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EDITORIAL

Looking Back on the Millennium in Medicine

The second millennium is over. The editors of the Journal first thought to ignore this passage. After all, the changing of the millennium would undoubtedly be the subject of incessant media attention. Why should we add to it? Yet, looking back, it is hard not to be moved by the astounding course of medical history over the past thousand years. No one alive in the year 1000 could possibly have imagined what was in store. Furthermore, medicine is one of the few spheres of human activity in which the purposes are unambiguously altruistic -- in itself, a remarkable achievement.

We therefore decided to yield to the temptation to comment on the end of the second millennium by choosing the most important medical developments of the past thousand years and reviewing them briefly. None of the developments we selected was an isolated discovery or event; instead, each was a series of notable steps -- some huge, some smaller -- along a path that led to a crucial body of knowledge in a particular area. That is the usual way medical science progresses. For example, Vesalius took giant steps toward elucidating human anatomy, but he was not alone, and what was important was the totality of the work in that area.

We deliberately restricted ourselves to developments that changed the face of clinical medicine, not preventive medicine or public health or health care delivery or medical ethics. Yet there is obviously overlap. Understanding the relation of microbes to disease, for example, inevitably affected not only clinical medicine, but also preventive medicine and public health. Indeed, it is hard to think of a more important advance in all three arenas than immunization. Medical ethics has become increasingly important as the power of clinical medicine grows, but we arbitrarily decided not to include that topic here.

Except for some early work by the ancient Greeks, much of it wrong, there were few advances in clinical medicine until the Renaissance. In the 1400 years between Galen and Vesalius, medicine was stagnant, dominated by the belief that illness reflected an imbalance in the four humors of the body -- blood, phlegm, yellow bile, and black bile. Life was nasty, brutish, and short, and medical care did not help. There are many reasons little progress was made until the Renaissance, but one of them was surely that the only fit pursuit for scholars in those centuries was considered to be knowledge of God, not of man. Only with the flowering of humanism that characterized the Renaissance did that change, and it changed very rapidly.

Readers will note that the developments we discuss were the work largely of white men in Europe and North America. For a variety of reasons, that is the way it was. In the new millennium, it will be different. That is one prediction we make with confidence. The other is that the pace of change will continue to

accelerate, as it did in the second millennium. Beyond this, it would be foolhardy to speculate about what the new millennium holds, just as it would have been impossible for anyone in the year 1000 to dream of everything that was to come.

Here, then, we present our choices for the most important medical developments of the past millennium. In what may be our only claim to distinction in the process, we arbitrarily chose 11, not 10. Obviously, many more could have been selected. We present them not in order of importance, but in rough chronologic order according to the first noteworthy step taken in a given area.

Elucidation of Human Anatomy and Physiology

The emergence of a comprehensive understanding of the structure and function of the organ systems of the human body stands -- without question -- as one of the most influential advances of the past millennium. Although the contributions of the Greek physician Galen early in the first millennium a.d. were extraordinarily important to anatomy and physiology, Galen also introduced numerous errors that were not corrected until the Renaissance. Perhaps the greatest anatomist of the Renaissance, if not of all time, was Andreas Vesalius (1514-1564), born in Brussels but educated in France and Italy. Vesalius's anatomical treatise, De Humani corporis fabrica libri septem ("Seven Books on the Structure of the Human Body"), published in 1543, is regarded as one of the most important works in medicine. The extraordinary illustrations in the Fabrica (not actually drawn by the great anatomist but by an unknown artist) set a new standard for the understanding of human anatomy.

Less than 100 years after Vesalius, William Harvey (1578-1657), an English physician and physiologist, established that the blood circulates within a closed system, with the heart serving as a pump. He showed that the pulse results from the filling of arteries with blood after cardiac contraction and that the right ventricle pumps blood to the pulmonary circulation and the left ventricle pumps blood to the systemic circulation. The importance of Harvey's work, published in 1628 in Exercitatio anatomica de motu cordis et sanguinis in animalibus ("On the Motion of the Heart and Blood in Animals"), cannot be overstated. The physiologic principles that he established led to an understanding of blood pressure (first measured in a horse in 1733 by the clergyman Stephen Hales) and, much later, the clinical use of cardiac catheterization (by Werner Forssmann, Andre Cournand, and Dickinson Richards) and open-heart surgery (by Robert Gross, Elliott Cutler, Charles Hufnagel, Alfred Blalock, and many others).

Considered together, the work of Vesalius and Harvey provided the intellectual underpinnings for many advances in human anatomy, physiology, clinical medicine, and surgery that followed during the remainder of the millennium.

Discovery of Cells and Their Substructures

The discovery of cells awaited the invention of the microscope by the Dutch lens maker Antony van Leeuwenhoek (1632-1723). At first, he made simple,

single lenses, but they were superbly ground. With an object held close to the lens under good illumination (and with his fortuitous nearsightedness), Leeuwenhoek was able for the first time to discern minute "animalcules" (probably bacteria and protozoa) and to discover that plant and animal tissues had complex inner structures. Later, Leeuwenhoek introduced compound lenses and built microscopes capable of magnifying objects 270 times. Using the microscope, a contemporary in England, Robert Hooke (1635-1702), formally described the plant cells in cork, each lying in its own compartment. Over a century later, in the early 1800s, Matthias Schleiden and Theodor Schwann observed that animal tissues were also composed of cells.

These observations set the stage for the era of cellular biology, which was to occupy the last 200 years of the millennium, ushered in by such giants as Rudolf Virchow, Ludwig Aschoff, and Carl Rokitansky. Improved light microscopes, more sophisticated staining techniques, and refined methods of preparing tissues for microscopy made possible ever deeper penetration into the structure of the cell. Observing microscopic changes in tissues and organs led to a better understanding of disease processes.

Even so, the rich substructure of cells remained unexplored until the early 1930s, when Ernst Ruska made the first primitive electron microscope (with magnification of 400 times). Later, when magnification reached 10,000 and more, the complex substructure of cells -- mitochondria, endoplasmic reticulum, ribosomes, and other organelles -- could be seen. Histochemical and immunocytochemical methods, together with functional studies, elucidated the specialized composition and activities of the various cell components. In the 1950s, George Palade developed ways of fractionating subcellular elements and was able to isolate mitochondria, endoplasmic reticulum, and the Golgi apparatus. The elegant choreography of the various elements in particular cell types could finally be appreciated.

The subsequent development of the scanning electron microscope and the technique of freeze-fracturing tissues enabled observers to appreciate the surprisingly complex topography of cells and their interconnections. Today, still more sophisticated methods, largely experimental, such as electron energy-loss spectroscopy and x-ray diffraction analysis, permit the chemical composition of cells and their organelles to be identified. The smallest unit of observation has become very small indeed.

Elucidation of the Chemistry of Life

The process of fermentation has fascinated humans since Neolithic times, and it is therefore not surprising that the transformation of crushed fruit to alcohol and then to vinegar, or the leavening of bread, should have played a major part in the development of modern biochemical ideas. The notion that "every Disease acts its tragedies by the strength of some Ferment," enunciated in 1659 by Thomas Willis (for whom the circle of Willis was named), was amplified over the next 200 years by scientists like Antoine Lavoisier, Jons Jakob Berzelius, Louis Pasteur, and others. With the development of quantitative physical chemistry, it became possible to express the course of enzymatic

reactions in mathematical terms (as shown by Leonor Michaelis and Maud Menten in 1913).

After 1860, Amadeo Avogadro's law, advanced in 1811, became accepted as a basis for the calculation of atomic weights and the determination of molecular structure (Avogadro's law holds that 1 mol of any substance contains the same number of molecules, 6.02×10^{23}). Application of Avogadro's law permitted the rapid elucidation early in the 20th century of the interconnected enzymatic reactions that are responsible for the stepwise oxidation of foodstuffs that fuels the vital activity of cells.

The study of thin slices of living organs in small gasometric vessels, pioneered by Otto Warburg (1883-1970), together with new techniques for chemical analysis, allowed the ingenious deduction of pathways of metabolism, such as the citric acid cycle, elucidated by Hans Krebs (1900-1981), and the urea cycle. The development of spectrophotometry, and the realization that oxidation and reduction involve electrons, stimulated the discovery of sequential electron transport by mitochondria.

The notion of such cascades of chemical reactions initiated by enzymes whose catalytic activity is determined by their complex structure and modulated by the products they generate is at the very root of modern biochemistry. Discovery of the inhibition or enhancement of the action of cellular enzymes by hormones, neurotransmitters, cytokines, and paracrine molecules, so that cells can communicate with each other, has led to an understanding not only of normal processes, but also of diseases such as diabetes mellitus.

From the standpoint of medical practice, the growth of knowledge about the inorganic composition of body fluids is probably just as important as the amassing of knowledge about the organic chemistry of cells. The relation of sodium to edema or dehydration, the importance of potassium in the losses incurred in diarrhea, the distribution of water in the body, and the implications of the disturbances in acid-base balance that accompany vomiting, circulatory shock, uremia, or uncontrolled diabetes -- all were clarified during the past hundred years and have become part of the basic knowledge required by doctors in every specialty for the delivery of good medical care.

Application of Statistics to Medicine

A natural starting point for a history of biostatistical thought in the past millennium is the work of Leonardo Fibonacci (c. 1170- after 1240), an Italian mathematician of the Middle Ages. By introducing Indian and Arabic mathematics and numbering to Europe in 1202, he freed Western thought from the limitations of the Roman-numeral system. This advance laid the foundation for modern computation and bookkeeping. Probability theory emerged only in the 16th and 17th centuries, when Pierre de Fermat (1601-1665) and Blaise Pascal (1623-1662) developed basic probabilistic calculations to analyze games of chance. Ideas of relative frequency were first applied to mortality statistics in 17th-century London at the time of the plague. John Graunt (1620-1674) introduced the notion of inference from a sample to an underlying

population and described calculations of life expectancy that launched the insurance industry in the 17th and 18th centuries.

The German mathematician Karl Friedrich Gauss (1777-1855) played a central part in the development of modern statistical reasoning. His method of least-squares analysis, developed around 1794, underlies much of modern regression analysis. Thomas Bayes (1702-1761), the 18th-century English theologian and mathematician, was the first to show how probability can be used in inductive reasoning.

One of the earliest clinical trials took place in 1747, when James Lind treated 12 scorbutic ship passengers with cider, an elixir of vitriol, vinegar, sea water, oranges and lemons, or an electuary recommended by the ship's surgeon. The success of the citrus-containing treatment eventually led the British Admiralty to mandate the provision of lime juice to all sailors, thereby eliminating scurvy from the navy. The origin of modern epidemiology is often traced to 1854, when John Snow demonstrated the transmission of cholera from contaminated water by analyzing disease rates among citizens served by the Broad Street Pump in London's Golden Square. He arrested the further spread of the disease by removing the pump handle from the polluted well.

Biostatistical reasoning developed rapidly in Great Britain in the late 19th and early 20th centuries. Sir Ronald Fisher (1890-1962), the most important figure in modern statistics, developed the analysis of variance and multivariate analysis. He also introduced the principle of randomization as a method for avoiding bias in experimental studies. In the United States, Jerzy Neyman, a Russian immigrant, developed the theories of estimation and testing that shaped contemporary biostatistical practice.

A landmark of quantitative observational research as a tool for exploring the determinants of disease was Sir Richard Doll's study of smoking among British physicians. Randomized clinical trials emerged in England in the 1950s and were adopted by the National Institutes of Health in the United States in the early 1960s; there followed an explosion of clinical trials of treatment for cancer, heart disease, diabetes, and other diseases. Biostatistical methods expanded rapidly during this period. Sir David Cox's 1972 paper on proportional-hazards regression ignited the fields of survival analysis and semiparametric inference (using partial specification of the probability distribution of the outcomes under investigation). Rapid improvements in computer support were essential to the growing role of empirical investigation and statistical inference.

Development of Anesthesia

Archeological evidence makes it clear that surgery was practiced in the form of trephination of the skull well before recorded history. Some who suffered through the procedure even survived it. Written records from ancient Greece, Egypt, and China refer to the use of opium, cannabis, and mandragora (mandrake) to produce anesthesia, analgesia, and amnesia. It is clear, however, that for most of recorded history surgical procedures were crude, quick, and

agonizing. Surgery was a fearsome treatment of last resort, rarely used. The development of anesthesia was the essential prelude to modern surgery.

The European scientific establishment laid the groundwork for the development of surgical anesthesia. In 1799, Sir Humphry Davy, the superintendent of the Pneumatic Institution in Clifton, England, recognized the analgesic properties of nitrous oxide when he inhaled it, during the course of his work, while he had a toothache. He coined the term "laughing gas" but carried the work no further.

Ether had been known to chemists since the 18th century, and chloroform was discovered in 1831, but the medical applications of inhaled agents to relieve the pain of surgery came about only after Horace Wells, a Connecticut dentist, used nitrous oxide to anesthetize 15 patients during December 1844. Flush with success, Wells persuaded his former partner, William Morton, to arrange a public exhibition of nitrous oxide anesthesia for a dental extraction at the Massachusetts General Hospital. The demonstration, in January 1845, was a disaster. The patient cried out in pain, and Wells was hooted from the room. Subsequently, Morton quietly accumulated experience with ether as an anesthetic during more than 30 procedures with the Boston surgeon Henry Jacob Bigelow. On the basis of this experience, Morton publicly demonstrated ether anesthesia on October 16, 1846, at the Massachusetts General Hospital, when John Collins Warren removed a tumor from Edward Gilbert Abbott's lower jaw. Within days, the event was reported in the Boston Medical and Surgical Journal (later to be renamed the New England Journal of Medicine). Before the end of the year, ether was in use in both England and Scotland.

In November 1847, the Scottish obstetrician James Young Simpson experimentally administered chloroform to himself and several friends in the dining room of his home, then administered it to a woman in childbirth and reported the results to the Edinburgh Medical and Chirugical Society -- all within six days. General anesthesia has improved immeasurably since then, with the development of safer anesthetics and refinements in monitoring during surgery. Only with the introduction of the routine use of muscle relaxants by Harold Griffith in Montreal in 1942 could it be said that the era of modern anesthesia had begun.

Discovery of the Relation of Microbes to Disease

For most of the past millennium, epidemic diseases such as smallpox were thought to be caused by miasmas (toxic vapors from decomposing organic matter), not by unseen transmissible organisms. Although Louis Pasteur (1822-1895) was not the first to see microbes, he established bacteriology as a science and is generally recognized as the most important bacteriologist of all time. His demonstration that culture fluid boiled in a "swan-neck" flask open to the air remained clear demolished the concept of spontaneous generation and represented a monumental conceptual change. His discovery proved that all living things, microbes included, come from other living things. In addition, Pasteur can be considered the father of fermentation. He noted that living microorganisms cause the transformation of wine to vinegar and suggested

heat treatment (now known as pasteurization) to destroy the microorganisms that had such unfavorable effects.

Pasteur's numerous contributions to medicine were remarkable. He showed how to separate a toxin from its bacterial source by filtration. In a highly publicized field trial, he demonstrated that vaccination of sheep with a culture of heat-attenuated Bacillus anthracis protected them against death on injection of virulent anthrax organisms. This dramatic result was a powerful stimulus to the field of immunology. Although the infectious nature of rabies was known, Pasteur suggested that its cause was not a bacterium. Drawing on his understanding of infectious agents, as well as intuition, he showed that the rabies agent, a virus, could be attenuated by serial intracerebral passage in the rabbit, a species other than its natural host. His immunization of a young boy, Joseph Meister, who was bitten by a rabid dog, dramatically prevented what had previously been an inevitably fatal disease.

Robert Koch (1843-1910), like Pasteur, was instrumental in establishing bacteriology as a scientific discipline. He developed the techniques of culturing on solid medium, staining bacteria, and sterilizing by dry heat. These powerful techniques ushered in the golden era of medical bacteriology, during which most bacterial pathogens were isolated. Koch was the first person to isolate bacteria (in this case, B. anthracis) in pure culture, and he discovered the cholera vibrio as well as the cause of tuberculosis, sometimes called Koch's bacillus. His patience in continuing to observe cultures of sputum from patients with tuberculosis for weeks at a time yielded the discovery that slow-growing pathogens exist. Similarly, he showed that Mycobacterium tuberculosis stained more slowly than other bacteria, taking 24 hours with the stains of the time. After identifying the tubercle bacillus, Koch used his newly formalized criteria, now known as Koch's postulates, to distinguish a bacterial pathogen from a nonpathogen. His discovery of the so-called Koch phenomenon, an altered local response to superinfection with M. tuberculosis, led to the development of the tuberculin test.

The application of antiseptic principles to surgery, introduced by Baron Joseph Lister (1827-1912), has saved innumerable lives. Inspired by Pasteur and his research on fermentation, Lister realized that the formation of pus was also a consequence of bacterial growth. Initially, he used carbolic acid spray to kill airborne bacteria. His realization that bacteria were also present on the surgeon's hands and instruments led to his insistence that antiseptics be used on hands, instruments, and dressings. In the pre-Listerian era even a trivial operation was often complicated by infection. With the adoption of Lister's antiseptic principles, it became safe to perform extensive surgical operations.

Elucidation of Inheritance and Genetics

For most of the past millennium, philosophical and religious beliefs were used to explain the transmission of genetic traits. The homunculus curled inside the head of a sperm symbolizes a popular 19th-century belief about inheritance. In just over a century, beliefs changed. Charles Darwin's 1858 theory -- that evolution depends on random variations that permit adaptation to changing environments -- is a milestone in the history of genetics. It laid the foundation

for modern concepts of mutation and of how offspring differ from their forebears. Gregor Mendel's revolutionary treatise on the segregation of traits in peas had been in print since 1865, but it was ignored until 1902, when William Bateson, after discovering Mendel's paper in an obscure journal, wrote Mendel's Principles of Heredity.

The key to genetic segregation, the chromosome, was discovered by Walther Flemming in 1875, and by the 1890s it was established as the structural unit of genetic heritage. Early in the 20th century, William Bateson coined the word "genetics," and Archibald Garrod started medical genetics with his proposal that inborn errors of metabolism were inherited according to Mendel's laws. In 1911, Thomas Hunt Morgan published linear maps of genes along fruit-fly chromosomes, using the same principles applied today for mapping human genetic diseases. George Beadle, Edward Tatum, and Boris Ephrussi linked genetics to biochemistry in the 1940s by showing that genes specify enzymes, which can be inactivated by mutation.

In 1943, Thomas Avery, Colin MacLeod, and Maclyn McCarty demonstrated genetic transmission -- not by proteins, as was then believed, but by DNA. Six years later, the four bases of the DNA molecule were described and the rules of base pairing (adenine with thymine and guanine with cytosine) were formulated by Erwin Chargaff. In 1952, Rosalind Franklin's x-ray diffraction pictures of DNA were a revelation that, along with Chargaff's rules, culminated in the elucidation of the double-helical structure of DNA by James Watson, Francis Crick, and Maurice Wilkins. Ten years later, Jacques Monod and Francois Jacob linked DNA to protein with their theory of messenger RNA, and in 1970, Frederick Sanger and Walter Gilbert devised ways of determining the sequence of bases in DNA. Simultaneously, David Baltimore and Harold Temin opened the way to genetic engineering (and treatments of human immunodeficiency virus infection) with their discovery of reverse transcriptase, which converts RNA into DNA.

Traveling by train from Denver to Chicago in 1949, William Castle acquainted Linus Pauling with the facts about sickle cell anemia, a disease Castle thought was due to "some type of molecular alignment." Thus stimulated, Pauling and his group demonstrated for the first time the molecular consequence of a mutation that causes a genetic disorder (hemoglobin S), and termed sickle cell anemia "a molecular disease." The sickle globin variation was later traced by Vernon Ingram to a single amino acid substitution in the molecule. Genetically engineered insulin was marketed in 1982, and a license to sell genetically modified living organisms for the purpose of manufacturing recombinant proteins was granted in 1986. In that same year a genetically engineered vaccine for hepatitis B was approved by the Food and Drug Administration. The complete sequence of the human genome is expected to be identified early in this millennium.

Knowledge of the Immune System

Immunology, a new science, emerged only toward the end of the 19th century. Edward Jenner (1749-1823), the English surgeon who used pustular fluid from cowpox lesions to vaccinate against smallpox, is often credited with founding

immunology, but his work was strictly pragmatic. Even Pasteur, who began his epochal work on the protective immunity induced by attenuated microbes in 1880, did not understand why his vaccines worked. Immunology really began in 1890, when Emil Behring and Kitasato Shibasaburo developed their diphtheria antitoxin and, in the process, discovered antibodies. Almost simultaneously, Elie Metchnikoff identified phagocytes and championed the cellular theory of immunity. Immunology flourished. Within 20 years, the main elements of clinical immunology -- allergy, autoimmunity, and transplantation immunity -- were described, and immunochemistry became a quantitative science.

Nevertheless, the central role of the lymphocyte in immunity was yet to be established; it was not known how the immune system can form an unlimited variety of antibodies, and therapy for immune-mediated diseases, including the prevention of allograft rejection, was primitive or nonexistent. The flowering of late-20th-century immunology began toward the end of the 1950s, when the focus shifted from serology to cells. The clonal-selection theory -- the idea that lymphocytes are genetically distinct clones -- signaled the start of the new era. The new emphasis on immune cells and the simultaneous emergence of molecular biology were the two most powerful influences on immunology since its inception. Within 15 years the synergistic union of new ideas and new techniques resulted in a detailed understanding of the immune response. Moreover, therapeutics in immunology acquired a logical basis. It is no coincidence that transplantation surgery evolved from the impossible to the routine during that time.

The development and deployment of vaccines against infectious diseases is a multidisciplinary achievement whose importance cannot be overstated. Vaccination against smallpox, which originated in India and probably China more than 1000 years ago, eventuated in the worldwide eradication of the virus through the fruitful union of medical science and international cooperation, mediated by the World Health Organization. Protection against measles, pioneered by Francis Home in the 18th century, became routine after the development of an effective vaccine by John Enders almost 200 years later. Enders, along with Thomas Weller and Frederick Robbins, also had a pivotal role in developing the poliomyelitis vaccine, which was perfected as an oral preparation of live attenuated virus by Albert Sabin and as a killed-virus vaccine by Jonas Salk in the 1950s.

Passive immunization against pneumococcal pneumonia -- by the injection of serotype-specific horse antibodies -- was introduced by Georg Klemperer in 1891 and widely used for almost 50 years, but the method was probably ineffective. The systematic purification of pneumococcal polysaccharides by Michael Heidelberger and others during the 1920s laid the foundation for the preparation of modern purified multivalent pneumococcal vaccines. Passive immunization was also used for protection against diphtheria toward the end of the 19th century, but the discovery in 1923 that protection could be achieved by inoculation of formaldehyde-treated diphtheria toxin (toxoid) eliminated the need for risky injections of horse serum.

A landmark in the history of vaccines is the hepatitis B surface antigen, the first vaccine produced by DNA technology. Until now, proteins and polysaccharides have been the mainstays of vaccines. The new millennium promises a potentially revolutionary form of vaccination based on sequences of DNA that encode microbial antigens.

Development of Body Imaging

Internal imaging of the human body has been possible only in the past century. Wilhelm Konrad Rontgen (1845-1923), a German physicist, discovered x-rays in 1895, a discovery for which he received the first Nobel prize for physics in 1901. Since then, imaging science has evolved in three overlapping stages.

During the first stage, the aim was to develop imaging techniques to define the morphologic features and function of the internal organs. In addition to x-rays, additional "rays" for this purpose were discovered, including ultrasound and emissions from radionuclide tracers. Contrast agents were developed to reveal previously indiscernible structures. These techniques all contributed greatly to the visualization of disease processes, enhanced the precision of therapies, and improved understanding of pathophysiology.

The second stage of the development of imaging was marked by the achievement of access to the vascular tree and by improved characterization of tissues. The interior of the heart and blood vessels could be delineated by contrast angiography. Other important new tools were computed tomography and magnetic resonance imaging, which permitted resolution of very small structures throughout the body. In 1979, Sir Godfrey Hounsfield and Allan Cormack were awarded the Nobel prize for medicine or physiology for their work on computerized axial tomography. Better imaging permitted the development of new treatments for cancer and vascular and cardiac diseases, as well as more accurate determination of the stages of a variety of disease processes. In the third, current stage of development, imaging methods are used to guide therapy directly -- from long-term guidance of cancer therapy to immediate, on-line guidance of minimally invasive surgery.

An interesting perspective on the development of imaging is provided by knowledge of those who participated in the story. In the earliest days after Rontgen's discovery, physicists and experimentalists, including both Thomas Edison and William Coolidge (of light-bulb fame), lent their experience to improving images. Some of the early progress resulted from the interest of people -- such as Harvey Cushing, a leading neurosurgeon of the early 20th century -- who were known for their accomplishments in other fields. As imaging expanded into all areas of medicine, the specialty of diagnostic radiology evolved and eventually became responsible for most advances in the field.

Today, radiologists are integrating the work of basic scientists from many areas for the advancement of imaging methods. They are collaborating with and becoming knowledgeable about the medical and surgical specialties they serve. The current advanced imaging techniques can be properly applied only

when both the imaging science and the medical science are brought to bear on a problem.

Discovery of Antimicrobial Agents

The discovery of antibiotics and other antimicrobial agents has changed the face of infectious disease. Previously lethal acute infections, such as bacterial meningitis and endocarditis, are now treatable; dreaded chronic afflictions, such as tuberculosis and malaria, can be arrested; and innumerable other infections, such as pneumonia and urinary tract infections, can be readily cured.

The earliest antimicrobial agents were plant products such as cinchona bark, used to treat malaria. Paul Ehrlich (1854-1915), a German bacteriologist best known for his proposal that chemicals ("magic bullets") exist that have the capacity to attach to microorganisms but not to host cells, founded the field of chemotherapy for infections. In 1910 he discovered salvarsan (also known as arsphenamine and "606," or the 606th compound he had tried) as a treatment for syphilis and showed that certain dyes had trypanocidal activity. Following Ehrlich's concept, Gerhard Domagk (1895-1964) found in 1935 that the red dye Prontosil dramatically cured streptococcal infections. The discovery that a breakdown product of Prontosil, sulfanilamide, was as effective as the parent drug led to the development of more active sulfonamide derivatives, which became the mainstays of the treatment of erysipelas, pneumococcal pneumonia, gonorrhea, and other infections in the years before and during World War II.

The concept of antibiotics (antimicrobial drugs that are produced by other microorganisms) dates back to the observation in 1877 by Pasteur and Joubert that products of a contaminating microorganism inhibited the growth of B. anthracis. This observation led others to pursue such interactions between microbial species. The most striking success was the discovery of penicillin. Sir Alexander Fleming's serendipitous observation in 1928 of the inhibition of colonies of Staphylococcus aureus by a contaminant mold (Penicillium notatum) marked the beginning of the antibiotic era. However, penicillin was too unstable to be useful and generated little interest until 1939, when a team at Oxford headed by Sir Howard Florey and Ernst Chain began their work to purify enough penicillin for clinical use.

Capitalizing on the observation that certain pathogenic microorganisms disappeared from infected soils, Rene Dubos at the Rockefeller Institute sought and obtained an antibiotic, named tyrothricin, from the soil bacillus Bacillus brevis. Although too toxic for clinical use, it was "proof of principle" by indicating the value of soil microorganisms as a source of antibiotics, and thus the field of antibiotic discovery was advanced. This work was a strong impetus for Florey to study the clinical use of penicillin.

The first patient treated by Florey's group at Oxford, in 1942, had a mixed streptococcal and staphylococcal infection. Within four days, there was dramatic improvement, but the meager supply of penicillin was exhausted after five days, and the patient relapsed and died. In the following half-century this

remarkable antibiotic has saved innumerable lives and reduced morbidity from a vast array of bacterial infections.

Selman Waksman (1888-1973), searching systematically among soil actinomycetes for antibiotics that might be effective against gram-negative bacilli that were unaffected by penicillin, discovered the second clinically important antibiotic, streptomycin, which is produced by a strain of Streptomyces griseus. Streptomycin was active against Haemophilus influenzae and many coliform bacteria. Most important, it was the first antimicrobial drug used in the treatment of tuberculosis. In rapid succession, other antimicrobials were introduced, including the tetracyclines, chloramphenicol, erythromycin, penicillin congeners, and cephalosporins. In the past decade, effective antiviral drugs have come into use and altered the course of disease in patients with herpesvirus and human immunodeficiency virus infections. The discovery and use of antimicrobials is doubtless one of the greatest accomplishments of medical science in the millennium just past.

Development of Molecular Pharmacotherapy

The development of pharmacotherapy has been on an ever-accelerating track; indeed, most of the historical milestones in this field were reached in the past few decades. The major advances in drug therapy could not occur until there was sufficient understanding of physiology and pathophysiology to permit rational identification of targets for drugs. Even before such scientific approaches were possible, however, careful observation allowed the development of empirical treatments, which until recently consisted of natural plant- or animal-based preparations. Such treatments were untested and of unproved benefit; their use was based on the opinion of "authorities," rather than on the scientific method. Interestingly, we seem to have come full circle in the past decade with the explosive growth in the use of so-called dietary supplements and other unproven "natural" cures.

The antimicrobial defense against infectious diseases marked the beginning of modern pharmacotherapy. Subsequent advances were made possible by new concepts in organic chemistry in the period before and just after World War II and by the recognition that the therapeutic effectiveness of natural products was due to specific constituents. The identification of these active constituents, coupled with the recognition that many drugs produce their effects by binding to specific macromolecules or receptors, made possible the search for more potent and specific therapies with improved efficacy and safety.

In the course of his experiments on the therapeutic potential of organic dyes, Ehrlich coined the word "chemotherapy" and extended the concept of the magic bullet from infectious diseases to cancer. After centuries of brutal treatments for cancer -- applications of lead or selenium, cautery, and knives -- some progress was made at the end of the 19th century. In 1896, the Scottish surgeon Thomas Beatson began to use ovariectomy for breast cancer, and in 1941 Charles Huggins showed the benefit of orchiectomy in prostate cancer. Chemotherapy for cancer as we know it today began in 1946, when Alfred Gilman and Frederick Philips showed that nitrogen mustard -- the mustard gas of World War I -- caused regression of lymphomas. It is hard to believe that

1999 marked the 50th anniversary of the introduction of methotrexate for the treatment of childhood leukemia by Sidney Farber and his group at Children's Hospital in Boston. In 1965, Barnett Rosenberg and his colleagues observed that bacterial growth was inhibited in vitro when an electric current was passed between platinum electrodes. This chance discovery was the birth of cis-platinum, one of the most effective agents against epithelial cancers.

Ahlquist's division of adrenergic receptors into alpha and beta subtypes led Sir James Black (b. 1924) to hypothesize that because the myocardial adrenergic receptor was of the beta subtype, he could develop an antagonist to that particular receptor that would prevent angina. This work led to the development of beta-blockers. The recognition that the gastric histamine receptor was not antagonized by traditional antihistamines led Black to propose that a novel antihistamine (that would block H_2 receptors) would reduce gastric output.

These strategies led to the development of drugs to antagonize or stimulate numerous other receptors and drug targets. The treatment of Parkinson's disease with levodopa, for example, is based on an understanding of dopaminergic receptors in the nigrostriatum. The revolution in molecular biology is now producing an explosion in the number and variety of potential drug targets, which is likely to ensure the continuation of the exponential growth in pharmacologic discovery, even while pharmacogenetics is beginning to explain variability among individual patients in the response to drugs.

In addition, the major social contributions made by pharmacotherapy to human well-being should not be ignored. The discovery of chlorpromazine in the late 1940s and of antidepressants several years later largely removed the social stigma of psychiatric disease, to the great benefit of those who suffer from it. The development of reversible means of contraception liberated women to plan their pregnancies and control their lives in a way no amount of social legislation could ever have done. Finally, the effective pharmacologic treatment and prevention of disease has extended life expectancy and reduced disability beyond the most optimistic hopes of physicians even a few decades ago -- and far beyond the dreams of their predecessors a thousand years ago. We are no more able than they were to predict what this new millennium will bring.

The Editors

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