful cooperation are without parallel. They accomplished whatever was necessary, often on short or instantaneous deadlines, and were vital for the successful completion of the endeavor.

Our authors, respected authorities in their fields and busy physicians and surgeons all, did an outstanding job in sharing their wealth of knowledge.

We would also like to acknowledge the professionalism of our colleagues at Elsevier: senior developmental editor Scott Scheidt, publication services manager Tina Rebane, senior project manager Amy Cannon, and publishing director Judith Fletcher.



CHAPTER 1

History of Surgery

Ira M. Rutkow, MD, MPH, DrPH

IMPORTANCE OF UNDERSTANDING SURGICAL HISTORY

It remains a rhetorical question whether an understanding of surgical history is important to the maturation and continued education and training of a surgeon. Conversely, it is hardly necessary to dwell on the heuristic value that an appreciation of history provides in developing adjunctive humanistic, literary, and philosophic tastes. Clearly, the study of medicine is a lifelong learning process that should be an enjoyable and rewarding experience. For a surgeon, the study of surgical history can contribute toward making this educational effort more pleasurable and can provide constant invigoration. Tracing the evolution of what one does on a daily basis and understanding it from a historical perspective become enviable goals. In reality, there is no way to separate present-day surgery and one's own clinical practice from the experience of all surgeons and all the years that have gone before. For budding surgeons, it is a magnificent adventure to appreciate what they are currently learning within the context of past and present cultural, economic, political, and social institutions. Active practitioners will find that study of the profession—dealing, as it rightly must, with all aspects of the human condition—affords an excellent opportunity to approach current clinical concepts in ways not previously appreciated.

In studying our profession's past, it is certainly easier to relate to the history of so-called modern surgery over the past 100 or so years than to the seemingly primitive practices of previous periods because the closer to the present, the more likely it is that surgical practices will resemble those of nowadays. Nonetheless, writing the history of modern surgery is in many respects more difficult than describing the development of surgery before the late 19th century. One significant reason for this difficulty is the ever-increasing pace of scientific development in conjunction with unrelenting fragmentation (i.e., specialization and subspecialization) within the profession. The craft of surgery is in constant flux, and the more rapid the change, the more difficult it is to obtain a satisfactory historical perspective. Only the lengthy passage of time permits a truly valid historical analysis.

HISTORICAL RELATIONSHIP BETWEEN SURGERY AND MEDICINE

Despite outward appearances, it was actually not until the latter decades of the 19th century that the surgeon truly emerged as a specialist within the whole of

medicine to become a recognized and respected clinical practitioner. Similarly, it was not until the first decades of the 20th century that surgery could be considered to have achieved the status of a bona fide profession. Before this time, the scope of surgery remained quite limited. Surgeons, or at least those medical men who used the sobriquet *surgeon,* whether university educated or trained in private apprenticeships, at best treated only simple fractures, dislocations, and abscesses and occasionally performed amputations with dexterity but also with high mortality rates. They managed to ligate major arteries for common and accessible aneurysms and made heroic attempts to excise external tumors. Some individuals focused on the treatment of anal fistulas, hernias, cataracts, and bladder stones. Inept attempts at reduction of incarcerated and strangulated hernias were made, and hesitatingly, rather rudimentary colostomies or ileostomies were created by simply incising the skin over an expanding intra-abdominal mass, which represented the end stage of a long-standing intestinal obstruction. Compound fractures of the limbs with attendant sepsis remained mostly unmanageable, with staggering morbidity being a likely surgical outcome. Although a few bold surgeons endeavored to incise the abdomen in the hope of dividing obstructing bands and adhesions, abdominal and other intrabody surgery was virtually unknown.

Despite it all, including an ignorance of anesthesia and antisepsis tempered with the not uncommon result of the patient suffering from or succumbing to the effects of a surgical operation (or both), surgery was long considered an important and medically valid therapy. This seeming paradox, in view of the terrifying nature of surgical intervention, its limited technical scope, and its damning consequences before the development of modern conditions, is explained by the simple fact that surgical procedures were usually performed only for external difficulties that required an objective anatomic diagnosis. Surgeons or followers of the surgical cause saw what needed to be fixed (e.g., abscesses, broken bones, bulging tumors, cataracts, hernias) and would treat the problem in as rational a manner as the times permitted. Conversely, the physician was forced to render subjective care for disease processes that were neither visible nor understood. After all, it is a difficult task to treat the symptoms of illnesses such as arthritis, asthma, heart failure, and diabetes, to name but a few, if there is no scientific understanding or internal knowledge of what constitutes their basic pathologic and physiologic underpinnings.

With the breathtaking advances made in pathologic anatomy and experimental physiology during the 18th and the first part of the 19th centuries, physicians would soon adopt a therapeutic viewpoint that had long been prevalent among surgeons. It was no longer a question of just treating symptoms; the actual pathologic problem could ultimately be understood. Internal disease processes that manifested themselves through difficult-to-treat external signs and symptoms were finally described via physiology-based experimentation or viewed pathologically through the lens of a microscope. Because this reorientation of internal medicine occurred within a relatively short time and brought about such dramatic results in the classification, diagnosis, and treatment of disease, the rapid ascent of mid-19th century internal medicine might seem more impressive than the agonizingly slow, but steady advance of surgery. In a seeming contradiction of mid-19th century scientific and social reality, medicine appeared as the more progressive branch, with surgery lagging behind. The art and craft of surgery, for all its practical possibilities, would be severely restricted until the discovery of anesthesia in 1846 and an understanding and acceptance of the need for surgical antisepsis and asepsis during the 1870s and 1880s. Still, surgeons never needed a diagnostic and pathologic revolution in the manner of the physician. Despite the imperfection of their scientific knowledge, the pre–modern era surgeon did cure with some technical confidence.

That the gradual evolution of surgery was superseded in the 1880s and 1890s by the rapid introduction of startling new technical advances was based on a simple culminating axiom—the four fundamental clinical prerequisites that were required before a surgical operation could ever be considered a truly viable therapeutic procedure had finally been identified and understood:

1. Knowledge of human anatomy
2. Method of controlling hemorrhage and maintaining intraoperative hemostasis
3. Anesthesia to permit the performance of pain-free procedures
4. Explanation of the nature of infection along with the elaboration of methods necessary to achieve an antiseptic and aseptic operating room environment

The first two prerequisites were essentially solved in the 16th century, but the latter two would not be fully resolved until the ending decades of the 19th century. In turn, the ascent of 20th century scientific surgery would unify the profession and allow what had always been an art and craft to become a learned vocation. Standardized postgraduate surgical education and training programs could be established to help produce a cadre of scientifically knowledgeable practitioners. Moreover, in a final snub to an unscientific past, newly established basic surgical research laboratories offered the means of proving or disproving the latest theories while providing a testing ground for bold and exciting clinical breakthroughs.

KNOWLEDGE OF HUMAN ANATOMY

Few individuals have had an influence on the history of surgery as overwhelmingly as that of the Brussels-born Andreas Vesalius (1514-1564) (Fig. 1-1). As professor of anatomy and surgery in Padua, Italy, Vesalius taught that human anatomy could be learned only through the study of structures revealed by human dissection. In particular, his great anatomic treatise *De Humani Corporis Fabrica Libri Septem* (1543) provided fuller and more detailed descriptions of human anatomy than any of his illustrious predecessors did. Most importantly, Vesalius corrected errors in traditional anatomic teachings propagated 13 centuries earlier by Greek and Roman authorities, whose

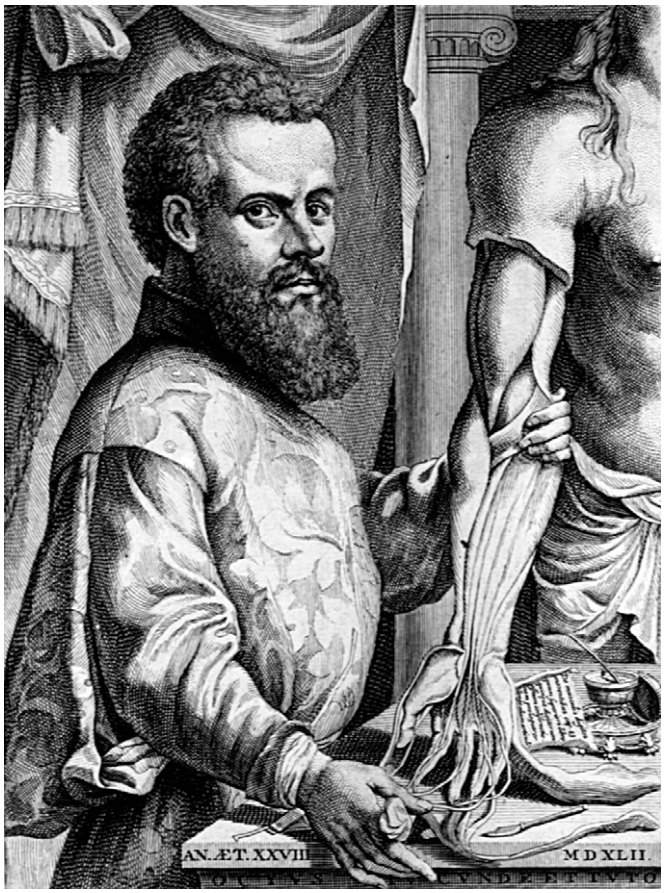


Figure 1-1 Andreas Vesalius (1514-1564).

findings were based on animal rather than human dissection. Even more radical was Vesalius' blunt assertion that anatomic dissection must be completed by physician/surgeons themselves—a direct renunciation of the long-standing doctrine that dissection was a grisly and loathsome task to be performed by a diener-like individual while from on high the perched physician/surgeon lectured by reading from an orthodox anatomic text. This principle of hands-on education would remain Vesalius' most important and long-lasting contribution to the teaching of anatomy. Vesalius' Latin *literae scriptae* ensured its accessibility to the most well-known physicians and scientists of the day. Latin was the language of the intelligentsia and the *Fabrica* became instantly popular, so it was only natural that over the next 2 centuries the work would go through numerous adaptations, editions, and revisions, though always remaining an authoritative anatomic text.

METHOD OF CONTROLLING HEMORRHAGE

The position of Ambroise Paré (1510-1590) (Fig. 1-2) in the evolution of surgery remains of supreme importance. He played the major role in reinvigorating and updating Renaissance surgery and represents severing of the final link between surgical thought and techniques of the

Figure 1-2 Ambroise Paré (1510-1590).

ancients and the push toward more modern eras. From 1536 until just before his death, Paré was either engaged as an army surgeon, during which he accompanied different French armies on their military expeditions, or performing surgery in civilian practice in Paris. Although other surgeons made similar observations about the difficulties and nonsensical aspects of using boiling oil as a means of cauterizing fresh gunshot wounds, Paré's use of a less irritating emollient of egg yolk, rose oil, and turpentine brought him lasting fame and glory. His ability to articulate such a finding in multiple textbooks, all written in the vernacular, allowed his writings to reach more than just the educated elite. Among Paré's important corollary observations was that when performing an amputation, it was more efficacious to ligate individual blood vessels than to attempt to control hemorrhage by means of mass ligation of tissue or with hot oleum. Described in his *Dix Livres de la Chirurgie avec le Magasin des Instruments Necessaires à Icelle* (1564), the free or cut end of a blood vessel was doubly ligated and the ligature was allowed to remain undisturbed in situ until, as a result of local suppuration, it was cast off. Paré humbly attributed his success with patients to God, as noted in his famous motto, "*Je le pansay. Dieu le guérit,*" that is, "I treated him. God cured him."

PATHOPHYSIOLOGIC BASIS OF SURGICAL DISEASES

Although it would be another 3 centuries before the third desideratum, that of anesthesia, was discovered, much of the scientific understanding concerning efforts to relieve discomfort secondary to surgical operations was based

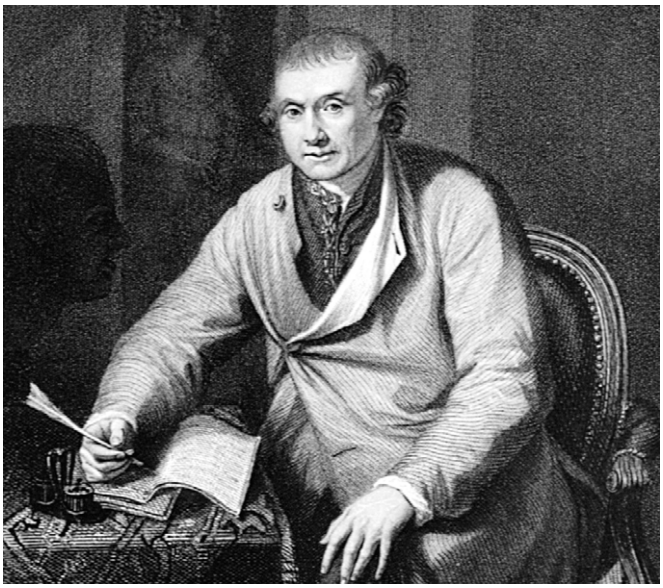


Figure 1-3 John Hunter (1728-1793).

on the 18th century work of England's premier surgical scientist, John Hunter (1728-1793) (Fig. 1-3). Considered one of the most influential surgeons of all time, his endeavors stand out because of the prolificacy of his written word and the quality of his research, especially in using experimental animal surgery as a way to understand the pathophysiologic basis of surgical diseases. Most impressively, Hunter relied little on the theories of past authorities but rather on personal observations, with his fundamental pathologic studies first described in the renowned textbook *A Treatise on the Blood, Inflammation, and Gun-Shot Wounds* (1794). Ultimately, his voluminous research and clinical work resulted in a collection of more than 13,000 specimens, which became one of his most important legacies to the world of surgery. It represented a unique warehousing of separate organ systems, with comparisons of these systems, from the simplest animal or plant to humans, demonstrating the interaction of structure and function. For decades, Hunter's collection, housed in England's Royal College of Surgeons, remained the outstanding museum of comparative anatomy and pathology in the world. That was until a World War II Nazi bombing attack of London created a conflagration that destroyed most of Hunter's assemblage.

ANESTHESIA

Since time immemorial, the inability of surgeons to complete pain-free operations had been among the most terrifying of medical problems. In the preanesthetic era, surgeons were forced to be more concerned about the speed with which an operation was completed than with the clinical efficacy of their dissection. In a similar vein, patients refused or delayed surgical procedures for as long as possible to avoid the personal horror of experiencing the surgeon's knife. Analgesic, narcotic, and soporific agents such as hashish, mandrake, and opium had been put to use for thousands of years. However, the systematic operative invasion of body cavities and the inevitable progression of surgical history could not occur until an effective means of rendering a patient insensitive to pain was developed.

As anatomic knowledge and surgical techniques improved, the search for safe methods to prevent pain became more pressing. By the early 1830s, chloroform, ether, and nitrous oxide had been discovered and so-called laughing gas parties and ether frolics were in vogue, especially in America. Young people were amusing themselves with the pleasant side effects of these compounds as itinerant so-called professors of chemistry traveled to hamlets, towns, and cities to lecture on and demonstrate the exhilarating effects of these new gases. It soon became evident to various physicians and dentists that the pain-relieving qualities of ether and nitrous oxide could be applicable to surgical operations and tooth extraction. On October 16, 1846, William T. G. Morton (1819-1868), a Boston dentist, persuaded John Collins Warren (1778-1856), professor of surgery at the Massachusetts General Hospital, to let him administer sulfuric ether to a surgical patient from whom Warren went on to painlessly remove a small, congenital vascular tumor of the neck. After the operation, Warren, greatly impressed with the new discovery, uttered his famous words: "Gentlemen, this is no humbug."

Few medical discoveries have been so readily accepted as inhalational anesthesia. News of the momentous event spread rapidly throughout the United States and Europe, and a new era in the history of surgery had begun. Within a few months after the first public demonstration in Boston, ether was used in hospitals throughout the world. Yet no matter how much it contributed to the relief of pain during surgical operations and decreased the surgeon's angst, the discovery did not immediately further the scope of elective surgery. Such technical triumphs awaited the recognition and acceptance of antisepsis and asepsis. Anesthesia helped make the illusion of surgical cures more seductive, but it could not bring forth the final prerequisite: all-important hygienic reforms.

Still, by the mid-19th century, both doctors and patients were coming to hold surgery in relatively high regard for its pragmatic appeal, technologic virtuosity, and unambiguously measurable results. After all, surgery appeared to some a mystical craft. To be allowed to consensually cut into another human's body, to gaze at the depth of that person's suffering, and to excise the demon of disease seemed an awesome responsibility. Yet it was this very mysticism, long associated with religious overtones, that so fascinated the public and their own feared but inevitable date with a surgeon's knife. Surgeons had finally begun to view themselves as combining art and nature, essentially assisting nature in its continual process of destruction and rebuilding. This regard for the natural would spring from the eventual, though preternaturally slow, understanding and use of Joseph Lister's (1827-1912) techniques (Fig. 1-4).

Figure 1-4 Joseph Lister (1827-1912).

ANTISEPSIS, ASEPSIS, AND UNDERSTANDING THE NATURE OF INFECTION

In many respects, the recognition of antisepsis and asepsis was a more important event in the evolution of surgical history than the advent of inhalational anesthesia was. There was no arguing that deadening of pain permitted a surgical operation to be conducted in a more efficacious manner. Haste was no longer of prime concern. However, if anesthesia had never been conceived, a surgical procedure could still be performed, albeit with much difficulty. Such was not the case with listerism. Without antisepsis and asepsis, major surgical operations more than likely ended in death rather than just pain. Clearly, surgery needed both anesthesia and antisepsis, but in terms of overall importance, antisepsis proved to be of greater singular impact.

In the long evolution of world surgery, the contributions of several individuals stand out as being preeminent. Lister, an English surgeon, can be placed on such a select list because of his monumental efforts to introduce systematic, scientifically based antisepsis in the treatment of wounds and the performance of surgical operations. He pragmatically applied others' research into fermentation and microorganisms to the world of surgery by devising a means of preventing surgical infection and securing its adoption by a skeptical profession.

It was evident to Lister that a method of destroying bacteria by excessive heat could not be applied to a surgical patient. He turned, instead, to chemical antisepsis and, after experimenting with zinc chloride and the sulfites, decided on carbolic acid. By 1865, Lister was instilling pure carbolic acid into wounds and onto dressings. He would eventually make numerous modifications in the technique of dressings, the manner of applying and retaining them, and the choice of antiseptic solutions of varying concentrations. Although the carbolic acid spray remains the best remembered of his many contributions, it was eventually abandoned in favor of other germicidal substances. Lister not only used carbolic acid in the wound and on dressings but also went so far as to spray it in the atmosphere around the operative field and table. He did not emphasize hand scrubbing but merely dipped his fingers into a solution of phenol and corrosive sublimate. Lister was incorrectly convinced that scrubbing created crevices in the palms of the hands where bacteria would proliferate. A second important advance by Lister was the development of sterile absorbable sutures. He believed that much of the deep suppuration found in wounds was created by previously contaminated silk ligatures. Lister evolved a carbolized catgut suture that was better than any previously produced. He was able to cut the ends of the ligature short, thereby closing the wound tightly, and eliminate the necessity of bringing the ends of the suture out through the incision, a surgical practice that had persisted since the days of Paré.

The acceptance of listerism was an uneven and distinctly slow process, for many reasons. First, the various procedural changes that Lister made during the evolution of his methodology created confusion. Second, listerism, as a technical exercise, was complicated with the use of carbolic acid, an unpleasant and time-consuming nuisance. Third, various early attempts to use antisepsis in surgery had proved abject failures, with many leading surgeons unable to replicate Lister's generally good results. Finally and most important, acceptance of listerism depended entirely on an understanding and ultimate recognition of the veracity of the germ theory, a hypothesis that many practical-minded surgeons were loath to accept.

As a professional group, German-speaking surgeons would be the first to grasp the importance of bacteriology and the germ theory. Consequently, they were among the earliest to expand on Lister's message of antisepsis, with his spray being discarded in favor of boiling and use of the autoclave. The availability of heat sterilization engendered sterile aprons, drapes, instruments, and sutures. Similarly, the use of facemasks, gloves, hats, and operating gowns also naturally evolved. By the mid-1890s, less clumsy aseptic techniques had found their way into most European surgical amphitheaters and were approaching total acceptance by American surgeons. Any lingering doubts about the validity and significance of the momentous concepts that Lister had put forth were eliminated on the battlefields of World War I. There, the importance of just plain antisepsis became an invaluable lesson for scalpel bearers, whereas the exigencies of the battlefield helped bring about the final maturation and equitable standing of surgery and surgeons within the worldwide medical community.

X-RAYS

Especially prominent among other late 19th century discoveries that had an enormous impact on the evolution of surgery was research conducted by Wilhelm Roentgen (1845-1923), which led to his 1895 elucidation of x-rays. Having grown interested in the phosphorescence from metallic salts that were exposed to light, Roentgen made a chance observation when passing a current through a vacuum tube and noticed a greenish glow coming from a screen on a shelf 9 feet away. This strange effect continued after the current was turned off. He found that the screen had been painted with a phosphorescent substance. Proceeding with full experimental vigor, Roentgen soon realized that there were invisible rays capable of passing through solid objects made of wood, metal, and other materials. Most significant, these rays also penetrated the soft parts of the body in such a manner that the more dense bones of his hand were able to be revealed on a specially treated photographic plate. In a short time, numerous applications were developed as surgeons rapidly applied the new discovery to the diagnosis and location of fractures and dislocations and the removal of foreign bodies.

Figure 1-5 Theodor Billroth (1829-1894).

TURN OF THE 20TH CENTURY

By the late 1890s, the interactions of political, scientific, socioeconomic, and technical factors set the stage for what would become a spectacular showcasing of surgery's newfound prestige and accomplishments. Surgeons were finally wearing antiseptic-looking white coats. Patients and tables were draped in white, and basins for bathing instruments in bichloride solution abounded. Suddenly all was clean and tidy, with conduct of the surgical operation no longer a haphazard affair. This reformation would be successful not because surgeons had fundamentally changed but because medicine and its relationship to scientific inquiry had been irrevocably altered. Sectarianism and quackery, the consequences of earlier medical dogmatism, would no longer be tenable within the confines of scientific truth.

With all four fundamental clinical prerequisites in place by the turn of the century and highlighted with the emerging clinical triumphs of various English surgeons, including Robert Tait (1845-1899), William Macewen (1848-1924), and Frederick Treves (1853-1923); German-speaking surgeons, among whom were Theodor Billroth (1829-1894) (Fig. 1-5), Theodor Kocher (1841-1917) (Fig. 1-6), Friedrich Trendelenburg (1844-1924), and Johann von Mikulicz-Radecki (1850-1905); French surgeons, including Jules Peán (1830-1898), Just Lucas-Championière (1843-1913), and Marin-Theodore Tuffiér (1857-1929); the Italians, most notably Eduardo Bassini (1844-1924) and Antonio Ceci (1852-1920); and several American surgeons, exemplified by William Williams Keen (1837-1932), Nicholas Senn (1844-1908), and John Benjamin Murphy (1857-1916), scalpel wielders had essentially explored all cavities of the human body.

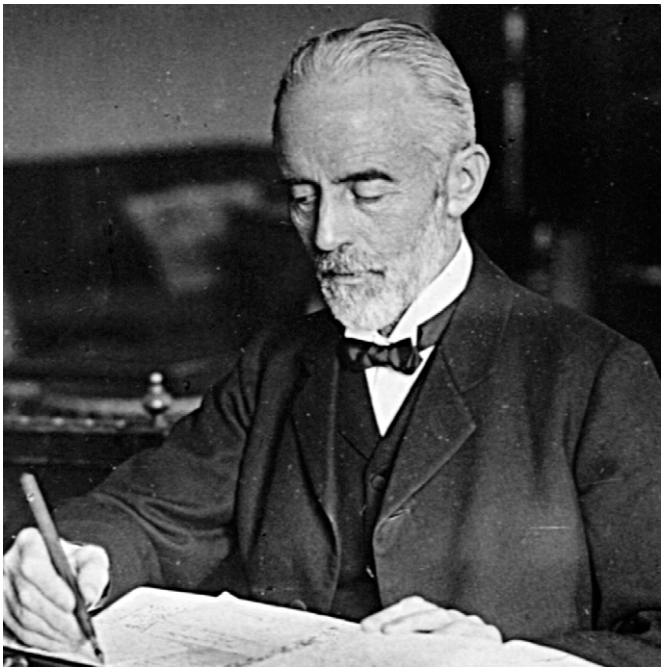


Figure 1-6 Theodor Kocher (1841-1917).

Nonetheless, surgeons retained a lingering sense of professional and social discomfort and continued to be pejoratively described by nouveau scientific physicians as *nonthinkers* who worked in little more than an inferior and crude manual craft.

It was becoming increasingly evident that research models, theoretical concepts, and valid clinical applica-

tions would be necessary to demonstrate the scientific basis of surgery to a wary public. The effort to devise new operative methods called for an even greater reliance on experimental surgery and absolute encouragement of it by all concerned parties. Most importantly, a scientific basis for therapeutic surgical recommendations—consisting of empirical data, collected and analyzed according to nationally and internationally accepted rules and set apart from individual authoritative assumptions—would have to be developed. In contrast to previously unexplainable doctrines, scientific research would triumph as the final arbiter between valid and invalid surgical therapies.

In turn, surgeons had no choice but to allay society's fear of the surgical unknown by presenting surgery as an accepted part of a newly established medical armamentarium. This would not be an easy task. The immediate consequences of surgical operations, such as discomfort and associated complications, were often of more concern to patients than was the positive knowledge that an operation could eliminate potentially devastating disease processes. Accordingly, the most consequential achievement by surgeons during the early 20th century was ensuring the social acceptability of surgery as a legitimate scientific endeavor and the surgical operation as a therapeutic necessity.

ASCENT OF SCIENTIFIC SURGERY

William Stewart Halsted (1852-1922) (Fig. 1-7), more than any other surgeon, set the scientific tone for this most important period in surgical history. He moved surgery from the melodramatics of the 19th century operating *theater* to the starkness and sterility of the modern operating *room,* commingled with the privacy and soberness of the research laboratory. As professor of surgery at the newly opened Johns Hopkins Hospital and School of Medicine, Halsted proved to be a complex personality, but the impact of this aloof and reticent man would become widespread. He introduced a new surgery and showed that research based on anatomic, pathologic, and physiologic principles and the use of animal experimentation made it possible to develop sophisticated operative procedures and perform them clinically with outstanding results. Halsted proved, to an often leery profession and public, that an unambiguous sequence could be constructed from the laboratory of basic surgical research to the clinical operating room. Most importantly, for surgery's own self-respect, he demonstrated during this turn-of-the-century renaissance in medical education that departments of surgery could command a faculty whose stature was equal in importance and prestige to that of other more academic or research-oriented fields such as anatomy, bacteriology, biochemistry, internal medicine, pathology, and physiology.

Figure 1-7 William Halsted (1852-1922).

As a single individual, Halsted developed and disseminated a different system of surgery so characteristic that it was referred to as a *school of surgery*. More to the point, Halsted's methods revolutionized the world of surgery and earned his work the epithet *halstedian principles*, which remains a widely acknowledged and accepted scientific imprimatur. Halsted subordinated technical brilliance and speed of dissection to a meticulous and safe, albeit sometimes slow performance. As a direct result, Halsted's effort did much to bring about surgery's self-sustaining transformation from therapeutic subservience to clinical necessity.

Despite his demeanor as a professional recluse, Halsted's clinical and research achievements were overwhelming in number and scope. His residency system of training surgeons was not merely the first such program of its kind; it was unique in its primary purpose. Above all other concerns, Halsted desired to establish a school of surgery that would eventually disseminate throughout the surgical world the principles and attributes that he considered sound and proper. His aim was to train able surgical teachers, not merely competent operating surgeons. There is little doubt that Halsted achieved his stated goal of producing "not only surgeons but surgeons of the highest type, men who will stimulate the first youth of our country to study surgery and to devote their energies and their lives to raising the standards of surgical science." So fundamental were his contributions that without them, surgery might never have fully developed and could have remained mired in a quasi-professional state.

The heroic and dangerous nature of surgery seemed appealing in less scientifically sophisticated times, but now, surgeons were courted for personal attributes beyond their unmitigated technical boldness. A trend toward hospital-based surgery was increasingly evident, owing in equal parts to new, technically demanding operations and to modern hospital physical structures

within which surgeons could work more effectively. The increasing complexity and effectiveness of aseptic surgery, the diagnostic necessity of the x-ray and clinical laboratory, the convenience of 24-hour nursing, and the availability of capable surgical residents living within a hospital were making the hospital operating room the most plausible and convenient place for a surgical operation to be performed.

It was obvious to both hospital superintendents and the whole of medicine that acute care institutions were becoming a necessity more for the surgeon than for the physician. As a consequence, increasing numbers of hospitals went to great lengths to supply their surgical staffs with the finest facilities in which to complete operations. For centuries, surgical operations had been performed under the illumination of sunlight or candles, or both. Now, however, electric lights installed in operating rooms offered a far more reliable and unwavering source of illumination. Surgery became a more proficient craft because surgical operations could be completed on stormy summer mornings, as well as on wet winter afternoons.

INTERNATIONALIZATION, SURGICAL SOCIETIES, AND JOURNALS

As the sophistication of surgery grew, internationalization became one of its underlying themes, with surgeons crossing the great oceans to visit and learn from one another. Halsted and Hermann Küttner (1870-1932), director of the surgical clinic in Breslau, Germany (now known as Wroclaw and located in southwestern Poland), instituted the first known official exchange of surgical residents in 1914. This experiment in surgical education was meant to underscore the true international spirit that had engulfed surgery. Halsted firmly believed that young surgeons achieved greater clinical maturity by observing the practice of surgery in other countries, as well as in their own.

An inevitable formation of national and international surgical societies and the emergence and development of periodicals devoted to surgical subjects proved to be important adjuncts to the professionalization process of surgery. For the most part, professional societies began as a method of providing mutual improvement via personal interaction with surgical peers and the publication of presented papers. Unlike surgeons of earlier centuries, who were known to closely guard so-called trade secrets, members of these new organizations were emphatic about publishing transactions of their meetings. In this way, not only would their surgical peers read of their clinical accomplishments, but a written record was also established for circulation throughout the world of medicine.

The first of these surgical societies was the Académie Royale de Chirurgie in Paris, with its *Mémoires* appearing sporadically from 1743 through 1838. Of 19th century associations, the most prominent published proceedings were the *Mémoires* and *Bulletins* of the Société de Chirurgie of Paris (1847), the *Verhandlungen* of the Deutsche Gesellschaft für Chirurgie (1872), and the *Transactions* of the American Surgical Association (1883). No surgical association that published professional reports existed in 19th century Great Britain, and the Royal Colleges of Surgeons of England, Ireland, and Scotland never undertook such projects. Although textbooks, monographs, and treatises had always been the mainstay of medical writing, the introduction of monthly journals, including August Richter's (1742-1812) *Chirurgische Bibliothek* (1771), Joseph Malgaigne's (1806-1865) *Journal de Chirurgie* (1843), Bernard Langenbeck's (1810-1887) *Archiv für Klinische Chirurgie* (1860), and Lewis Pilcher's (1844-1917) *Annals of Surgery* (1885), had a tremendous impact on updating and continuing the education of surgeons.

WORLD WAR I

Austria-Hungary and Germany continued as the dominating forces in world surgery until World War I. However, results of the conflict proved disastrous to the central powers (Austria-Hungary, Bulgaria, Germany, and the Ottoman Empire), especially to German-speaking surgeons. Europe took on a new social and political look, with the demise of Germany's status as the world leader in surgery a sad but foregone conclusion. As with most armed conflicts, because of the massive human toll, especially battlefield injuries, tremendous strides were made in multiple areas of surgery. Undoubtedly, the greatest surgical achievement was in the treatment of wound infection. Trench warfare in soil contaminated by decades of cultivation and animal manure made every wounded soldier a potential carrier of any number of pathogenic bacilli. On the battlefront, sepsis was inevitable. Most attempts to maintain aseptic technique proved inadequate, but the treatment of infected wounds by antisepsis was becoming a pragmatic reality.

Surgeons experimented with numerous antiseptic solutions and various types of surgical dressing. A principle of wound treatment entailing débridement and irrigation eventually evolved. Henry Dakin (1880-1952), an English chemist, and Alexis Carrel (1873-1944) (Fig. 1-8), the Nobel prize–winning French American surgeon, were the principal protagonists in the development of this extensive system of wound management. In addition to successes in wound sterility, surgical advances were made in the use of x-rays in the diagnosis of battlefield injuries, and remarkable operative ingenuity was evident in reconstructive facial surgery and the treatment of fractures resulting from gunshot wounds.

AMERICAN COLLEGE OF SURGEONS

For American surgeons, the years just before World War I were a time of active coalescence into various social and educational organizations. The most important and influential of these societies was the American College of Surgeons, founded by Franklin Martin (1857-1935), a Chicago-based gynecologist, in 1913. Patterned after the

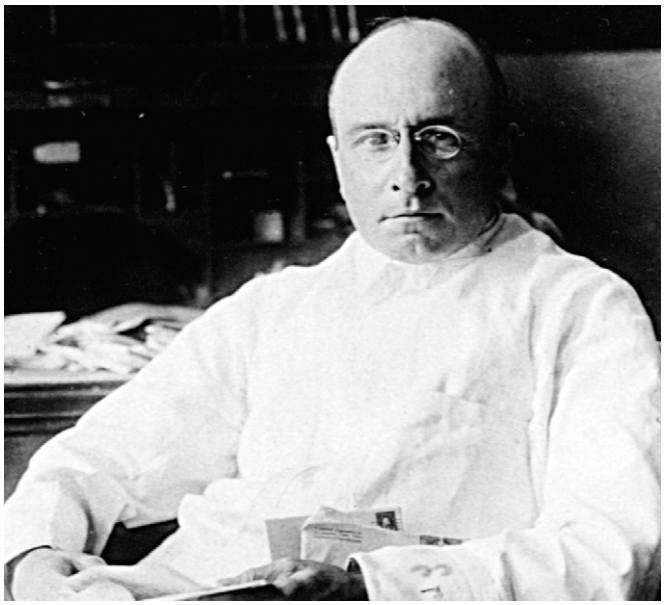


Figure 1-8 Alexis Carrel (1873-1944).

Royal Colleges of Surgeons of England, Ireland, and Scotland, the American College of Surgeons established professional, ethical, and moral standards for every graduate in medicine who practiced in surgery and conferred the designation *Fellow of the American College of Surgeons* (FACS) on its members. From the outset, its primary aim was the continuing education of surgical practitioners. Accordingly, the requirements for fellowship were always related to the educational opportunities of the period. In 1914, an applicant had to be a licensed graduate of medicine, receive the backing of three fellows, and be endorsed by the local credentials committee.

In view of the stipulated peer recommendations, many practitioners, realistically or not, viewed the American College of Surgeons as an elitist organization. With an obvious so-called blackball system built into the membership requirements, there was a difficult-to-deny belief that many surgeons who were immigrants, females, or members of particular religious and racial minorities were granted fellowships sparingly. Such inherent bias, in addition to questionable accusations of fee splitting along with unbridled contempt of certain surgeons' business practices, resulted in some very prominent American surgeons never being permitted the privilege of membership.

The 1920s and beyond proved to be a prosperous time for American society and its surgeons. After all, the history of world surgery in the 20th century is more a tale of American triumphs than it ever was in the 18th or 19th centuries. Physicians' incomes dramatically increased and surgeons' prestige, aided by the ever-mounting successes of medical science, became securely established in American culture. Still, a noticeable lack of standards and regulations in surgical specialty practice became a serious concern to leaders in the profession. The difficulties of World War I had greatly accentuated this realistic need for specialty standards when many of the physicians who were self-proclaimed surgical specialists were found to be unqualified by military examining boards. In ophthalmology, for example, more than 50% of tested individuals were deemed unfit to treat diseases of the eye.

It was an unmistakable reality that there were no established criteria with which to distinguish a well-qualified ophthalmologist from an upstart optometrist or to clarify the differences in clinical expertise between a well-trained, full-time ophthalmologic specialist and an inadequately trained, part-time general practitioner/ophthalmologist. In recognition of the gravity of the situation, the self-patrolling concept of a professional examining board, sponsored by leading voluntary ophthalmologic organizations, was proposed as a mechanism for certifying competency. In 1916, uniform standards and regulations were set forth in the form of minimal educational requirements and written and oral examinations, and the American Board for Ophthalmic Examinations, the country's first, was formally incorporated. By 1940, six additional surgical specialty boards were established, including orthopedic (1934), colon and rectal (1934), urologic (1935), plastic (1937), surgical (1937), and neurologic (1940).

As order was introduced into surgical specialty training and the process of certification matured, it was apparent that the continued growth of residency programs carried important implications for the future structure of medical practice and the social relationship of medicine to overall society. Professional power had been consolidated, and specialization, which had been evolving since the time of the Civil War, was now recognized as an essential, if not integral part of modern medicine. Although the creation of surgical specialty boards was justified under the broad imprimatur of raising the educational status and evaluating the clinical competency of specialists, board certification undeniably began to restrict entry into the specialties.

As the specialties evolved, the political influence and cultural authority enjoyed by the profession of surgery were growing. This socioeconomic strength was most prominently expressed in reform efforts directed toward the modernization and standardization of America's hospital system. Any vestiges of so-called kitchen surgery had essentially disappeared, and other than numerous small private hospitals predominantly constructed by surgeons for their personal use, the only facilities where major surgery could be adequately conducted and postoperative patients appropriately cared for were the well-equipped and physically impressive modern hospitals. For this reason, the American College of Surgeons and its expanding list of fellows had a strong motive to ensure that America's hospital system was as up to date and efficient as possible.

On an international level, surgeons were confronted with the lack of any formal organizational body. Not until the International College of Surgeons was founded in 1935 in Geneva would such a society exist. At its inception, this organization was intended to serve as a liaison to the existing colleges and surgical societies in the

various countries of the world. However, its goals of elevating the art and science of surgery, creating greater understanding among the surgeons of the world, and affording a means of international postgraduate study never came to full fruition, in part because the American College of Surgeons adamantly opposed the establishment—and continues to do so—of a viable American chapter of the International College of Surgeons.

WOMEN SURGEONS

One of the many overlooked areas of surgical history concerns the involvement of women. Until recent times, women's options for obtaining advanced surgical training were severely restricted. The major reason was that through the mid-20th century, only a handful of women had performed enough surgery to become skilled mentors. Without role models and with limited access to hospital positions, the ability of the few practicing female physicians to specialize in surgery seemed an impossibility. Consequently, women surgeons were forced to use different career strategies than men and to have more divergent goals of personal success to achieve professional satisfaction. Despite these difficulties and through the determination and aid of several enlightened male surgeons, most notably William Byford (1817-1890) of Chicago and William Keen of Philadelphia, a small cadre of female surgeons did exist in late 19th century America. Mary Dixon Jones (1828-1908), Emmeline Horton Cleveland (1829-1878), Mary Harris Thompson (1829-1895), Anna Elizabeth Broomall (1847-1931), and Marie Mergler (1851-1901) would act as a nidus toward greater equality of the genders in 20th century surgery.

AFRICAN AMERICAN SURGEONS

There is little disputing the fact that both gender and racial bias have influenced the evolution of surgery. Every aspect of society is affected by such discrimination, and African Americans, like women, were innocent victims of injustices that forced them into never-ending struggles to attain competency in surgery. As early as 1868, a department of surgery was established at Howard University. However, the first three chairmen were all white Anglo-Saxon Protestants. Not until Austin Curtis was appointed professor of surgery in 1928 did the department have its first African American head. Like all black physicians of his era, he was forced to train at so-called Negro hospitals, in Curtis' case Provident Hospital in Chicago, where he came under the tutelage of Daniel Hale Williams (1858-1931), the most influential and highly regarded of early African American surgeons. In 1897, Williams received considerable notoriety when he reported successful suturing of the pericardium for a stab wound of the heart.

With little likelihood of obtaining membership in the American Medical Association or its related societies, in 1895 African American physicians joined together to form the National Medical Association. Black surgeons identified an even more specific need when the Surgical Section of the National Medical Association was opened in 1906. These National Medical Association surgical clinics, which preceded the Clinical Congress of Surgeons of North America, the forerunner to the annual congress of the American College of Surgeons, by almost half a decade, represented the earliest instances of organized so-called show-me surgical education in the United States.

Figure 1-9 Charles Drew (1904-1950).

Admittance to surgical societies and attainment of specialty certification were important social and psychological accomplishments for early African American surgeons. When Daniel Williams was named a Fellow of the American College of Surgeons in 1913, the news spread rapidly throughout the African American surgical community. Still, African American surgeons' fellowship applications were often acted on rather slowly, which suggested that denials based on race were clandestinely conducted throughout much of the country. As late as the mid-1940s, Charles Drew (1904-1950) (Fig. 1-9), chairman of the department of surgery at Howard University School of Medicine, acknowledged that he refused to accept membership in the American College of Surgeons because this so-called nationally representative surgical society had, in his opinion, not yet begun to freely accept capable and well-qualified African American surgeons. Claude H. Organ, Jr. (1926-2005) (Fig. 1-10), was a distinguished editor, educator, and historian. Among his books, the two-volume *A Century of Black Surgeons: The U.S.A. Experience* and the authoritative *Noteworthy Publications by African-American Surgeons* underscored the numerous contributions made by African American surgeons to the nation's health care system. In addition,

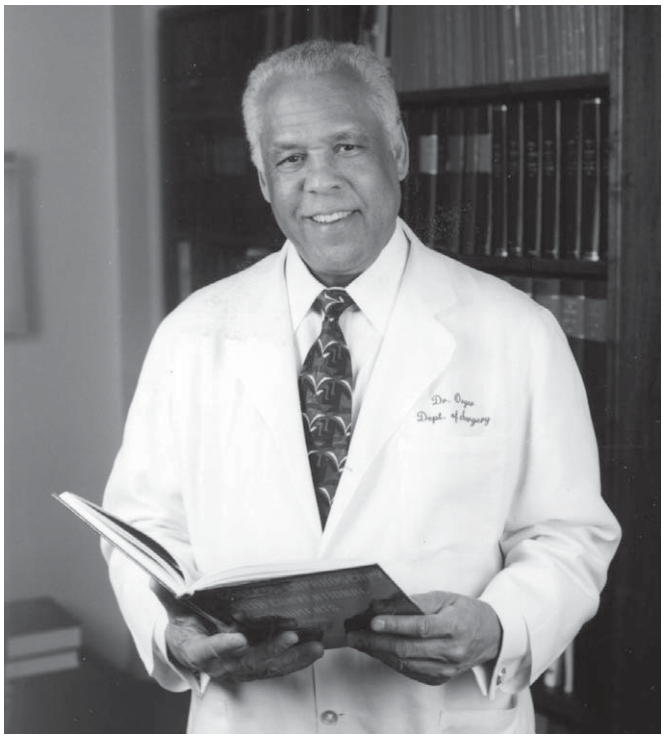


Figure 1-10 **Claude H. Organ, Jr. (1926-2005).** (Courtesy of the American College of Surgeons and Dr. James C. Thompson.)

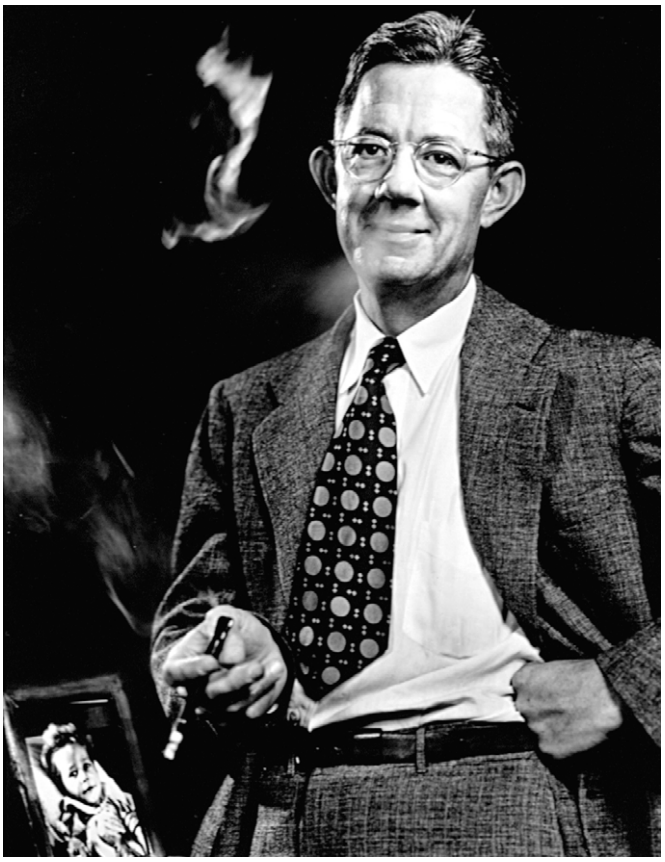


Figure 1-11 **Alfred Blalock (1899-1964).**

as the long-standing editor-in-chief of *Archives of Surgery*, as well as serving as president of the American College of Surgeons and chairman of the American Board of Surgery, Organ wielded enormous influence over the direction of American surgery.

MODERN ERA

Despite the global economic depression in the aftermath of World War I, the 1920s and 1930s signaled the ascent of American surgery to its current position of international leadership. Highlighted by educational reforms in its medical schools, Halsted's redefinition of surgical residency programs, and the growth of surgical specialties, the stage was set for the blossoming of scientific surgery. Basic surgical research became an established reality as George Crile (1864-1943), Alfred Blalock (1899-1964) (Fig. 1-11), Dallas Phemister (1882-1951), and Charles Huggins (1901-1997) became world-renowned surgeon-scientists.

Much as the ascendancy of the surgeon-scientist brought about changes in the way in which the public and the profession viewed surgical research, the introduction of increasingly sophisticated technologies had an enormous impact on the practice of surgery. Throughout the evolution of surgery, the practice of surgery—the art, the craft, and finally, the science of working with one's hands—had largely been defined by its tools. From the crude flint instruments of ancient peoples, through the simple tonsillotomes and lithotrites of the 19th century, up to the increasingly complex surgical instruments developed in the 20th century, new and improved instruments usually led to a better surgical result. Progress in surgical instrumentation and surgical techniques went hand in hand.

Surgical techniques would, of course, become more sophisticated with the passage of time, but by the conclusion of World War II, essentially all organs and areas of the body had been fully explored. In fact, within a short half-century the domain of surgery had become so well established that the profession's foundation of basic operative procedures was already completed. As a consequence, there were few technical surgical mysteries left. What surgery now needed to sustain its continued growth was the ability to diagnose surgical diseases at earlier stages, to locate malignant growths while they remained small, and to have more effective postoperative treatment so that patients could survive ever more technically complex operations. Such thinking was exemplified by the introduction in 1924 of cholecystography by Evarts Graham (1883-1957) and Warren Cole (1898-1990). In this case, an emerging scientific technology introduced new possibilities into surgical practice that were not necessarily related solely to improvements in technique. To the surgeon, the discovery and application of cholecystography proved most important, not only because it brought about more accurate diagnoses of cholecystitis but also because it created an influx of surgical patients where

few had previously existed. If surgery was to grow, large numbers of individuals with surgical diseases were needed.

It was an exciting era for surgeons, with important clinical advances being made both in the operating room and in the basic science laboratory. Among the most notable highlights were the introduction in 1935 of pancreaticoduodenectomy for cancer of the pancreas by Allen Oldfather Whipple (1881-1963) and a report in 1943 on vagotomy for operative treatment of peptic ulcer disease by Lester Dragstedt (1893-1976). Frank Lahey (1880-1953) stressed the importance of identifying the recurrent laryngeal nerve during the course of thyroid surgery; Owen Wangensteen (1898-1981) successfully decompressed mechanical bowel obstructions by using a newly devised suction apparatus in 1932; George Vaughan (1859-1948) successfully ligated the abdominal aorta for aneurysmal disease in 1921; Max Peet (1885-1949) presented his splanchnic resection for hypertension in 1935; Walter Dandy (1886-1946) performed intracranial section of various cranial nerves in the 1920s; Walter Freeman (1895-1972) described prefrontal lobotomy as a means of treating various mental illnesses in 1936; Harvey Cushing (1869-1939) introduced electrocoagulation in neurosurgery in 1928; Marius Smith-Petersen (1886-1953) described a flanged nail for pinning a fracture of the neck of the femur in 1931 and introduced Vitallium cup arthroplasty in 1939; Vilray Blair (1871-1955) and James Brown (1899-1971) popularized the use of split-skin grafts to cover large areas of granulating wounds; Earl Padgett (1893-1946) devised an operative dermatome that allowed calibration of the thickness of skin grafts in 1939; Elliott Cutler (1888-1947) performed a successful section of the mitral valve for relief of mitral stenosis in 1923; Evarts Graham completed the first successful removal of an entire lung for cancer in 1933; Claude Beck (1894-1971) implanted pectoral muscle into the pericardium and attached a pedicled omental graft to the surface of the heart, thus providing collateral circulation to that organ, in 1935; Robert Gross (1905-1988) reported the first successful ligation of a patent arterial duct in 1939 and resection for coarctation of the aorta with direct anastomosis of the remaining ends in 1945; and John Alexander (1891-1954) resected a saccular aneurysm of the thoracic aorta in 1944.

With such a wide variety of technically complex surgical operations now possible, it had clearly become impossible for any single surgeon to master all the manual skills as well as the pathophysiologic knowledge necessary to perform such cases. Therefore, by the middle of the century, a consolidation of professional power inherent in the movement toward specialization, with numerous individuals restricting their surgical practice to one highly structured field, had become among the most significant and dominating events in 20th century surgery. Ironically, the United States, which had been much slower than European countries to recognize surgeons as a distinct group of clinicians separate from physicians, would now spearhead this move toward surgical specialization with great alacrity. Clearly, the course of surgical fragmentation into specialties and subspecialties was gathering tremendous speed as the dark clouds of World War II settled over the globe. The socioeconomic and political ramifications of this war would bring about a fundamental change in the way that surgeons viewed themselves and their interactions with the society in which they lived and worked.

LAST HALF OF THE 20TH CENTURY

The decades of economic expansion after World War II had a dramatic impact on surgery's scale, particularly in the United States. It was as though being victorious in battle permitted medicine to become big business overnight, with the single-minded pursuit of health care rapidly transformed into society's largest growth industry. Spacious hospital complexes were built that not only represented the scientific advancement of the healing arts but also vividly demonstrated the strength of American's postwar socioeconomic boom. Society was willing to give surgical science unprecedented recognition as a prized national asset.

The overwhelming impact of World War II on surgery was the sudden expansion of the profession and the beginnings of an extensive distribution of surgeons throughout the country. Many of these individuals, newly baptized to the rigors of technically complex trauma operations, became leaders in the construction and improvement of hospitals, multispecialty clinics, and surgical facilities in their hometowns. Large urban and community hospitals established surgical education and training programs and found it a relatively easy matter to attract interns and residents. For the first time, residency programs in general surgery were rivaled in growth and educational sophistication by those in all the special fields of surgery. These changes served as fodder for further increases in the number of students entering surgery. Not only would surgeons command the highest salaries, but society was also enamored of the drama of the operating room. Television series, movies, novels, and the more-than-occasional live performance of a heart operation on network broadcast beckoned the lay individual.

Despite lay approval, success and acceptability in the biomedical sciences are sometimes difficult to determine, but one measure of both in recent times has been awarding of the Nobel Prize in medicine and physiology. Society's continued approbation of surgery's accomplishments is seen in the naming of nine surgeons as Nobel laureates (Table 1-1).

CARDIAC SURGERY AND ORGAN TRANSPLANTATION

Two clinical developments truly epitomized the magnificence of post–World War II surgery and concurrently fascinated the public: the maturation of cardiac surgery as a new surgical specialty and the emergence of organ transplantation. Together, they would stand as signposts along the new surgical highway. Fascination with the

Table 1-1 Surgeons Named Nobel Laureates in Medicine and Physiology

SURGEON	COUNTRY	FIELD (YEAR OF AWARD)
Theodor Kocher (1841-1917)	Switzerland	Thyroid disease (1909)
Allvar Gullstrand (1862-1930)	Sweden	Ocular dioptrics (1911)
Alexis Carrel (1873-1944)	France and United States	Vascular surgery (1912)
Robert Bárány (1876-1936)	Austria	Vestibular disease (1914)
Frederick Banting (1891-1941)	Canada	Insulin (1922)
Walter Hess (1881-1973)	Switzerland	Midbrain physiology (1949)
Werner Forssmann (1904-1979)	Germany	Cardiac catheterization (1956)
Charles Huggins (1901-1997)	United States	Oncology (1966)
Joseph Murray (1919-)	United States	Organ transplantation (1990)

heart goes far beyond that of clinical medicine. From the historical perspective of art, customs, literature, philosophy, religion, and science, the heart has represented the seat of the soul and the wellspring of life itself. Such reverence also meant that this noble organ was long considered a surgical untouchable. Whereas the late 19th and 20th centuries witnessed a steady march of surgical triumphs in opening successive cavities of the body, the final achievement awaited the perfection of methods for surgical operations in the thoracic space.

Such a scientific and technologic accomplishment can be traced back to the repair of cardiac stab wounds by direct suture and the earliest attempts at fixing faulty heart valves. As triumphant as Luther Hill's (1862-1946) first known successful suture of a wound that penetrated a cardiac chamber was in 1902, it would not be until the 1940s that the development of safe intrapleural surgery could be counted on as something other than an occasional event. During World War II, Dwight Harken (1910-1993) gained extensive battlefield experience in removing bullets and shrapnel in or in relation to the heart and great vessels without a single fatality. Building on his wartime experience, Harken and other pioneering surgeons, including Charles Bailey (1910-1993) of Philadelphia and Russell Brock (1903-1980) of London, proceeded to expand intracardiac surgery by developing operations for the relief of mitral valve stenosis. The procedure was progressively refined and evolved into the open commissurotomy repair used today.

Despite mounting clinical successes, surgeons who operated on the heart had to contend not only with the quagmire of blood flowing through an area where difficult dissection was taking place but also with the unrelenting to-and-fro movement of a beating heart. Technically complex cardiac repair procedures could not be developed further until these problems were solved. John Gibbon (1903-1973) (Fig. 1-12) addressed this enigma by devising a machine that would take on the work of the heart and lungs while the patient was under anesthesia, in essence pumping oxygen-rich blood through the circulatory system while bypassing the heart so that the organ could be operated on at leisure. The first successful open heart operation in 1953, conducted with the use of a heart-lung machine, was a momentous surgical contribution. Through single-mindedness of purpose, Gibbon's research paved the way for all future cardiac surgery, including procedures for correction of congenital heart defects, repair of heart valves, and transplantation of the heart.

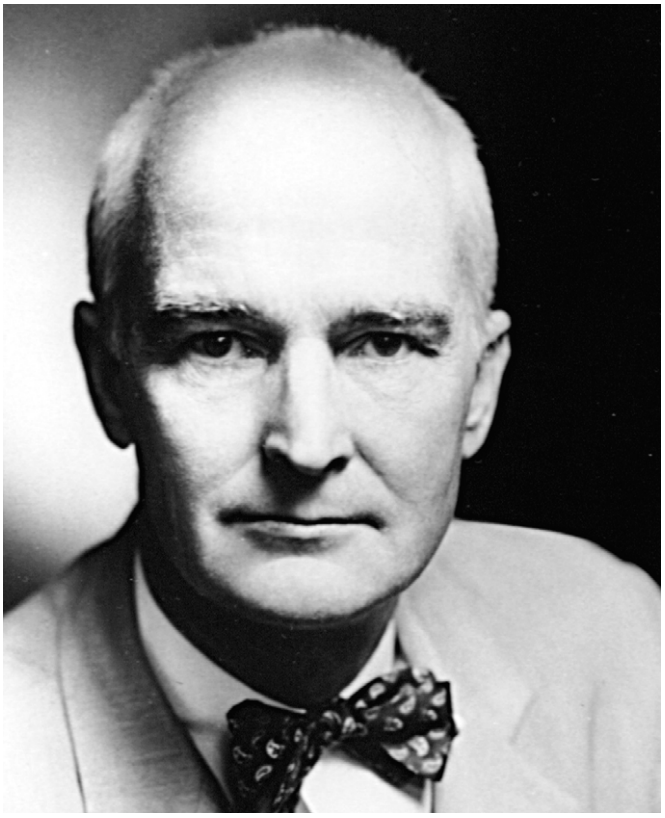


Figure 1-12 John Gibbon (1903-1973).

Since time immemorial, the focus of surgery was mostly on excision and repair. However, beginning in the 20th century, the opposite end of the surgical spectrum—reconstruction and transplantation—became realities. Nineteenth century experience had shown that skin and bone tissues could be autotransplanted from one site to another in the same patient. It would take the horrendous and mutilating injuries of World War I to decisively

advance skin transplants and legitimize the concept of surgery as a method of reconstruction. With Harold Gillies (1882-1960) of England and America's Vilray Blair establishing military-based plastic surgery units to deal with complex maxillofacial injuries, a turning point in the way in which society viewed surgery's raison d'être occurred. Now, not only would surgeons enhance nature's healing powers, but they could also dramatically alter what had previously been little more than one's physical foregone conclusion. For example, Hippolyte Morestin (1869-1919) described a method of mammaplasty in 1902. John Staige Davis (1872-1946) of Baltimore popularized a manner of splinting skin grafts and later wrote the first comprehensive textbook on this new specialty, *Plastic Surgery: Its Principles and Practice* (1919). Immediately after the war, Blair would go on to establish the first separate plastic surgery service in a civilian institution at Barnes Hospital in St. Louis. Vladimir Filatov (1875-1956) of Odessa, Russia, used a tubed pedicle flap in 1916, and in the following year, Gillies introduced a similar technique.

What about the replacement of damaged or diseased organs? After all, even at the midpoint of the century, the very thought of successfully transplanting worn-out or unhealthy body parts verged on scientific fantasy. At the beginning of the 20th century, Alexis Carrel developed revolutionary new suturing techniques to anastomose the smallest of blood vessels. Using his surgical élan on experimental animals, Carrel began to transplant kidneys, hearts, and spleens. Technically, his research was a success, but some unknown biologic process always led to rejection of the transplanted organ and death of the animal. By the middle of the century, medical researchers had begun to clarify the presence of underlying defensive immune reactions and the necessity of creating immunosuppression as a method to allow the host to accept the foreign transplant. Using high-powered immunosuppressant drugs and other modern modalities, kidney transplantation soon blazed the way, and it was not long before a slew of organs and even whole hands were being replaced.

POLITICAL AND SOCIOECONOMIC INFLUENCES

Despite the 1950s and 1960s witnessing some of the most magnificent advances in the history of surgery, by the 1970s, political and socioeconomic influences were starting to overshadow many of the clinical triumphs. It was the beginning of a schizophrenic existence for surgeons in that complex and dramatic lifesaving operations were completed to innumerable accolades, while concurrently, public criticism of the economics of medicine, in particular, high-priced surgical practice, portrayed the scalpel holder as an acquisitive, financially driven, selfish individual. This was in stark contrast to the relatively selfless and sanctified image of the surgeon before the growth of specialty work and the introduction of government involvement in health care delivery.

Although they are philosophically inconsistent, the dramatic and theatrical features of surgery that make surgeons heroes from one perspective and symbols of corruption, mendacity, and greed from the opposite point of view are the very reasons why society demands so much of its surgeons. There is the precise and definitive nature of surgical intervention, the expectation of success that surrounds an operation, the short time frame in which outcomes are realized, the high income levels of most surgeons, and the almost insatiable inquisitiveness of lay individuals concerning all aspects of the act of consensually cutting into another human's flesh. These phenomena, ever more sensitized in an age of mass media and instantaneous telecommunication, make surgeons seem more accountable than their medical colleagues and, simultaneously, symbolic of the best and the worst in medicine. In ways previously unimaginable, this vast social transformation of surgery controls the fate of the individual practitioner in the present era to a much greater extent than surgeons as a collective force are able to control it by their attempts to direct their own profession.

20TH CENTURY SURGICAL HIGHLIGHTS

Among the difficulties in studying 20th century surgery is the abundance of famous names and important written contributions—so much so that it becomes a difficult and invidious task to attempt any rational selection of representative personalities along with their significant journal or book-length writings. Although many justly famous names might be missing, the following description of surgical advances is intended to chronologically highlight some of the stunning clinical achievements of the past century.

In 1900, the German surgeon Hermann Pfannenstiel (1862-1909) described his technique for a suprapubic surgical incision. That same year, William Mayo (1861-1939) presented his results on partial gastrectomy before the American Surgical Association. The treatment of breast cancer was radically altered when George Beatson (1848-1933), professor of surgery in Glasgow, Scotland, proposed oophorectomy and the administration of thyroid extract as a possible cure (1901). John Finney (1863-1942) of The Johns Hopkins Hospital authored a paper on a new method of gastroduodenostomy, or widened pyloroplasty (1903). In Germany, Fedor Krause (1856-1937) was writing about total cystectomy and bilateral ureterosigmoidostomy. In 1905, Hugh Hampton Young (1870-1945) of Baltimore was presenting early studies of his radical prostatectomy for carcinoma. William Handley (1872-1962) was surgeon of the Middlesex Hospital in London when he authored *Cancer of the Breast and Its Treatment* (1906). In that work he advanced the theory that in breast cancer, metastasis is due to extension along lymphatic vessels and not to dissemination via the bloodstream. That same year, José Goyanes (1876-1964) of Madrid used vein grafts to restore arterial flow. William Miles (1869-1947) of England first wrote about his technique of abdominoperineal resection in 1908, the same year that Friedrich Trendelenburg (1844-1924) attempted pulmonary embolectomy. Three years later, Martin Kirschner (1879-1942) of Germany described a wire for skeletal traction and for stabilization of bone fragments or joint

immobilization. Donald Balfour (1882-1963) of the Mayo Clinic provided the initial account of his important operation for resection of the sigmoid colon, as did William Mayo for his radical operation for carcinoma of the rectum in 1910.

In 1911, Fred Albee (1876-1945) of New York City began to use living bone grafts as internal splints. Wilhelm Ramstedt (1867-1963), a German surgeon, described a pyloromyotomy (1912) at the same time that Pierre Fredet (1870-1946) was reporting a similar operation. In 1913, Henry Janeway (1873-1921) of New York City developed a technique for gastrostomy in which he wrapped the anterior wall of the stomach around a catheter and sutured it in place, thereby establishing a permanent fistula. Hans Finsterer (1877-1955), professor of surgery in Vienna, improved on Franz von Hofmeister's (1867-1926) description of a partial gastrectomy with closure of a portion of the lesser curvature and retrocolic anastomosis of the remainder of the stomach to the jejunum (1918). Thomas Dunhill (1876-1957) of London was a pioneer in thyroid surgery, especially in his operation for exophthalmic goiter (1919). William Gallie (1882-1959) of Canada used sutures fashioned from the fascia lata in herniorrhaphy (1923). Barney Brooks (1884-1952), professor of surgery at Vanderbilt University in Nashville, Tennessee, initially introduced clinical angiography and femoral arteriography in 1924. Five years later, Reynaldo dos Santos (1880-1970), a Portuguese urologist, reported the first translumbar aortogram. Cecil Joll (1885-1945), professor of surgery in London, fully described the treatment of thyrotoxicosis by means of subtotal thyroidectomy in the 1930s.

In 1931, George Cheatle (1865-1951), professor of surgery in London, and Max Cutler (1899-1984), a surgeon from New York City, published their important treatise *Tumours of the Breast*. In that same year, Cutler detailed his systemic use of ovarian hormone in the treatment of chronic mastitis. Around the same time, Ernst Sauerbruch (1875-1951) of Germany completed the first successful surgical intervention for cardiac aneurysm, and his countryman Rudolph Nissen (1896-1981) removed an entire bronchiectatic lung. Geoffrey Keynes (1887-1982) of St. Bartholomew's Hospital in England articulated the basis for the opposition to radical mastectomy and his favoring of radium treatment in breast cancer (1932). The Irish surgeon Arnold Henry (1886-1962) devised an operative approach for femoral hernia in 1936. Earl Shouldice (1891-1965) of Toronto first began to experiment with a groin hernia repair based on overlapping layers brought together by a continuous wire suture during the 1930s. René Leriche (1879-1955) proposed an arteriectomy for arterial thrombosis in 1937 and, later, periarterial sympathectomy to improve arterial flow. Leriche also enunciated a syndrome of aortoiliac occlusive disease in 1940. In 1939, Edward Churchill (1895-1972) of the Massachusetts General Hospital performed a segmental pneumonectomy for bronchiectasis. Charles Huggins (1901-1997) (Fig. 1-13), a pioneer in endocrine therapy for cancer, found that antiandrogenic treatment consisting of orchiectomy or the administration of estrogens could produce long-term regression in patients with advanced prostatic cancer. These observations formed the basis for the current treatment of prostate and breast cancer by hormonal manipulation; Dr. Huggins was awarded the Nobel Prize in 1966 for these monumental discoveries. Clarence Crafoord (1899-1984) pioneered his surgical treatment of coarctation of the aorta in 1945. The following year, Willis Potts (1895-1968) completed an anastomosis of the aorta to a pulmonary vein for certain types of congenital heart disease. Chester McVay (1911-1987) popularized a repair of groin hernias based on the pectineal ligament in 1948. Working at Georgetown University Medical Center in Washington, DC, Charles Hufnagel (1916-1989) designed and inserted the first workable prosthetic heart valve in a man (1951). That same year, Charles Dubost (1914-1991) of Paris performed the first successful resection of an abdominal aortic aneurysm and insertion of a homologous graft. Robert Zollinger (1903-1994) and Edwin Ellison (1918-1970) first described their eponymic polyendocrine adenomatosis in 1955. The following year, Donald Murray (1894-1976) completed the first successful aortic valve homograft. At the same time, John Merrill (1917-1986) was performing the world's first successful homotransplantation of the human kidney between identical twin brothers. Francis D. Moore (1913-2001) (Fig. 1-14) defined objectives of metabolism in surgical patients and in 1959 published his widely quoted book *Metabolic Care of the Surgical Patient*. Moore was also a driving force in the field of transplantation and pioneered the technique of using radioactive isotopes to locate abscesses and tumors. In the 1960s, Jonathan E. Rhoads (1907-2002) (Fig. 1-15), in collaboration with colleagues Harry Vars and Stan Dudrick, described the technique of total parenteral nutrition, which has become an important and lifesaving treatment in the management of a critically ill patient who cannot tolerate standard enteral feedings. James D. Hardy (1918-2003), at the University of Mississippi, performed the first lung (1963) and heart (1964) transplants in a human.

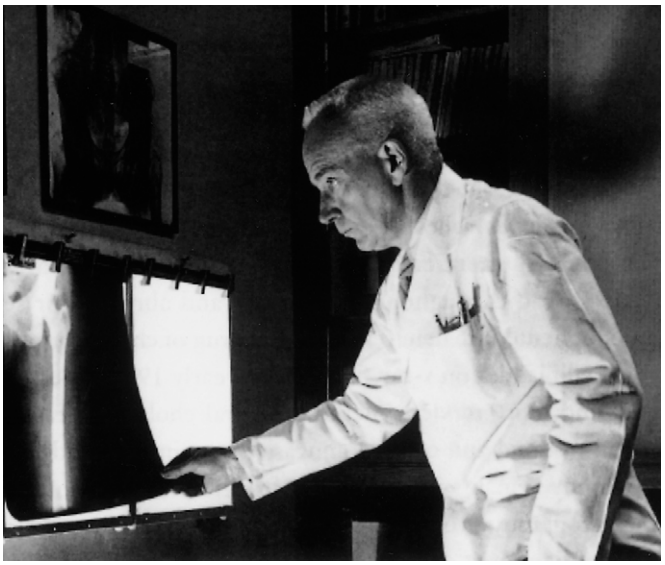


Figure 1-13 Charles Huggins (1901-1997). (Used with permission from the University of Chicago Hospitals.)

Figure 1-14 Francis D. Moore (1913-2001).

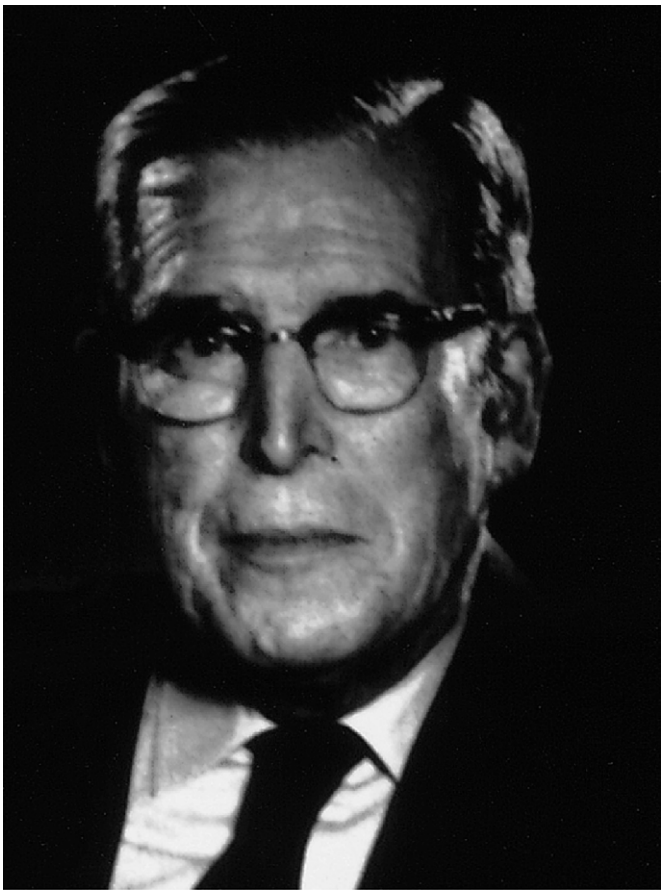


Figure 1-15 **Jonathan Rhoads (1907-2002).** (Courtesy of James C. Thompson, MD.)

FUTURE TRENDS

Throughout most of its evolution, the practice of surgery has been largely defined by its tools and the manual aspects of the craft. The last decades of the 20th century saw unprecedented progress in the development of new instrumentation and imaging techniques. These refinements have not come without noticeable social and economic cost. Advancement will assuredly continue, for if the study of surgical history offers any lesson, it is that progress can always be expected, at least relative to technology. There will be more sophisticated surgical operations with better results. Eventually, automation may even robotize the surgeon's hand for certain procedures. Still, the surgical sciences will always retain their historical roots as fundamentally a manually based art and craft.

In many respects, the surgeon's most difficult future challenges are not in the clinical realm but instead in better understanding the socioeconomic forces that affect the practice of surgery and in learning how to effectively manage them. Many splendid schools of surgery now exist in virtually every major industrialized city, but none can lay claim to dominance in all the disciplines that make up surgery. Likewise, the presence of authoritative individual personalities who help guide surgery is more unusual today than in previous times. National aims and socioeconomic status have become overwhelming factors in securing and shepherding the future growth of surgery worldwide. In light of an understanding of the intricacies of surgical history, it seems an unenviable and obviously impossible task to predict what will happen in the future. In 1874, John Erichsen (1818-1896) of London wrote that "the abdomen, chest, and brain will forever be closed to operations by a wise and humane surgeon." A few years later Theodor Billroth remarked, "A surgeon who tries to suture a heart wound deserves to lose the esteem of his colleagues." Obviously, the surgical crystal ball is a cloudy one at best.

To study the fascinating history of our profession, with its many magnificent personalities and outstanding scientific and social achievements, may not necessarily help us predict the future of surgery. However, it does shed much light on the clinical practices of our own time. To a certain extent, if surgeons in the future wish to be regarded as more than mere technicians, the profession needs to better appreciate the value of its past experiences. Surgery has a distinguished heritage that is in danger of being forgotten. Although the future of the art, craft, and science of surgery remains unknown, it assuredly rests on a glorious past.

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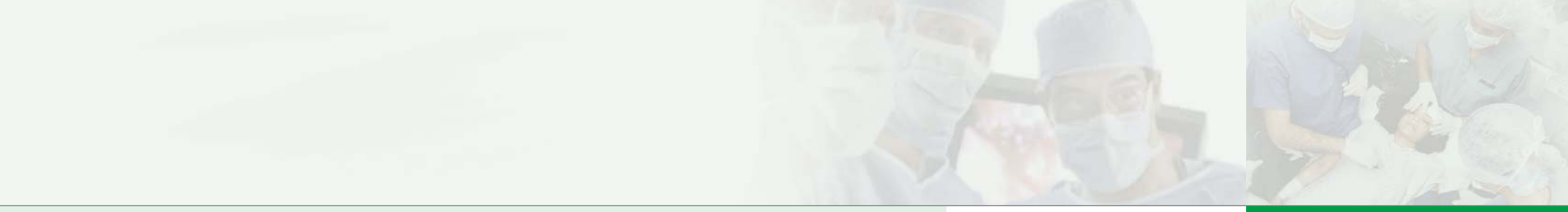

CHAPTER 2

Ethics in Surgery

Ronald A. Carson, PhD

Renewed public attention is being paid to ethics today. There are governmental ethics commissions, research ethics boards, and corporate ethics committees. Some of these institutional entities are little more than window dressing, whereas others are investigative bodies called into being, for example, on suspicion that financial records have been altered or data have been presented in a deceptive manner. However, many of these groups do important work, and the fact that they have been established at all suggests that we are not as certain as we once were, or thought we were, about where the moral boundaries are and how we would know if we overstepped them. In search of insight and guidance, we turn to ethics. In the professions, which are largely self-regulating, and especially in the medical profession, whose primary purpose is to be responsive to people in need, ethics is at the heart of the enterprise.

It is important to be clear at the outset about what ethics is and is not. Although physicians are expected to uphold such standards of professionalism as reporting impaired colleagues, medical ethics is not primarily about keeping transgressors in line. That is the domain of laws, courts, and boards of medical examiners. Ethics has to do with discerning where the lines should be drawn in the first place and to what we should aspire. It is about thinking through what we believe is good or bad or right or wrong and why we think that way. The emphasis is on reflecting and deliberating. Ethical reflection is especially useful in a social and cultural environment such as ours in which values often conflict.

The ethical precepts of the medical profession have traditionally been summarized in various oaths and codes. For example, it is still customary for students to repeat the Hippocratic Oath, or some contemporary adaptation of it, on graduation from medical school. The American College of Surgeons' Statements on Principles contains a fellowship pledge that includes a promise to maintain the College's historical commitment to "the ethical practice of medicine."[1] The American College of Obstetricians and Gynecologists (ACOG) subscribes to a code of ethics that governs the patient-physician relationship, physician conduct and practice, conflicts of interest, professional relationships, and societal responsibilities.[2] Moreover, ACOG's publication *Ethics in Obstetrics and Gynecology* is exemplary in its comprehensiveness and specificity in discussing ethical issues ranging from reproductive choice to end-of-life care.[3] Several other surgical subspecialties, as well as anesthesiology, have also given careful thought to ethical issues that arise in practice, research, education, and the introduction of innovative surgical technologies and techniques.[4-13]

Since 1847, the American Medical Association has promulgated a statement of ethical principles. Although this code has evolved over time to accommodate changes in society and medicine, it has always enunciated the ethical principles on which the profession perceives itself to be grounded. The most recent version of this statement of principles is more patient centered than ever before. It asserts that "a physician must recognize responsibility to patients first and foremost" and spells out this responsibility as the provision of "competent medical care, with compassion and respect for human dignity and rights." Principle VIII states, "A physician shall, while caring for a patient, regard responsibility to the patient as paramount."[14]

Responsibility to the patient in contemporary clinical ethics entails maximal patient participation, as permitted by the patient's condition, in decisions regarding the course of care. For the surgeon, this means arriving at an accurate diagnosis of the patient's complaint, making a treatment recommendation based on the best knowledge available, and then talking with the patient about the merits and drawbacks of the recommended course in light of the patient's life values. For the patient, maximal participation in decision making means having a conversation with the surgeon about the recommendation, why it seems reasonable and desirable, what the alternatives are, if any, and what the probable risks are of accepting the recommendation or pursuing an alternative course.

This view of ethically sound clinical care has evolved over the latter half of the 20th century from a doctor-knows-best ethic that worked reasonably well for both patients and physicians at a time when medical knowledge was limited and most of what medicine could do for patients could be carried in the doctor's black bag or handled in a small, uncluttered office or operating room.

The subsequent explosion of biomedical knowledge and the resulting proliferation of treatment options, many of them involving new technologic apparatus and interventions, were accompanied by a growing dissatisfaction with medical paternalism. As medicine grew more complex and doctors became more reliant on specialty knowledge and instrumentation, physicians and patients became less familiar with each other. Patients could no longer assume that they and their physicians shared a common set of personal values sufficient to guide physicians in judging what was best for their patients. For example, faced with a variety of treatment options, women in whom breast cancer is diagnosed and men in whom prostate cancer is diagnosed want to personally participate in decisions that will affect not only their bodies but also their lives.

In response to these new complexities and following on the various rights movements of the 1960s, some bioethicists began to advocate giving pride of place to patient autonomy (respecting patients' right to decide by seeking their consent to treatment) over physician beneficence (doing what, in the physician's judgment, is in the patient's best interest) in the hierarchy of principles governing ethical medicine (autonomy, nonmaleficence, beneficence, and justice).[15]

Consent is permission, granted by the patient to the surgeon, to make a diagnostic or therapeutic intervention on the patient's behalf. For consent to be valid, it must be informed. The patient must be provided all relevant information. To be valid, it must also be voluntary, that is, as free from coercion as possible while recognizing that in extremis the patient's condition itself may be inherently coercive. The surgeon's ethical objective is to judiciously provide the patient sufficient information with which to decide what course to follow. This entails selectively presenting all information pertinent to the patient's condition regarding benefits, risks, and alternatives while avoiding overwhelming the patient with extraneous data. To walk the line between what is pertinent and what is extraneous requires prudent judgment.

Informed consent has become a baseline best-practice ethical standard in modern medical care. It is a necessary but insufficient condition for ethically sound patient care. More moral work remains to be done if the physician-patient relationship is to be more than a contractual arrangement for rendering services. The ultimate goal is to achieve the best outcome, not only in terms of adherence to ethical principles of practice but also in keeping with patients' moral values, with what matters most to patients in their relationships and their lives. Achieving this goal certainly entails the provision of information and the granting of consent, but this exchange must take place in the context of a conversation about how the proposed intervention will affect a particular patient's life.

In 1984, Jay Katz foresaw the moral work that would be required to construct a contemporary medical ethic capable of overcoming what he termed a prevailing *silence* between doctors and patients. Katz was referring to the practice of physicians deciding what was best for patients and patients abiding by the decision. He proposed that this silence be supplanted by "meaningful conversation" based on "the humaneness of consenual understanding."[16(pxvii)]

Meaningful conversation requires conversation partners jointly committed to treating the patient's ailment in a context of mutual respect and understanding. In addition to enhancing mutuality and promoting understanding, meaningful conversation contributes to better health outcomes and to patients' satisfaction with their care. It stands to reason that patients whose doctors are responsive to their questions are likely to feel better. Is such attentiveness a luxury in today's time-conscious, monitored, and managed environment? On the contrary, studies show that when doctors miss clues to emotional and social matters that their patients cannot broach explicitly, visits tend to be prolonged as the patient continues to try to elicit an acknowledgment from the physician of concerns that may not seem immediately relevant to the patient's chief complaint.[17]

Anticipating the need for physicians to cultivate the ability to engage patients in meaningful conversation, the Accreditation Council for Graduate Medical Education (ACGME) has included ethical and professional skills and behavior among the general clinical competencies on which residency training programs are evaluated. Accreditation criteria for programs include adherence to accepted ethical principles of patient care, as well as respectful personal interactions with diverse patients, families, and other professionals.[18]

In the growing literature on diversity in clinical medicine it has become commonplace to use the shorthand concept of cultural competence. This may be a misnomer in that competence denotes mastery of a body of knowledge whereas what is wanted is improved cross-cultural interactions between patients and physicians. Culture is not a data set to be mastered and applied but a concept that is dynamic and personal and interpersonal. Culture plays a significant role in influencing the way we think about illness and health.

At its most basic, culture is a pattern of shared beliefs, values, and behavior. Culture includes, but is not limited to, the language we use, shared customs and practices, and the way we think about relationships. A culture may be religious, social, or professional (we speak, for example, of the culture of medicine), and it unquestionably affects interactions between patients and clinicians—often beneath the awareness of either party to the relationship. At its best, studied attention to cultural sensitivity in clinical medicine is aimed at raising physicians' awareness of the significance of cultural factors in their practice. Some efforts to increase cultural awareness generalize about the so-called Hispanic, African American, or Asian American patient. Knowledge of community

values may be useful in caring for patients from different communities, but the risk of stereotyping is great if insufficient attention is paid to the individual patient from a particular community, whatever it is. Culturally competent care is no substitute for patient-centered care. Practically speaking, when cultural differences between patients and their physicians are not taken into account, patient dissatisfaction and poorer health outcomes may result.

In many cultures, patients traditionally are not told that they have cancer or other life-threatening conditions. In some cultures, disclosure of a grave prognosis is believed to cause patients to suffer unnecessarily, whereas withholding such information is believed to encourage hope. Being direct and explicit may be considered insensitive. Families may try to protect their loved one by taking on decision-making responsibility. It would be unfair to impose the standards of disclosure common in one culture on patients from another culture who may not want to know. This is all useful information that can contribute to culturally appropriate care—as long as one keeps in mind the caveat mentioned before, that patients are not solely the products of their culture and should therefore be related to as individuals who may share some of their culture's attitudes and beliefs but not others. Joseph Betancourt describes the case of an elderly Italian woman whose son asked her surgeon not to inform her that she had metastatic colon cancer for fear that it would sap her will to live.[19] Decision-making and truth-telling processes vary not only from culture to culture but also from family to family. Exploring the reasons for and the consequences of a preference for secrecy can lead to culturally sensitive and ethically appropriate care.

What practical steps can be taken by clinicians to evaluate patient attitudes and behavior relative to the patient's cultural context so that the physician and patient together can reach mutually desired goals of care? Marjorie Kagawa-Singer and her colleagues at the University of California, Los Angeles,[20] developed a useful tool for ascertaining patients' levels of cultural influence. It goes by the acronym RISK:

Resources: On what tangible resources can the patient draw, and how readily available are they?
Individual identity and acculturation: What is the context of the patient's personal circumstances and her degree of integration within her community?
Skills: What skills are available to the patient that allow him to adapt to the demands of the condition?
Knowledge: What can be discerned from a conversation with the patient about the beliefs and customs prevalent in her community and relevant to illness and health, including attitudes about decision making and other issues that may affect the physician-patient relationship?

RISK, therefore, encompasses resources, identity, skills, and knowledge.

Nowhere are respectful personal interactions more in demand than in the care of patients near the end of life.

In 1998 the American College of Surgeons adopted a *Statement on Principles Guiding Care at the End of Life,*[21(p46)] which includes the following principles:

- Respect the dignity of both patient and caregivers.
- Be sensitive to and respectful of the patient's and family's wishes.
- Use the most appropriate measures that are consistent with the choices of the patient or the patient's legal surrogate.
- Ensure alleviation of pain and management of other physical symptoms.
- Recognize, assess, and address psychological, social, and spiritual problems.
- Ensure appropriate continuity of care by the patient's primary and/or specialist physician.
- Provide access to therapies that may realistically be expected to improve the patient's quality of life.
- Provide access to appropriate palliative care and hospice care.
- Respect the patient's right to refuse treatment.
- Recognize the physician's responsibility to forgo treatments that are futile.

A Surgeons Palliative Care Workgroup was convened in 2001 to put these principles into operation and to introduce the precepts and techniques of palliative care into surgical practice and education by means of symposia, a palliative care website, and focused contributions to the surgical literature.

In a paper introducing a monthly series from members of the work group written for and by surgeons, Geoffrey P. Dunn and Robert A. Milch observe that caring for patients near the end of life offers surgeons an "opportunity to rebalance decisiveness with introspection, detachment with empathy," and thereby "restore the integrity of our relationships with our patients."[22(p328)] Other contributions to this series provide expert discussions of such ethically difficult issues as decision making in palliative surgery[23]; chronic pain management and opioid tolerance[24,25]; withdrawing life support, including tube feeding, hydration, and total parenteral nutrition[26,27]; management of dyspnea,[28] depression, and anxiety[29]; and attending to dying patients' spiritual needs.[30] Two themes thread their way through these discussions. Patients in a surgeon's care near the end of life stand not only to gain from the surgeon's cognitive and technical expertise as long as rescue is an option but also to benefit from the surgeon's attentiveness and guidance when what ails the patient cannot be remedied or reversed.[31] Moreover, surgeons themselves can derive satisfaction from staying the course with dying patients and their families, responding to their trust, seeing them through difficult times, and caring for them even when curative options are no longer indicated or available.[32]

Among other responsibilities articulated in the American Medical Association's Principles of Medical Ethics, two suggest a growing sense within the profession of medicine's role as a public-spirited profession:

1. Contributing to betterment of the health of the community
2. Supporting access to medical care for everyone

Additional evidence of public-spiritedness is to be found in the association's Declaration of Professional Responsibility, which was forged in response to the terrorist attacks on New York and Washington in September 2001. Subtitled *Medicine's Social Contract with Humanity,* this unprecedented oath contains the following declaration[33]:

> We, the members of the world community of physicians, solemnly commit ourselves to
>
> I. Respect human life and the dignity of every individual.
> II. Refrain from supporting or committing crimes against humanity and condemn all such acts.
> III. Treat the sick and injured with competence and compassion and without prejudice.
> IV. Apply our knowledge and skill when needed, although doing so may put us at risk.
> V. Protect the privacy and confidentiality of those for whom we care and breach that confidence only when keeping it would seriously threaten their health and safety and that of others.
> VI. Work freely with colleagues to discover, develop, and promote advances in medicine and public health that ameliorate suffering and contribute to human well-being.
> VII. Educate the public and polity about present and future threats to the health of humanity.
> VIII. Advocate for social, economic, educational, and political changes that ameliorate suffering and contribute to human well-being.
> IX. Teach and mentor those who follow us for they are the future of our caring profession.
>
> We make these promises solemnly, freely, and on our personal and professional honor.

Recognizing the social value of volunteerism, the Governors' Committee on Socioeconomic Issues of the American College of Surgeons created the Giving Back project in the year 2000. Based on survey data from 500 fellows, the committee recommended that the college "Promote surgeon volunteerism as 'The right thing to do' and 'Part of being a physician.'"[34]

Taken together, these three documents, along with the emphasis on professional values in the medical ethics literature and the ACGME *General Competencies*, indicate a renewed commitment on the part of clinicians to competent, respectful, compassionate patient care and a growing awareness within the profession of the ethical obligations of physicians in their various roles as clinicians, researchers, educators, and citizens that arise from and extend beyond the traditional patient-physician relationship.[35-37]

Contemporary clinical ethics is evolving toward a relational understanding of interactions between doctors and patients. In the parlance of ethics, this means that ethical principles are being supplemented by moral virtues. Adherence to principles leads one to ask: What should I do? Attention to virtues prompts the question: What kind of person or doctor should I be? How to conduct oneself with patients in an economic and social environment that rewards haste, encourages narrow self-interest and inattention to the patient as a person, and is increasingly inhospitable to underserved populations is motivating a re-evaluation of medical professionalism not only at the bedside but in society as well.

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3 CHAPTER

Molecular and Cell Biology

Tien C. Ko, MD and B. Mark Evers, MD

- Human Genome
- Recombinant DNA Technology
- Cell Signaling
- Cell Division Cycle
- Apoptosis
- Human Genome Project
- Novel Treatment Strategies
- Ethical, Psychological, and Legal Implications

Since the 1980s there has been an explosion in knowledge regarding molecular and cellular biology. These advances will transform the practice of surgery to one that is based on molecular techniques for prevention, diagnosis, and treatment of many surgical diseases. This has been made possible by achievements of the Human Genome Project, which is intended to reveal the complete genetic instruction of humans. The core knowledge of molecular and cellular biology has been presented in detail in several textbooks.[1,2] An overview of the field is presented here, with emphasis on basic concepts and techniques.

HUMAN GENOME

Mendel first defined *genes* as information-containing elements that are distributed from parents to offspring. Genes contain the design that is essential for the development of each human. The field of molecular biology began in 1944 when Avery demonstrated that DNA was the hereditary material that made up genes. Translation of this genetic information into RNA and then protein leads to the expression of specific biologic characteristics or phenotypes. Major advances made in the field of molecular biology are listed in Table 3-1. In this section the structure of genes and DNA are reviewed, as are the processes by which genetic information is translated into biologic characteristics.

Structure of Genes and DNA

DNA is composed of two antiparallel strands of unbranched polymer wrapped around each other to form a right-handed double helix (Fig. 3-1).[3] Each strand is composed of four types of deoxyribonucleotides containing the bases adenine (A), cytosine (C), guanine (G), and thymine (T). The nucleotides are joined together by phosphodiester bonds that join the 5′ carbon of one deoxyribose group to the 3′ carbon of the next. Whereas the sugar-phosphate backbone remains constant, the attached bases can vary to encode different genetic information. The nucleotide sequences of the opposing strands of DNA are complementary to each other, thus allowing the formation of hydrogen bonds that stabilize the double-helix structure. Complementary base pairs require that A always pair with T and C always pair with G. For example, if the sense strand (5′-3′ direction) of DNA has the nucleotide sequence GAATTC, the complementary antisense strand (3′-5′ direction) has the sequence CTTAAG.

The entire human genetic information, or human genome, contains 3×10^9 nucleotide pairs. However, less than 10% of the DNA sequences are copied into either messenger RNA (mRNA) molecules, which encode proteins, or structural RNA, such as transfer RNA (tRNA) or ribosomal RNA (rRNA) molecules. Each nucleotide sequence in a DNA molecule that directs the synthesis of a functional RNA molecule is called a *gene* (Fig. 3-2). DNA sequences that do not encode genetic information may have structural or other unknown functions. Human genes commonly contain more than 100,000 nucleotide pairs, yet most mRNA molecule–encoding proteins consist of only 1000 nucleotide pairs. Most of the extra nucleotides consist of long stretches of noncoding sequences called *introns* that interrupt the relatively short segments of coding sequences called *exons*. For example, the thyroglobulin gene has 300,000 nucleotide bases and 36

introns, whereas its mRNA has only 8700 nucleotide bases. The processes by which genetic information encoded in DNA is transferred to RNA and protein molecules are discussed later.

The human genome contains 24 different DNA molecules; each DNA has 10^8 bases and is packaged in a separate chromosome. Thus, the human genome is organized into 22 different autosomes and 2 different sex chromosomes. Because humans are diploid organisms, each somatic cell contains 2 copies of each different autosome and 2 sex chromosomes for a total of 46 chromosomes. One copy of chromosomes is inherited from the mother and one is inherited from the father. Germ cells contain only 22 autosomes and 1 sex chromosome. Each chromosome contains three types of specialized DNA sequences that are important in the replication or segregation of chromosomes during cell division (Fig. 3-3). To replicate, each chromosome contains many short, specific DNA sequences that act as *replication origins*. A second sequence element, called a *centromere,* attaches DNA to the mitotic spindle during cell division. The third sequence element is a *telomere,* which contains G-rich repeats located at each end of the chromosome. During DNA replication, one strand of DNA becomes a few bases shorter at its 3′ end because of limitation in the replication machinery. If this is not remedied, DNA molecules will become progressively shorter in their telomere segments with each cell division. This problem is solved by an enzyme called *telomerase,* which periodically extends the telomerase sequence by several bases.

Each chromosome, when stretched out, would span the cell nucleus thousands of times. To facilitate DNA

Table 3-1 Major Events in Molecular Biology

YEAR	EVENT
1941	Genes are found to encode proteins
1944	DNA is determined to carry the genetic information
1953	DNA structure is determined
1962	Restriction endonucleases are discovered
1966	Genetic code is deciphered
1973	DNA cloning technique is established
1976	First oncogene is discovered
1977	Human growth hormone is produced in bacteria
1978	Human insulin gene is cloned
1981	First transgenic animal is produced
1985	Polymerase chain reaction is invented First tumor suppressor gene is discovered
1990	Human Genome Project is created
1998	First mammal is cloned

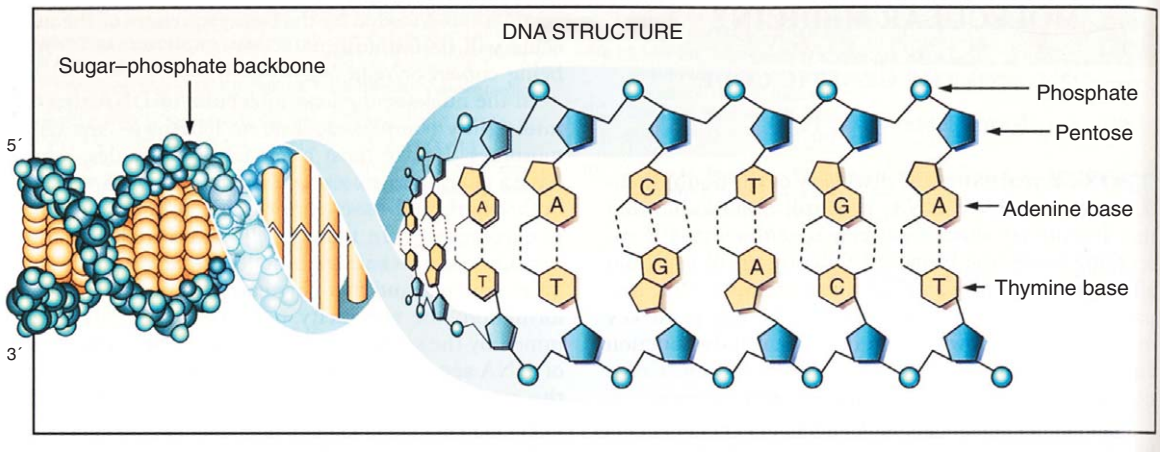

Figure 3-1 DNA double-helix structure. The sequence of four bases (guanine, adenine, thymine, and cytosine) determines the specificity of genetic information. The bases face inward from the sugar-phosphate backbone and form pairs (*dashed lines*) with complementary bases on the opposing strand. (Adapted from Rosenthal N: DNA and the genetic code. N Engl J Med 331:39, 1994. Copyright © 1994 Massachusetts Medical Society. All rights reserved.)

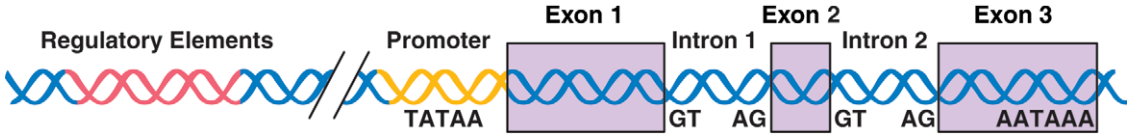

Figure 3-2 Gene structure. The DNA sequences that are transcribed as RNA are collectively called *the gene* and include exons (expressed sequences) and introns (intervening sequences). Introns invariably begin with the nucleotide sequence GT and end with AG. An AT-rich sequence in the last exon forms a signal for processing the end of the RNA transcript. Regulatory sequences that make up the promoter and include the TATA box occur close to the site where transcription starts. Additional regulatory elements are located at variable distances from the gene. (Adapted from Rosenthal N: Regulation of gene expression. N Engl J Med 331:932, 1994. Copyright © 1994 Massachusetts Medical Society. All rights reserved.)

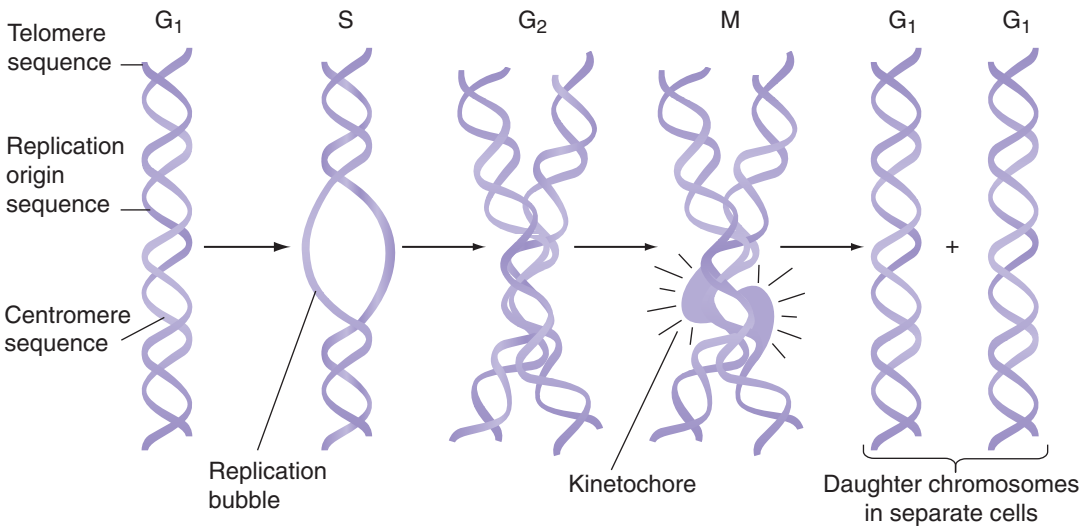

Figure 3-3 Chromosome structure. Each chromosome has three types of specific sequences that facilitate its replication during the cell cycle. Origins of replication are located throughout each chromosome to facilitate DNA synthesis. The centromere holds the duplicated chromosome together and is attached to the mitotic spindle through a protein complex called a *kinetochore.* Telomere sequences are located at each end of the chromosome and are replicated in a special way to preserve chromosome integrity.

replication and segregation, each chromosome is packaged into a compact structure with the aid of special proteins, including histones. DNA and histones form a repeated array of particles called *nucleosomes;* each consists of an octomeric core of histone proteins around which the DNA is wrapped twice. The condensed complex of DNA and proteins is known as *chromatin.* Not only does chromosome packaging facilitate DNA replication and segregation, but it also influences the activity of genes, which will be discussed later.

DNA Replication and Repair

Before cell division, DNA must be precisely duplicated such that a complete set of chromosomes can be passed to each progeny. DNA replication must occur rapidly, yet with extremely high accuracy. In humans, DNA is replicated at the rate of approximately 50 nucleotides per second with an error rate of one in every 10^9 base pair replications. This efficient replication of genetic material requires an elaborate replication machinery consisting of several enzymes. Because each strand of DNA double helix encodes nucleotide sequences complementary to its partner strand, both strands contain identical genetic information and serve as templates for the formation of an entirely new strand. DNA replication occurs in the 5′-to-3′ direction along each strand by the sequential addition of complementary deoxyribonucleoside triphosphates.

Eventually, two complete DNA double helices are formed that contain identical genetic information. The fidelity of DNA replication is of critical importance because any mistake, called a *mutation,* will result in wrong DNA sequences being copied to daughter cells. Change in a single base pair is called a *point mutation,* which can result in one of two types of mutation (Fig. 3-4). A single amino acid change as the consequence of a point mutation is called a *missense mutation.* Missense mutations may cause changes in the structure of the protein that lead to altered biologic activity. If the point mutation results in replacement of an amino acid codon with a stop codon, it is called a *nonsense mutation.* Nonsense mutations lead to premature termination of translation and often result in loss of the encoded protein. If there is an addition or deletion of a few base pairs, it is called a *frameshift mutation*, which leads to the introduction of unrelated amino acids or a stop codon (see Fig. 3-4). Some mutations are silent and will not affect the function of the organism. Several proofreading mechanisms are used to eliminate mistakes during DNA replication.

RNA and Protein Synthesis

In the early 1940s, geneticists demonstrated that genes specify the structure of individual proteins. The transfer of information from DNA to protein proceeds through the synthesis of an intermediate molecule known as *RNA.* RNA, like DNA, is made up of a linear sequence of nucleotides composed of four complementary bases. RNA differs from DNA in two respects:

1. Its sugar-phosphate backbone contains ribose instead of deoxyribose sugar
2. Thymine (T) is replaced by uracil (U), a closely related base that pairs with adenine (A)

RNA molecules are synthesized from DNA by a process known as *DNA transcription,* which uses one strand of DNA as a template. DNA transcription differs from DNA replication in that RNA is synthesized as a single-stranded molecule and is relatively short in comparison to DNA. Several classes of RNA transcripts are made, including

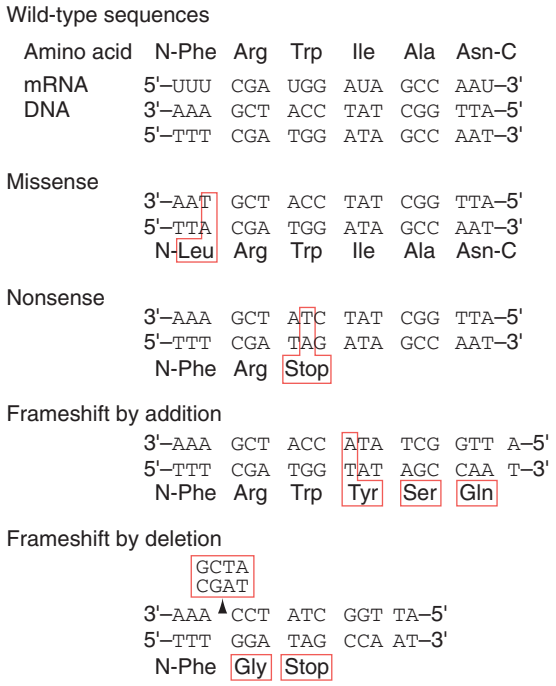

Figure 3-4 Different types of mutations. Point mutations involve alteration in a single base pair. Small additions or deletions of several base pairs directly affect the sequence of only one gene. A wild-type peptide sequence and the mRNA and DNA encoding it are shown at the *top.* Altered nucleotides and amino acid residues are enclosed in a *box*. Missense mutations lead to a change in a single amino acid in the encoding protein. In a nonsense mutation, a nucleotide base change leads to the formation of a stop codon that results in premature termination of translation, thereby generating a truncated protein. Frameshift mutations involve the addition or deletion of any number of nucleotides that is not a multiple of three, thus causing a change in the reading frame. (From Lodish HF, Baltimore D, Berk A, et al (eds): Molecular Cell Biology, 3rd ed. New York, Scientific American, 1998, p 267, with permission.)

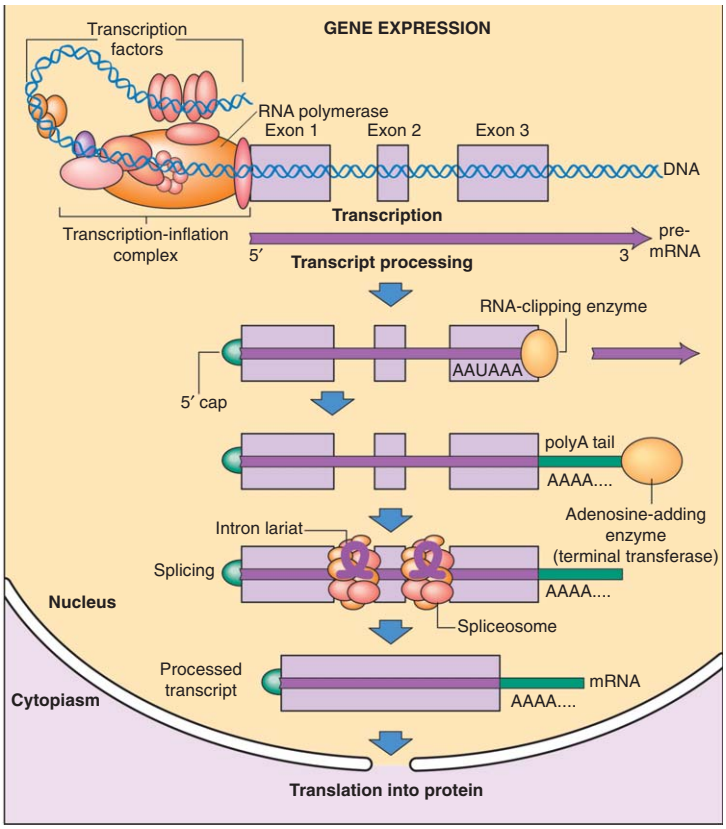

Figure 3-5 Process of gene transcription. Gene expression begins with binding of multiple protein factors to enhancer sequences and promoter sequences. These factors help form the transcription-initiation complex, which includes the enzyme RNA polymerase and multiple polymerase-associated proteins. The primary transcript (pre-mRNA) includes both exon and intron sequences. Post-transcriptional processing begins with changes at both ends of the RNA transcript. At the 5′ end, enzymes add a special nucleotide cap; at the 3′ end, an enzyme clips the pre-mRNA approximately 30 base pairs after the AAUAAA sequence in the last exon. Another enzyme adds a polyadenylate (polyA) tail, which consists of as many as 200 adenine nucleotides. Next, spliceosomes remove the introns by cutting the RNA at the boundaries between exons and introns. The process of excision forms lariats of the intron sequences. The spliced mRNA is then mature and can leave the nucleus for protein translation in the cytoplasm. (Adapted with permission from Rosenthal N: Regulation of gene expression. N Engl J Med 331:932, 1994. Copyright © 1994 Massachusetts Medical Society. All rights reserved.)

mRNA, tRNA, and rRNA. Even though all these RNA molecules are involved in the translation of information from RNA to protein, only mRNA serves as the template. RNA synthesis is a highly selective process, with only about 1% of the entire human DNA nucleotide sequence transcribed into functional RNA sequences. DNA nucleotide sequences that code for proteins are called *exons* and are separated by noncoding sequences called *introns* (see Fig. 3-2). After RNA transcription, intron sequences are removed by RNA-processing enzymes (Fig. 3-5). This RNA-processing step, called *RNA splicing,* occurs in the nucleus. Although each cell contains the same genetic material, only specific genes are transcribed. RNA transcription is controlled by regulatory proteins that bind to specific sites on DNA close to the coding sequence of a gene. The complex regulation of gene transcription occurs during development and tissue differentiation and allows differential patterns of gene expression.

Once in the cytoplasm, RNA directs the synthesis of a particular protein through a process called *RNA translation*. The sequence of nucleotides in mRNA is translated into the amino acid sequence of a protein. Each triplet of nucleotides forms a codon that specifies one amino acid. Because RNA is composed of four types of nucleotides, there are 64 possible codon triplets (4×4×4). However, only 20 amino acids are commonly found in proteins, so most amino acids are specified by several codons. The rule by which different codons are translated into amino acids is called the *genetic code* (Table 3-2).

Protein translation requires a ribosome, which is composed of more than 50 different proteins and several rRNA molecules. Ribosomes bind an mRNA molecule at the initiation codon (AUG) and begin translation in the

Table 3-2 The Genetic Code

FIRST POSITION (5′ END)	SECOND POSITION U	C	A	G	THIRD POSITION (3′ END)
U (uracil)	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop	Stop	A
	Leu	Ser	Stop	Trp	G
C (cytosine)	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A (adenine)	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G (guanine)	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

5′-to-3′ direction. Protein synthesis ceases once one of the three termination codons is encountered. The rate of protein synthesis is controlled by initiation factors that respond to the external environment, such as growth factor and nutrients. These regulatory factors help coordinate cell growth and proliferation.

Control of Gene Expression

The human body is made up of millions of specialized cells, each performing predetermined functions. This is characteristic of all multicellular organisms. In general, different human cell types contain the same genetic material (i.e., DNA), yet they synthesize and accumulate different sets of RNA and protein molecules. This difference in gene expression determines whether a cell is a hepatocyte or a cholangiocyte. Gene expression can be controlled at six major steps in the synthetic pathway from DNA to RNA to protein.[4,5] The first control is at the level of gene transcription, which determines when and how often a given gene is transcribed into RNA molecules. The next step is RNA processing control, which regulates how many mature mRNA molecules are produced in the nucleus. The third step is RNA transport control, which determines which mature mRNA molecules are exported into the cytoplasm where protein synthesis occurs. The fourth step involves mRNA stability control, which determines the rate of mRNA degradation. The fifth step involves translational control, which determines how often mRNA is translated by ribosomes into proteins. The final step is post-translational control, which regulates the function and fate of protein molecules.

Control of gene transcription is the best studied step of regulation for most genes. RNA synthesis begins with assembly and binding of the *general transcription machinery* to the *promoter* region of a gene (see Fig. 3-5). The promoter is located upstream of the transcription initiation site at the 5′ end of the gene and consists of a stretch of DNA sequence primarily composed of T and A nucleotides (i.e., the *TATA box*). The general transcription machinery is composed of several proteins, including RNA polymerase II and general transcription proteins. These general transcription factors are abundantly expressed in all cells and are required for the transcription of most mammalian genes. The rate of assembly of the general transcription machinery to the promoter determines the rate of transcription, which is regulated by *gene regulatory proteins*. In contrast to the small number of general transcription proteins, there are thousands of different gene regulatory proteins. Most bind to specific DNA sequences, called *regulatory elements,* to either activate or repress transcription.

Gene regulatory proteins are expressed in small amounts in a cell, and different selections of proteins are expressed in different cell types. Similarly, different combinations of regulatory elements are present in each gene to allow differential control of gene transcription. Many human genes have more than 20 regulatory elements; some bind transcriptional activators, whereas others bind transcriptional repressors. Ultimately, the balance between transcriptional activators and repressors determines the rate of transcription, which can vary by a factor of more than 10^6 between genes that are expressed and those that are repressed. Most regulatory elements are located at a distance (i.e., thousands of nucleotide bases) away from the promoter. These distant regulatory elements are brought into the proximity of the promoter through DNA bending, thus enabling control of promoter activity. In summary, the combination of regulatory elements and the types of gene regulatory proteins expressed determines where and when a gene is transcribed.

Post-translational control is another important step in the regulation of gene expression because most proteins are modified in one form or another.[6] Modifications such as proteolytic cleavage, disulfide formation, glycosylation, lipidation, and biotinylation allow the protein to achieve the proper structural conformation essential for its biologic activity. The complexity of regulation is greatly increased by additional amino acid modifications that can occur at multiple sites of a protein. Examples of amino acid modification include phosphorylation, acetylation, methylation, ubiquitination, and sumoylation.

RECOMBINANT DNA TECHNOLOGY

Advances in recombinant DNA technology, beginning in the 1970s, have greatly facilitated study of the human genome. It is now routine practice in molecular laboratories to excise a specific region of DNA, produce unlimited copies of it, and determine its nucleotide sequences. Furthermore, isolated genes can be altered (engineered) and transferred back into cells in culture or into the germline of an animal or plant so that the altered gene is inherited as part of the organism's genome. The most important recombinant DNA technology includes the ability to cut DNA at specific sites by restriction nucleases, rapidly amplify DNA sequences, quickly determine

the nucleotide sequences, clone a DNA fragment, and create a DNA sequence.[7]

Restriction Nucleases

Restriction nucleases are bacterial enzymes that cut the DNA double helix at specific sequences of four to eight nucleotides. More than 400 restriction nucleases have been isolated from different species of bacteria and they recognize over 100 different specific sequences. Restriction enzyme protects the bacterial cell from foreign DNA, whereas native DNA is protected from cleavage by methylation at vulnerable nucleotides. Commonly used restriction enzymes often recognize a six–base pair palindromic sequence, such as GAATTC. Each restriction nuclease will cut a DNA molecule into a series of specific fragments. These fragments have either cohesive or blunt ends, depending on the restriction nuclease, and can be rejoined to other DNA fragments with the same cohesive ends (Fig. 3-6, top panel). By using a combination of different restriction enzymes, a restriction map of each DNA can be created, thus facilitating the isolation of individual genes. Restriction nucleases have also been used for the manipulation of individual genes.

Polymerase Chain Reaction

An ingenious technique to rapidly amplify a segment of a DNA sequence in vitro was developed in 1985 by Saiki and coworkers.[8] This method, called *polymerase chain reaction (PCR),* can enzymatically amplify a segment of DNA a billion-fold.[9] The PCR technique is made possible by the availability of purified heat-stable DNA polymerase from bacteria and the ability to synthesize small segments of DNA (oligonucleotides). The principle of the PCR technique is illustrated in the bottom panel of Figure 3-6.

To amplify a segment of DNA, two single-stranded oligonucleotides, or primers, must be synthesized, each designed to complement one strand of the DNA double helix and lying on opposite sides of the region to be amplified. The PCR reaction mixture consists of the double-stranded DNA sequence (the template), two DNA oligonucleotide primers (heat stable), DNA polymerase, and four types of deoxynucleotide triphosphate. Each round of amplification involves three thermally controlled steps. First, the reaction mixture is briefly heated to 94°C to separate the double-helix structure of the DNA template into two single strands. Next, the reaction mixture is cooled to below 55°C, which results in hybridization of the two DNA primers to complementary sequences on each strand of the DNA template. Finally, the reaction is heated to 72°C to allow DNA synthesis downstream of each primer. Each round of PCR requires only about 5 minutes and results in a doubling of the double-stranded DNA molecules, which serve as templates for subsequent reactions. After only 32 cycles, more than a billion copies of the desired DNA segment is produced. Not only is the PCR technique extremely powerful, but it is also the most sensitive technique to detect a single copy of a DNA or RNA molecule in a sample. To detect RNA molecules, they must first be transcribed into complementary DNA

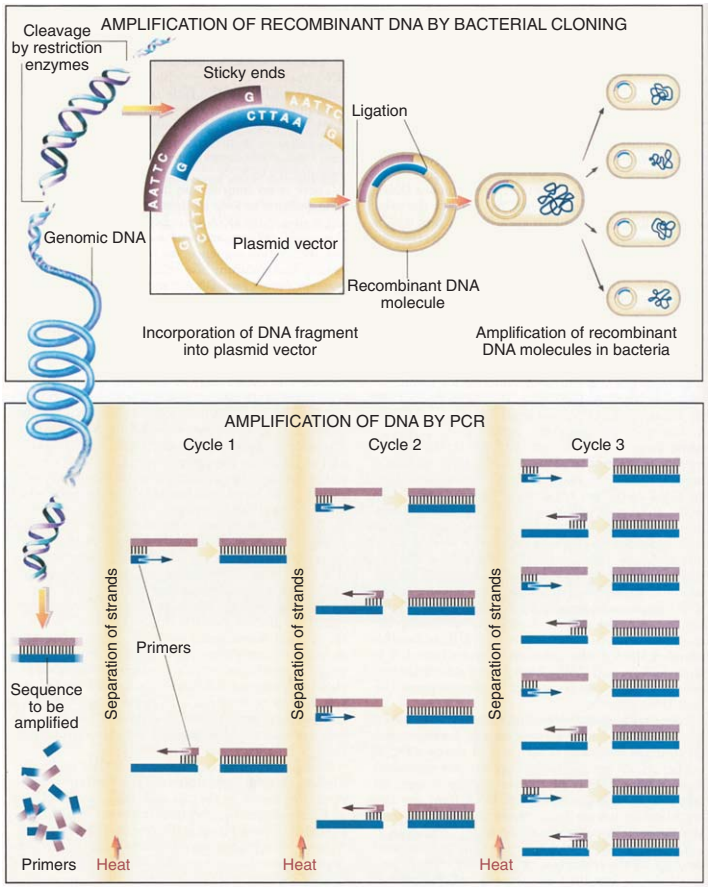

Figure 3-6 Amplification of recombinant DNA and amplification by polymerase chain reaction (PCR). At the *top,* the DNA segment to be amplified is separated from surrounding genomic DNA by cleavage with a restriction enzyme. The enzymatic cuts often produce staggered or "sticky" ends. In the example shown, the restriction enzyme *Eco*RI recognizes the sequence GAATTC and cuts each strand between G (guanine) and A (adenine); the two strands of genomic DNA are shown as *black* (C denotes cytosine and T denotes thymine). The same restriction enzyme cuts the circular plasmid DNA (*gray*) at a single site, thereby generating sticky ends that are complementary to the sticky ends of the genomic DNA fragment. The cut genomic DNA and the remainder of the plasmid, when mixed together in the presence of a ligase enzyme, form smooth joints on each side of the plasmid–genomic DNA junction. This new molecule—recombinant DNA—is carried into bacteria, which replicate the plasmid as they grow in culture. At the *bottom,* the DNA sequence to be amplified is selected by primers, which are short, synthetic oligonucleotides that correspond to sequences flanking the DNA to be amplified. After an excess of primers is added to the DNA, together with a heat-stable DNA polymerase, the strands of both the genomic DNA and the primers are separated by heating and allowed to cool. A heat-stable polymerase elongates the primers on either strand, thus generating two new identical double-stranded DNA molecules and doubling the number of DNA fragments. Each cycle takes just a few minutes and doubles the number of copies of the original DNA fragment. (From Rosenthal N: Tools of the trade—recombinant DNA. N Engl J Med 331:316, 1994. Copyright © 1994 Massachusetts Medical Society. All rights reserved.)

sequences with the enzyme *reverse transcriptase*. The number of research and clinical applications for PCR continues to grow. In molecular laboratories, PCR has been used for direct cloning of DNA, in vitro mutagenesis, engineering of DNA, analysis of allelic sequence variations, and sequencing of DNA. PCR techniques are also used in many clinical applications, including the diagnosis of genetic diseases, assay of infectious agents, and genetic fingerprinting for forensic samples.

DNA Sequencing

DNA encodes information for proteins and, ultimately, the phenotype of a human being. Each gene may contain over 3000 nucleotide bases. Identification of the nucleotide sequences of a fragment of DNA has been made possible through the development of rapid techniques that take advantage of the ability to separate DNA molecules of different lengths, even those differing by only a single nucleotide. Currently, the standard method for sequencing DNA is based on an enzymatic method requiring in vitro DNA synthesis. This method is rapid and can be automated to allow sequencing of large segments of DNA. With these techniques it is possible to determine the boundaries of a gene and the amino acid sequence of the protein that it codes. Sequencing techniques have enabled the identification and in vitro synthesis of important proteins such as insulin, interferon, hemoglobin, and growth hormones.

DNA Cloning

DNA cloning techniques allow identification of a gene of interest from the human genome. First, DNA fragments are generated by digesting the entire DNA content of a cell with a restriction nuclease. The DNA fragments are joined to a self-replicating genetic element (a virus or a plasmid) that is also digested with the same restriction nuclease. Viruses or plasmids are small circular DNA molecules that occur naturally and can replicate rapidly when introduced into bacterial cells. They are extremely useful vectors for propagating a segment of DNA. Once the DNA fragments are inserted into viruses or plasmids, they are introduced into bacterial cells that have been made transiently permeable to DNA. These transfected cells are able to produce large copies of viruses or plasmids containing the DNA fragment. With this method a collection of bacteria plasmids containing the entire human genome can be created. This human DNA library can then be used to identify genes of interest.

DNA Engineering

One of the most important outcomes of recombinant DNA technologies is the ability to generate new DNA molecules of any sequence through DNA engineering. New DNA molecules can be synthesized either by the PCR method or by using automated oligonucleotide synthesizers. PCR can be used to amplify any known segment of the human genome and to redesign its two ends. Automated oligonucleotide synthesizers enable the rapid production of DNA molecules up to about 100 nucleotides in length. The sequence of such synthetic DNA molecules is entirely determined by the experimenter. Larger DNA molecules are formed by combining two or more DNA molecules that have complementary cohesive ends created by restriction enzyme digestion. One powerful application of DNA engineering is the synthesis of large quantities of cellular proteins for medical application. Most cellular proteins are produced in small amounts in human cells, which makes it difficult to purify and study these proteins. However, with DNA engineering, it is possible to place a human gene into an expression vector that is engineered to contain a highly active promoter. When the vector is transfected into bacterial, yeast, insect, or mammalian cells, it will initiate the production of a large amount of mRNA of the human gene, thereby leading to the production of a large quantity of protein. With these expression vectors it is possible to make a single protein that accounts for 1% to 10% of the total cellular protein. The protein can easily be purified and used for scientific studies or clinical applications. Medically useful proteins, such as human insulin, growth hormone, interferon, and viral antigens for vaccines, have been made by engineering expression vectors containing these genes of interest.

DNA engineering techniques are also important for solving problems in cell biology. One of the fundamental challenges of cell biology is to identify the biologic functions of the protein product of a gene. With the use of DNA engineering techniques, it is now possible to alter the coding sequence of a gene in order to alter the functional properties of its protein product or the regulatory region of a gene and thus produce an altered pattern of its expression in the cell. The coding sequence of a gene can be changed in such subtle ways that the protein encoded by the gene has only one or a few alterations in its amino acid sequence. The modified gene is then inserted into an expression vector and transfected into the appropriate cell type to examine the function of the redesigned protein. With this strategy one can analyze which parts of the protein are important for fundamental processes such as protein folding, enzyme activity, and protein-ligand interactions.

Transgenic Animals

The ultimate test of the function of a gene is to either overexpress the gene in an organism and see what effect it has or delete it from the genome and evaluate the consequences. It is much easier to overexpress a gene of interest than to delete it from the genome of an organism.[10] To overexpress a gene, the DNA fragment encoding the gene of interest, or the *transgene*, must be constructed with recombinant DNA techniques.[9,11] The DNA fragment must contain all the components necessary for efficient expression of the gene, including a promoter and a regulatory region that drives transcription.

The type of promoter used can determine whether the transgene is expressed in many tissues of the transgenic animal or in a specific tissue. For example, selective expression in the acinar pancreas can be achieved by

placing the amylase promoter 5′ upstream of the coding sequence of the transgene. The transgene DNA fragments are then introduced into the male pronucleus of a fertilized egg via microinjection techniques. Typically, 2% to 6% of injected embryos will have the transgene integrated into their germline DNA. Animals are then screened for the presence of the transgene. Analysis of these animals has provided important insight into the functions of many human genes, as well as animal models of human diseases. For example, transgenic animals engineered to overexpress a mutant form of the gene for β-amyloid protein precursor (the *APP* gene) have neuropathologic changes similar to those in patients with Alzheimer's disease. This transgenic model not only supports the role of the *APP* gene in the development of Alzheimer's disease but is also a model for testing methods of prevention or treatment of Alzheimer's disease.

A major disadvantage of using transgenic animals is that they will reveal only dominant effects of the transgene because these animals still retain two normal copies of the gene in their genome. Therefore, it is extremely useful to produce animals that do not express both copies of the gene of interest.[12] These *knockout* animals are much more difficult to develop than transgenic animals and require gene-targeting techniques. To knock out a gene, it is important to modify the gene of interest by DNA engineering to create a nonfunctioning gene. This altered gene is inserted into a vector and then inserted into germ cell lines. Although most mutated genes are inserted randomly into one of the chromosomes, rarely a mutated gene will replace one of the two copies of the normal gene by *homologous recombination*. Germ cells with one copy of the normal gene and one copy of the mutated gene will give rise to heterozygous animals. Heterozygous males and females are generated and can then be bred to produce animals that are homozygous for the mutated gene. These knockout animals can be studied to determine which cellular functions are altered in comparison to normal animals, thereby identifying the biologic function of the gene of interest. The ability to produce knockout animals that lack a known normal gene has greatly facilitated studies of the functions of specific mammalian genes.

RNA Interference

Because the majority of the approximately 30,000 to 40,000 human genes encoding potential proteins have unknown function, uncovering their biologic activities has been an area of intense investigation. The most effective way to assess the function of a gene is by using reverse genetics (i.e., target deletion of the expression of a specific gene) and examining the biologic consequences. Until recently, only a few reverse genetic approaches have been available, such as homologous recombination and antisense oligonucleotide strategies. Each of these technologies has significant limitations that make reverse genetic studies both slow and costly. However, a new powerful tool was developed in 1998 by Andrew Fire and Craig Mello that is based on silencing of specific genes by double-stranded RNA (dsRNA).[13] This technology, termed *RNA interference* (RNAi), requires the synthesis of a dsRNA that is homologous to the target gene.[14] Once taken up by the cells, the dsRNA is cleaved into 21- to 23-nucleotide-long RNA molecules called *short interfering RNAs* (siRNAs) by an enzyme complex (Dicer-RDE-1) (Fig. 3-7).[15] The antisense strand of the siRNA binds to the target mRNA, which leads to its degradation by an RNAi silencing complex. Recent advancement has allowed the direct design and synthesis of siRNAs, as well as placement of these siRNAs into viral vectors. Not only will this technology transform future studies in the analysis of gene function, but potentially, siRNAs may also be used as gene therapy to silence the function of specific genes.

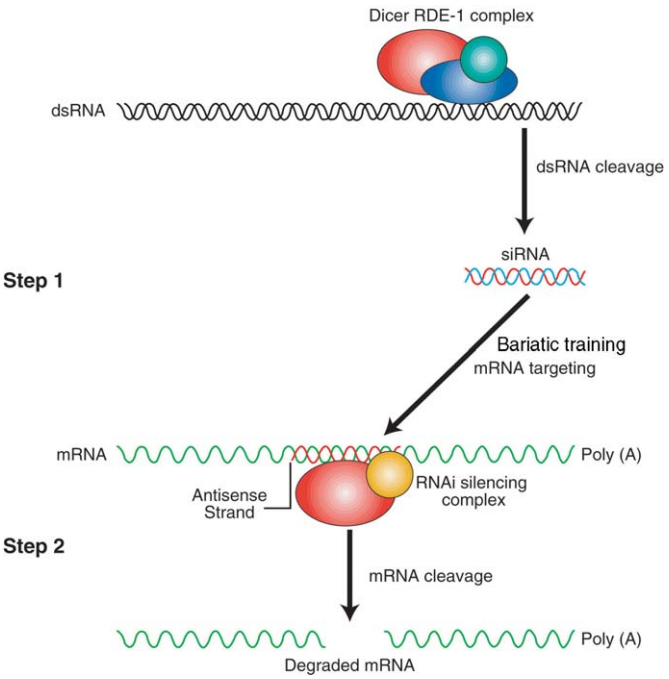

Figure 3-7 RNA interference. Long double-stranded RNA (dsRNA) is processed by the Dicer-RDE-1 complex to form short interfering RNA (siRNA). The antisense strand of siRNA is used by an RNA interference (RNAi) silencing complex to guide specific mRNA cleavage, thus promoting mRNA degradation. RDE-1, RNAi deficient-1.

CELL SIGNALING

The human body is composed of billions of cells that must be coordinated to form specific tissues. Both neighboring and distant cells influence the behavior of cells through intercellular signaling mechanisms. Whereas normal cell signaling ensures the health of the human, abnormal cell signaling can lead to diseases such as cancer. Through powerful molecular techniques, the sophisticated signaling mechanisms used by mammalian cells are becoming better understood. This section reviews the general principles of intercellular signaling and examines the signaling mechanisms of two main families of cell surface receptor proteins.[16]

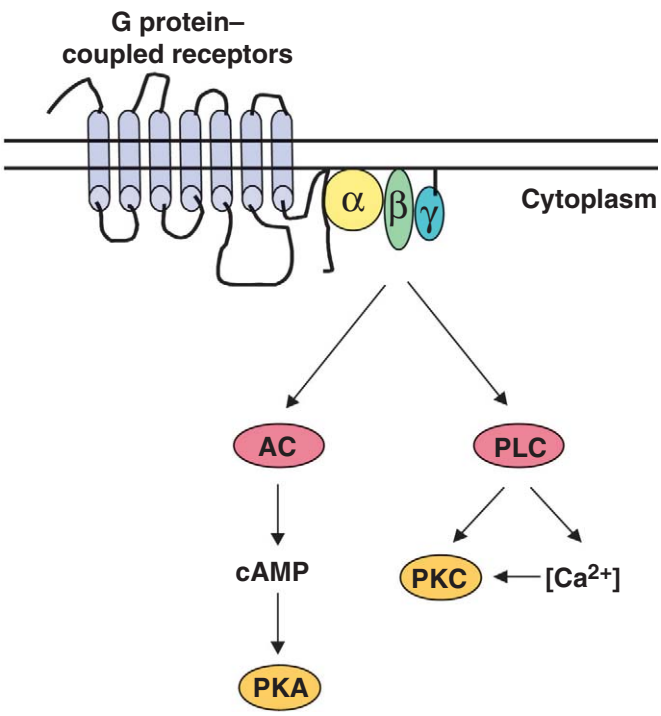

Figure 3-8 G protein–coupled receptor signaling pathway. G protein–coupled receptors are seven-transmembrane domain proteins that are activated by the binding of ligands. Activated receptors initiate a cascade of events leading to amplification of the original signal. First, the receptor activates a trimer G protein consisting of α, β, and γ subunits. G proteins can activate adenylyl cyclase (AC) to generate cyclic adenosine monophosphate (cAMP) or phospholipase C (PLC) to release intracellular calcium. cAMP can activate protein kinase A (PKA), whereas PLC or intracellular calcium can activate protein kinase C (PKC).

Ligands and Receptors

Cells communicate with one another by means of multiple signaling molecules, including proteins, small peptides, amino acids, nucleotides, steroids, fatty acid derivatives, and even dissolved gases such as nitric oxide and carbon monoxide. Once these signaling molecules are synthesized and released by a cell, they may act on the signaling cell (autocrine signaling), affect adjacent cells (paracrine signaling), or enter the systemic circulation to act on distant target cells (endocrine signaling). These signaling molecules, also called *ligands,* bind to specific proteins, called *receptors,* expressed in either the plasma membrane or the cytoplasm of the target cells. On ligand binding, the receptor becomes activated and generates a cascade of intracellular signals that alter the behavior of the cell. Each human cell is exposed to hundreds of different signals from its environment, but it is genetically programmed to respond to only specific sets of signals. Cells may respond to one set of signals by proliferating, to another set by differentiating, and to another by achieving cell death. Furthermore, different cells may respond to the same set of signals with different biologic activities.

Most extracellular signals are mediated by hydrophilic molecules that bind to receptors on the cell surface of the target cells. These cell surface receptors are divided into three classes based on the transduction mechanism used to propagate signals intracellularly. *Ion channel–coupled receptors* are involved in rapid synaptic signaling between electrically excitable cells. These receptors form gated ion channels that open or close rapidly in response to neurotransmitters. *G protein–coupled receptors* regulate the activity of other membrane proteins through a guanosine triphosphate–binding regulatory protein called *G protein*.[17] *Enzyme-coupled receptors* either act directly as enzymes or are associated with enzymes.[18,19] Most of these receptors are protein kinases or are associated with protein kinases that phosphorylate specific proteins in the cell.

Some extracellular signals are small hydrophobic molecules, such as steroid hormones, thyroid hormones, retinoids, and vitamin D. They communicate with target cells by diffusing across the plasma membrane and binding to intracellular receptor proteins. These cytoplasmic receptors are structurally related and constitute the intracellular receptor superfamily. On ligand activation, the intracellular receptors enter the nucleus, bind specific DNA sequences, and regulate transcription of the adjacent gene.

Some dissolved gases, such as nitric oxide and carbon monoxide, act as local signals by diffusing across the plasma membrane and activating intracellular enzymes in the target cells. In the case of nitric oxide, it binds and activates the enzyme guanylyl cyclase, which leads to production of the intracellular mediator cyclic guanosine monophosphate (cGMP).

G Protein–Coupled Receptors

G protein–coupled receptors are the largest family of cell surface receptors and mediate cellular responses to a broad range of signaling molecules, including hormones, neurotransmitters, and local mediators.[20] These receptors include β-adrenergic receptors, α_2-adrenergic receptors, and glucagon receptors. They share a similar structure with an extracellular domain that binds ligand and an intracellular domain that binds to a specific trimeric G protein. There are at least six distinct trimeric G proteins based on their intracellular signaling mechanisms; each is composed of three different polypeptide chains, called α, β, and γ.[17] Upon ligand binding, the G protein–coupled receptor activates its trimeric G protein (Fig. 3-8). Activated trimeric G protein alters the concentration of one or more small intracellular signaling molecules, referred to as *second messengers*.

Two major second messengers regulated by G protein–coupled receptors are cyclic adenosine monophosphate (cAMP) and calcium. cAMP is synthesized by the enzyme adenylyl cyclase and can be rapidly degraded by cAMP phosphodiesterase.[21] Intracellular calcium is stored in the endoplasmic reticulum and released into the cytoplasm upon proper signaling. Some trimeric G proteins can activate adenylyl cyclase, whereas others inhibit its activity. Trimeric G protein can also activate the enzyme phospholipase C, which produces the necessary signal

molecules to activate release of calcium from the endoplasmic reticulum. Activation of phospholipase C can also lead to activation of protein kinase C (PKC), which initiates a cascade of kinases. Changes in cAMP or calcium concentrations in the cell directly affect the activities of specific kinases that phosphorylate target proteins. The end result is altered biologic activity of these target proteins, which leads to a specific biologic response to the initial signal molecule. Despite the differences in signaling details, all G protein–coupled receptors use a complex cascade of intracellular mediators to greatly amplify the biologic response to the initial extracellular signals.

Enzyme-Coupled Receptors

Enzyme-coupled receptors are a diverse family of transmembrane proteins with similar structure. Each receptor has an extracellular ligand-binding domain and a cytosolic domain that either has intrinsic enzyme activity or is associated directly with an enzyme. Enzyme-coupled receptors are classified according to the type of enzymatic activity used for their intracellular signal transduction. Some receptors have guanylyl cyclase activity and generate cGMP as an intracellular mediator. Others have tyrosine kinase activity or are associated with tyrosine kinase proteins that phosphorylate specific tyrosine residues on intracellular proteins to propagate intracellular signals. Finally, some enzyme-coupled receptors have serine/threonine kinase activity and can phosphorylate specific serine or threonine residues to transduce intracellular signals.

The receptors for most known growth factors belong to the tyrosine kinase receptor family.[18,19] These include receptors for epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin, insulin-like growth factor-I (IGF-I), vascular endothelial growth factor (VEGF), and macrophage colony-stimulating factor (M-CSF). These growth factor receptors play crucial roles during normal development and tissue homeostasis. Furthermore, many of the genes that encode proteins in the intracellular signaling cascades that are activated by receptor tyrosine kinases were first identified as oncogenes in cancer cells. Inappropriate activation of these proteins causes a cell to proliferative excessively.

Similar to G protein–coupled receptors, tyrosine kinase receptors use a complex cascade of intracellular mediators to propagate and amplify the initial signals (Fig. 3-9). Upon ligand binding, the tyrosine kinase receptor dimerizes, which activates the kinase. Activated receptor kinase initiates an intracellular relay system, first by cross-phosphorylation of tyrosine residues of the cytoplasmic domain of the receptor. Next, small intracellular signaling proteins bind to phosphotyrosine residues on the receptor and form a multiprotein signaling complex from which the signal propagates to the nucleus. The Ras proteins serve as crucial links in the signaling cascade.[22] Upon activation, Ras proteins initiate a cascade of serine/threonine phosphorylation that converges on mitogen-activated protein (MAP) kinases. Activated MAP kinases relay signals downstream by phosphorylating transcription factors, thereby leading to regulation of gene expression.

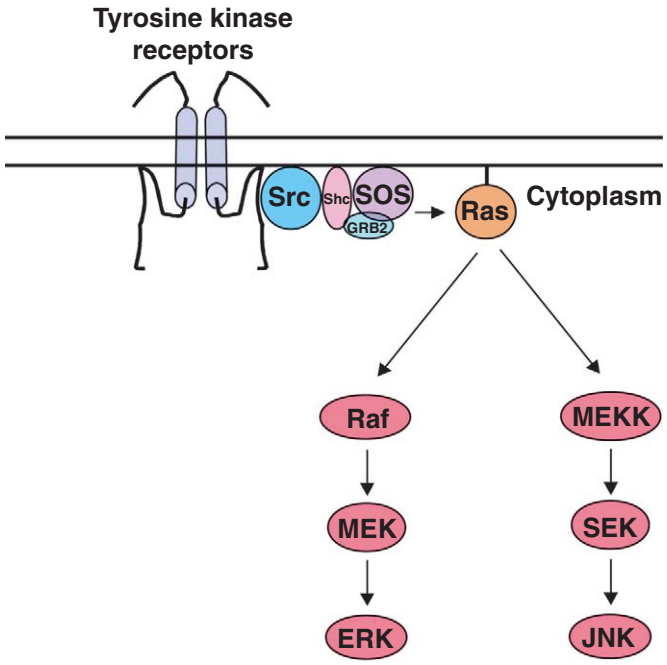

Figure 3-9 Tyrosine kinase receptor signaling pathway. Tyrosine kinase receptors are single transmembrane proteins that form a dimer on ligand binding. The activated receptors bind to several proteins (Src, Shc, SOS, GRB2) to form a multiprotein signal complex. This protein complex can activate Ras, which can initiate several kinase cascades. One kinase cascade includes the Raf, MEK, and ERK members, whereas another includes the MEKK, SEK, and JNK proteins.

As mentioned previously, human cells integrate many different extracellular signals and respond with biologic behaviors such as proliferation, differentiation, and programmed cell death. In the following sections we review the mechanisms governing these important biologic processes.

CELL DIVISION CYCLE

The cell division cycle is the fundamental means by which organisms propagate and by which normal tissue homeostasis is maintained. The cell division cycle is an organized sequence of complex biologic processes that is traditionally divided into four distinct phases (Fig. 3-10). Replication of DNA occurs in the S phase (S=synthesis), whereas nuclear division and cell fission occur in the mitotic phase, or M phase. The intervals between these two phases are called the G_1 and G_2 phase (G=gap). After division, cells enter the G_1 phase, where they are able to receive extracellular signals and a determination is made whether to proceed with DNA replication or to exit the cell cycle. In this section we review the proteins that regulate progression through each phase of the cell cycle and how they control key checkpoints of the cell cycle. Then we discuss how many cell cycle proteins are mutated or deleted in human cancers.

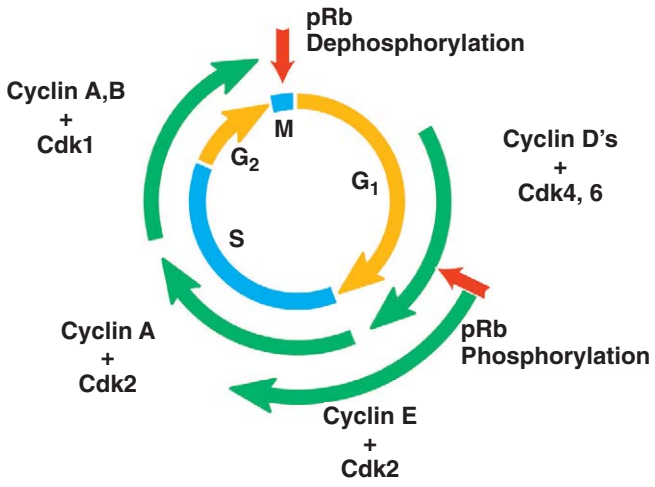

Figure 3-10 Mechanisms regulating mammalian cell cycle progression. The cell cycle consists of four phases: G_1 (first gap) phase, S (DNA synthetic) phase, G_2 (second gap) phase, and M (mitotic) phase. Progression through the cell cycle is regulated by a highly conserved family of serine/threonine protein kinases that are composed of a regulatory subunit (the cyclins) and a catalytic subunit (the cyclin-dependent kinases [Cdks]). Cell cycle progression can be inhibited by a class of regulators called the *cyclin kinase inhibitors* and by phosphorylation of the retinoblastoma (pRb) protein.

Regulation of the Cell Division Cycle by Cyclin, Cyclin-Dependent Kinase, and Cdk Inhibitory Proteins

Progression of the mammalian cell cycle through these specific phases is governed by the sequential activation and inactivation of a highly conserved family of regulatory proteins, cyclin-dependent kinases (Cdks).[23] Cdk activation requires the binding of a regulatory protein (cyclin) and is controlled by both positive and negative phosphorylation. Cdk activities are inhibited by Cdk inhibitory proteins (CKIs). The active cyclin/Cdk complex is involved in the phosphorylation of other cell cycle regulatory proteins. Cyclin proteins are classified according to their structural similarities. Each cyclin exhibits a cell cycle/phase–specific pattern of expression. In contrast, Cdk proteins are expressed throughout the cell cycle. The cyclins, Cdks, and CKIs form the fundamental regulatory units of the cell cycle machinery.

Cell Cycle Checkpoints

In proliferating cells, cell cycle progression is regulated at two key checkpoints, the G_1/S and the G_2/M transitions. Progression through early to mid G_1 is dependent on Cdk4 and Cdk6, which are activated by association with one of the D-type cyclins, D1, D2 or D3.[23] Progression through late G_1 and into the S phase requires the activation of Cdk2, which is sequentially regulated by cyclins E and A, respectively. The subsequent activation of Cdk1 (cdc2) by cyclin B is essential for the transition from G_2 into the M phase. There are two families of CKIs: the CIP/KIP family and the INK family. The four known INK proteins ($p15^{INK4B}$, $p16^{INK4A}$, $p18^{INK4C}$, and $p19^{INK4D}$) selectively bind and inhibit Cdk4 and Cdk6 and are expressed in a tissue-specific pattern. The three members of the CIP/KIP family ($p21^{CIP1}$, $p27^{KIP1}$, and $p57^{KIP2}$) share a conserved amino-terminal domain that is sufficient for both binding to cyclin/Cdk complexes and inhibition of Cdk-associated kinase activity. Each CIP/KIP protein can inhibit all known Cdks. One of the key targets of the G_1 Cdks is the retinoblastoma tumor suppressor protein (pRb), which belongs to the Rb family of pocket proteins (pRb, p107, p130).[24] In their hypophosphorylated form, pocket proteins can sequester cell cycle regulatory transcription factors, including heterodimers of the E2F and DP families of proteins.[25] Phosphorylation of pRb, first by cyclin D–dependent kinases and then by cyclin E/Cdk2 during late G_1, leads to release of E2F/DP and subsequent activation of genes that participate in the entry into S phase.

Oncogenes and Tumor Suppressor Genes

The genes encoding cell cycle regulatory proteins are often targets of mutation during neoplastic transformation. If the mutated gene is cancer causing, it is referred to as an *oncogene* and its normal counterpart is called a *proto-oncogene*. Many proto-oncogenes have been identified and they are typically involved in relay of stimulatory signals from growth factor receptors to the nucleus. They include the intracellular signaling protein Ras, as well as the cell cycle regulatory protein cyclin D1. Mutation of a single copy of a proto-oncogene is sufficient to bring about increased cellular proliferation, one of the hallmarks of cancer. Several antiproliferative gene–encoding proteins such as pRb, p15, and p16 also negatively control the cell division cycle. These genes are often referred to as *tumor suppressor genes* because they prevent excess and uncontrolled cellular proliferation. These genes are inactivated in some forms of cancer to bring about loss of control of proliferation. However, unlike proto-oncogenes, both copies of a tumor suppressor gene must be deleted or inactivated during malignant transformation.

APOPTOSIS

Cell proliferation must be balanced by an appropriate process of cell elimination to maintain tissue homeostasis. Physiologic cell death is a genetic program pathway and is called *apoptosis*. Apoptosis has been implicated in various physiologic functions, including the remodeling of tissues during development, removal of senescent cells and cells with genetic damage beyond repair, and maintenance of tissue homeostasis. In this section we review the biologic and morphologic features of apoptosis and the molecular machinery that controls apoptosis.

Biochemical and Morphologic Features of Apoptosis

Apoptosis is a physiologic process of cell elimination, in contrast to another form of cell death called *necrosis*.

Necrosis is a passive, adenosine triphosphate–independent form of cell death that requires an acute nonphysiologic injury (i.e., ischemia, mechanical injury, or toxins) and results in destruction of the cytoplasmic and organelle membranes with subsequent cellular swelling and lysis.[15] Lysis of necrotic cells releases cytoplasmic and organelle contents into the extracellular milieu, thereby resulting in inflammation with surrounding tissue necrosis and destruction. In contrast, apoptosis is a highly regulated energy-requiring form of cell death that is genetically programmed. Apoptotic cells undergo the following sequence of morphologic and biochemical events:

1. In the early phase of apoptosis, cells exhibit a shrunken cytoplasm and detach from neighboring cells. One of the earliest biochemical features of apoptotic cells is the externalization of phosphatidyl serine residues on the plasma membrane. It has been proposed that these signaling intermediates may be involved in alerting surrounding cells to the occurrence of apoptosis.
2. Middle events include chromatin condensation with resultant crescent-shaped nuclei and subsequent nuclear fragmentation. During this phase, activation of endonuclease results in the fragmentation of DNA into 180– to 200–base pair internucleosomal sized fragments.
3. Late in apoptosis, the cells begin to fragment into discrete plasma membrane–bound vesicles termed *apoptotic bodies,* which are then phagocytized by neighboring cells and macrophages without inducing an inflammatory response.

The molecular machinery that governs apoptosis can be divided into three parts (Fig. 3-11):

1. Signaling of apoptosis by a stimulus
2. Regulation by proapoptotic and antiapoptotic factors
3. The execution machinery

These molecular events result in the morphologic and biochemical characteristics of the apoptotic cell.

Apoptotic Stimuli

Many stimuli activate the process of apoptosis (see Fig. 3-11), including DNA damage through ionizing radiation, growth factor and nutritional deprivation, activation of certain death receptors (e.g., Fas receptor [FasR] and tumor necrosis factor receptor [TNF-R1]), metabolic or cell cycle perturbations, oxidative stress, and many chemotherapeutic agents. Signal sensors proximal in the apoptotic pathway recognize these stimuli and include cell surface receptors requiring ligand binding and intracellular sensors detecting the loss of an advantageous environment for survival or irreparable damage. The nerve growth factor (NGF)/TNF receptor family is the typical example of membrane receptor signal sensors and includes the FasR and TNF-R1 receptors.[26] FasR is a 45-kd protein expressed at the surface of activated T cells, hepatocytes and enterocytes and can be found expressed in tissues, including the liver, heart, lung, kidney, and small intestine.

Extensive studies with the T-cell model have revealed the downstream events of receptor activation. Binding of a death-promoting ligand to the receptor triggers the death signal, which results in a conformational change in the intracellular region of the receptor. This change in protein structure allows binding of cytoplasmic adapter proteins. These receptor-adapter protein complexes, such as the Fas-activated death domain (FADD), catalyze the activation of downstream proteases involved in the execution phase of apoptosis. Intracellular signal sensors include the p53 tumor suppressor gene. The identification of DNA damage activates p53 functional activity and results in G_1 phase cell cycle arrest to allow DNA repair; however, irreparable damage commits the cell to death by apoptosis.[27] This differential function may be a result of the intracellular expression levels of p53. Finally, the lack of certain survival factors results in decreased cytoplasmic signals from cell surface receptors, such as interleukin-2 (IL-2) receptors, on activated T cells. This loss of exogenous survival signals culminates in activation of the endogenous death program. Similar results have been seen with serum withdrawal or growth factor receptor blockade, both of which induce apoptosis. Regardless of the many different signals and signal sensors involved in the activation of apoptosis, each of these pathways converge to activate a common central execution process, the caspase cascade.

Caspases

Caspases, or *c*ysteine *asp*artate prote*ases*, are highly conserved proteins first recognized as the *ced-3* gene product from the nematode *Caenorhabditis elegans*.[28] The sequence of Ced-3 exhibits homology to the mammalian IL-1β converting enzyme (ICE), which is now known as *caspase 1*. To date there are 14 known mammalian caspases, each of which is intimately involved in the conserved biochemical pathway that mediates apoptotic cell death. These proteolytic enzymes are synthesized as inactive proenzymes that require cleavage for activation. Each activated caspase has specific functions that may overlap with those of other caspases. This overlap in function shows the evolutionary significance of apoptosis. The protein substrates cleaved by activated caspases play a functional role in the morphologic and biochemical features seen in apoptotic cells.

As indicated in Figure 3-11, activated caspases result in the destruction of cytoskeletal and structural proteins (α-fodrin and actin), nuclear structural components (NuMA and lamins), and cell adhesion factors (FAK). They induce cell cycle arrest through Rb cleavage, cytoplasmic release of p53 by cleavage of the regulatory double minute 2 (MDM2) protein, and subsequent nuclear translocation and activation of PKC-δ. DNA repair enzymes, such as poly (adenosine diphosphate [ADP]-ribose) polymerase and the 140-kd component of DNA replication complex C, are inactivated by caspase proteolysis. Finally, DNA fragmentation is induced by the activation and nuclear translocation of a 45-kd cytoplasmic protein called *DNA fragmentation factor (DFF).* Although there is no known caspase involved in the

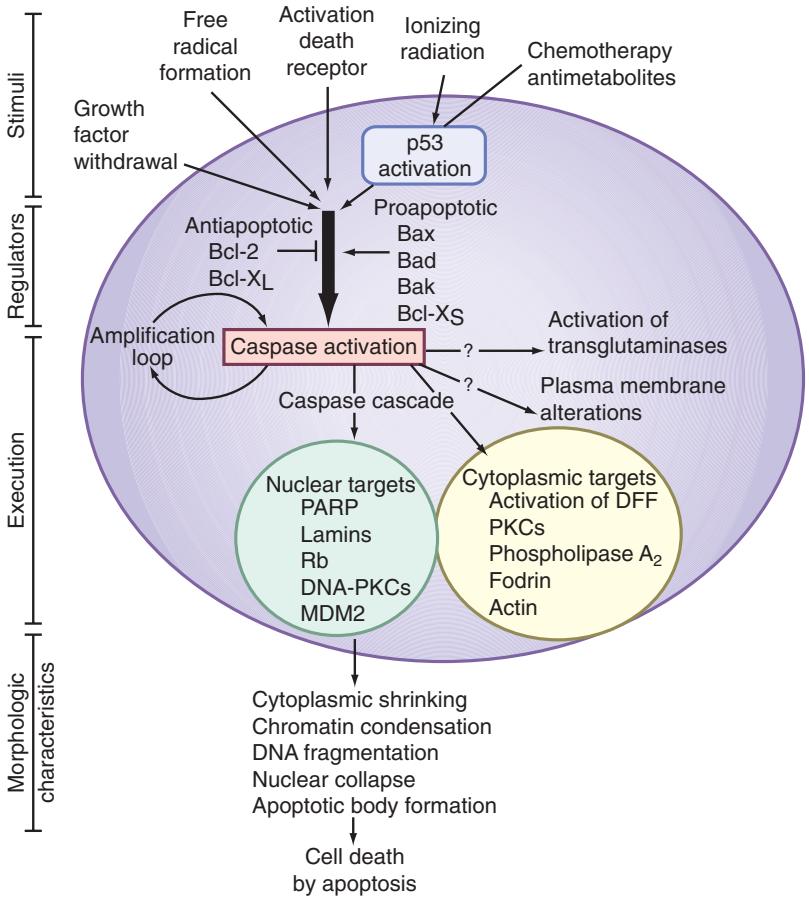

Figure 3-11 The apoptotic pathway of cell death. The molecular mechanisms involved in apoptosis are divided into three parts. First, stimuli of the apoptotic pathway include DNA damage by ionizing radiation or chemotherapeutic agents (p53 activation), activation of death receptors such as Fas and tumor necrosis factor-α, free radical formation, and loss of growth factor signaling. Second, progression of these stimuli to the central execution pathway is either positively or negatively regulated by expression of the Bcl-2 family of proteins. Third, the execution phase of apoptosis involves the activation of a family of evolutionarily conserved proteases called *caspases.* Caspase activation targets various nuclear and cytoplasmic proteins for activation or destruction, thereby leading to the morphologic and biochemical characteristics of apoptosis. (From Papaconstantinou HT, Ko TC: Cell cycle and apoptosis regulation in GI cancers. In Evers BM [ed]: Molecular Mechanisms in Gastrointestinal Cancer. Austin, TX, RG Landes, 1999, p 59, with permission.)

redistribution of phosphatidyl serine residues on the plasma membrane, caspase inhibitors have been shown to block this event. Overall, the net effect of caspase activation is to halt cell cycle progression, disable homeostatic and repair mechanisms, initiate detachment of the cell from its surrounding tissue structures, disassemble structural components, and mark the dying cell for engulfment by surrounding cells and macrophages.

Bcl-2 Family

The process of apoptosis is regulated by the expression of certain intracellular proteins belonging to the *Bcl-2* family of genes (see Fig. 3-11).[29] Bcl-2 is a potent inhibitor of apoptosis and is predominantly expressed in cholangiocytes, colonic epithelial cells, and pancreatic duct cells. The precise mechanism of apoptotic inhibition by Bcl-2 is not known, but this protein is found on organelle membranes and may function as an antioxidant, protease inhibitor, or gatekeeper to prevent the apoptotic machinery from entering a target organelle. Other proteins in this family include Bcl-x_L, Bcl-x_s, Bax, Bak, and Bad. Bcl-x_L is another inhibitor of apoptosis. Bcl-x_s, Bax, Bak, and Bad function as proapoptotic regulators by dimerizing with Bcl-2 and Bcl-x_L and inhibiting their function. Furthermore, it has been shown that the proapoptotic protein Bax exhibits channel-forming activity in lipid membranes, which is blocked by Bcl-2. Increasing evidence suggests that the balance or ratio of these proapoptotic and antiapoptotic proteins is important for signaling the cell to commit to or inhibit apoptosis.

The complex molecular machinery of apoptosis, involving signaling, regulation of activation, promotion, or inhibition, and then execution, is a carefully choreo-

graphed process. Perturbations in this process at any of these three phases can result in loss of the apoptotic cell elimination pathway. Because apoptosis is a key regulator of cell number and therefore tissue homeostasis, it is easy to see how dysregulation of apoptosis can result in diseases.

HUMAN GENOME PROJECT

One of the most significant scientific undertakings of all times involves identification and sequencing of the entire human genome. The Human Genome Project was initiated in 1990, and the first versions of the DNA sequences of the human genome were published in 2001.[30,31] The Human Genome Project has had a significant impact on the field of medicine by providing clinicians with an unprecedented arsenal of genetic information that will, it is hoped, lead to a better understanding and treatment of a variety of genetic diseases. As an example, the Human Genome Project is providing new information on the genetic variations in the human population by identifying DNA variants such as single nucleotide polymorphisms (SNPs), which occur about once every 300 to 500 bases along the 3 billion-base human genome.[32] SNPs are thought to serve as genetic markers for identifying disease genes by linkage studies in families or by the discovery of genes involved in human diseases. These findings may lead to better screening and help implement preventive medical therapy in the hope of reducing the development of certain diseases in patients found to have predisposing conditions. It is anticipated that knowing the sequence of human DNA will allow scientists to better understand a host of diseases. With new information and techniques to unravel the mysteries of human biology, this knowledge will dramatically accelerate the development of new strategies for the diagnosis, prevention, and treatment of disease, not just for single-gene disorders, but for more common complex diseases, such as diabetes, heart disease, and cancer, for which genetic differences may contribute to the risk of contracting the disease and the response to particular therapies.

The transition from genetics to genomics marks the evolution from an understanding of single genes and their individual functions to a more global understanding of the actions of multiple genes and their control of biologic systems. Technology emanating from the Human Genome Project is currently available to assess an array of genes that may change (either increase or decrease) over time or with treatment. Such technology using so-called DNA chips provides one of the most promising approaches to large-scale studies of genetic variations, detection of heterogeneous gene mutations and gene expression. DNA chips, which are also called *microarrays,* generally consist of a thin slice of glass or silicone about the size of a postage stamp on which threads of synthetic nucleic acids are arrayed.[33,34] Literally thousands of genes can be assessed on a single DNA chip. A clinical example of the use of microarrays includes the detection of human immunodeficiency virus (HIV) sequence variations, p53 gene mutations in breast tissue, and expression of cytochrome P-450 genes. In addition, microarray technology has been applied to genomic comparisons across species, genetic recombination, and large-scale analysis of gene copy number and expression, as well as protein expression in cancers.

As genome technology moves from the laboratory to the clinical setting, new methods will make it possible to read the instructions contained in an individual person's DNA. Such knowledge may predict future disease and alert patients and their health care providers to initiate preventive strategies. Individual DNA profiles, as well as the DNA profiles of tumors, may provide better stratification of patients for cancer therapies. The Human Genome Project is certain to have an important impact on all areas of clinical medicine. All surgical disciplines will be directly affected by this information. We focus on some specific examples where we foresee major developments that will greatly influence our clinical management.

Transplantation

Despite the remarkable advances made in transplantation, organ procurement, and immunosuppression, a significant impediment remains the availability of suitable organs. The level of organ and tissue demand cannot be met by organ donation alone. Xenotransplantation has been proposed as a possible solution to the problem of organ availability and suitability for transplantation. A number of investigators have examined the possibility of using xenotransplanted organs. However, although short-term successes have been reported, there have been no long-term survivors with the use of these techniques. Data obtained from the Human Genome Project may enable transplant investigators to genetically engineer animals to potentially have more specific combinations of human antigens. It is anticipated that in the future, animals can be developed whose immune systems have been engineered to more closely resemble that of humans, thus eliminating dependence on organ donors.

Another possibility to address the organ donation problem is the potential for organ cloning. With the recent cloning of sheep and cattle, this topic has received a considerable amount of attention. Although the issue of whole-animal cloning is fascinating, the area that offers the greatest hope for transplant patients is the growing field of stem cell biology. By identifying stem cells of interest, the information gathered from the Human Genome Project could enable scientists to develop organ-cloning techniques that will revolutionize the field of transplantation. These pluripotent stem cells have the ability to divide without limit and to give rise to many types of differentiated and specialized tissues with a specific purpose. It is anticipated that the identification of stem cells and the potential modification of these cells by gene therapy may allow investigators to genetically engineer tissues of interest.

Oncology

The results of the Human Genome Project will have far-reaching effects on diagnostic studies, treatment, and counseling of cancer patients and family members.[34]