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ABSTRACT

Background. The biological, chemical, behavioral and physical sciences provide the fuel for innovation, discovery and technology that continuously improves the quality of the human condition. Computer power derived from the dramatic breakthroughs of the digital revolution has made extraordinary computational capacity available for diagnostic imaging, bioinformatics (the science of information) and numerous aspects of how we practice dentistry in the 21st century.

Overview. The biological revolution was initiated by the identification of the structure for DNA in 1953, a discovery that continues to catalyze improvements in patient care through new and better diagnostics, treatments and biomaterials. Humanity's most basic and recognizable characteristics—including the face—are now better understood through the elucidation of our genome and proteome, the genes and proteins they encode. Health care providers are beginning to use personalized medicine that is based on a person's genetic makeup and predispositions to disease development.

Conclusions. Advances in the fields of genetics, developmental and stem cell biology, and many other disciplines continue to fuel innovative research findings that form the basis for new diagnostic tests, therapeutic interventions and procedures that improve the quality of life for patients. Scientists are on the threshold of applying knowledge in stem cell biology to regenerative medicine and dentistry, heralding an era when clinicians can consider using biological engineering to replace tissues and organs lost to disease or trauma.

Key Words. Discovery; molecular biology; chairside application.
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Science is the fuel for the engine of technology and clinical practice. How do we formulate a diagnosis and prognosis? What are the ways of treating the diseases and disorders that challenge the human condition? Is one outcome better than another? The answers to these questions come from our sustained investment in the science that fuels our educational system. Bright minds exposed to questions such as these have created and will continue to create technology that improves patient care.

We think of the Scientific Revolution of the 16th and 17th centuries as the intellectual and technological movement that shaped the modern world. Yet, today we live in another time of scientific revolution, characterized by great speed and enormous accomplishment in the chemical, physical and biological realms of inquiry—from discovery to application. In the 20th century, scientists identified the structure and function of DNA and applied it to cellular and molecular biology to better understand the microbial and human ecosystems and their interdependence.[1-4]

The scientific disciplines in the 21st century are being shaped by

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the merging of biology, genetics, engineering and computational sciences to create discoveries at the interfaces of these disciplines. When combined with the key ingredient of well-trained clinicians, this merger has resulted in remarkable strides in our understanding of disease and allows for more rapid advances, particularly at the molecular level. Even more so than in the past, dentistry will rely on science to create new diagnostic tests and therapies to improve patient care.[5-10] Optimizing care for patients must be our goal.

In this all-too-brief review, we highlight a few select examples of discoveries, drawn from the last 50 to 60 years, to celebrate the 150th anniversary of the American Dental Association (ADA). Readers should appreciate that this review is but a small sampler of the incredible scientific advances that have shaped what we know, how we think and how we practice clinical dentistry in the dawn of the 21st century. We have attempted to do this by focusing on specific themes and ideas to highlight prominent scientific discoveries and attainment of knowledge that have had an impact on patient care. Science knows no geopolitical boundaries and we recognize the profound contributions of scientists working in other countries. However, because this supplement commemorates the 150th anniversary of the ADA, we have concentrated on the scientific contributions of scientists who have worked in the United States.

LINKAGE OF DENTISTRY AND GENETICS

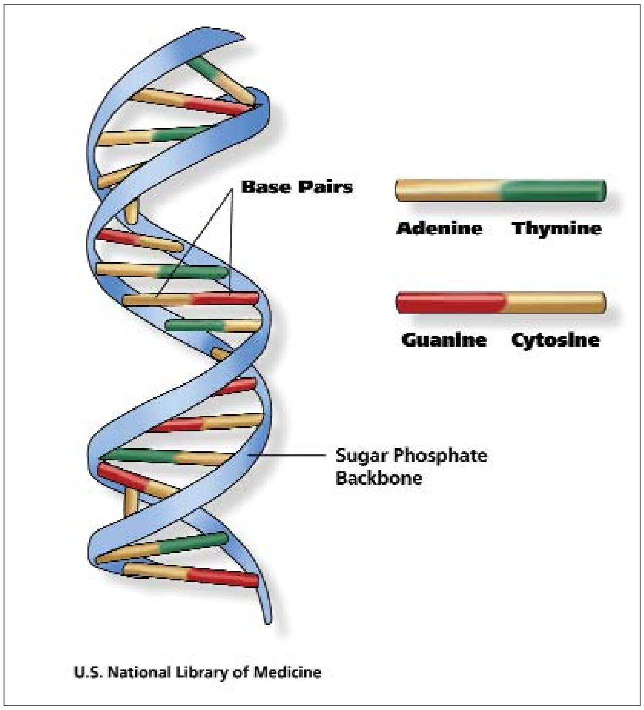
The engine of science has contributed to significant advances by mapping and deciphering the nucleotide letters of the human genome and by describing the proteome, the information that comprises all the genes and their encoded proteins that make us human. This has resulted in remarkably precise diagnostic tests and rapid improvements in patient treatment. One of the most extraordinary scientific discoveries of the 20th century was elucidating the structure and possible functions of DNA (see illustration[11]). Significantly, it was a dentist, Norman Simmons, who first isolated sufficiently pure DNA in 1952 (see photograph[12]); Rosalind Franklin then created the first x-ray crystallography images from that DNA. These images led James Watson, Francis Crick and Maurice Wilkins to predict the structure of DNA in 1953.[1] In Wilkins' acceptance speech for the Nobel Prize in Physiology or Medicine in 1962, he credited Norman Simmons for "having refined techniques of isolating DNA and thereby helping a great many workers, including ourselves."[13]

Norman Simmons received a bachelor's degree in science in 1935 from the City College of New York, New York City; a Doctor of Dental Medicine degree in 1939 from Harvard, Boston; and a Doctor of Philosophy degree in 1950 from the University of Rochester, Rochester, N.Y. His doctoral thesis was titled "Investigation of Submaxillary Mucoid and the Defense Mechanisms of the Mouth."[14]

Simmons was nominated for the Nobel Prize in Physiology or Medicine in 1972 in recognition of his fundamental studies of changes in light absorption associated with conformational changes within proteins and polypeptides: the so-called "Cotton effects" (named after Aimé Cotton). These studies led him to explore the structure of viral particles.[15] Thereafter, his fundamental scientific work in nuclear medicine and oral biology at the University of California, Los Angeles (UCLA), as well as his studies of the isolation of tobacco mosaic virus DNA and RNA, served as the foundation that led to the development of numerous nucleic acid and polypeptide biomarkers for disease diagnostics.

Robert Gorlin earned a bachelor's degree from Columbia University, New York City, and a dental degree in 1947 from Washington University School of Dentistry, St. Louis. He then made the University of Minnesota School of Dentistry, Minneapolis, his home base for the second half of the 20th century. Gorlin was widely known for his ability to deftly integrate his encyclopedic knowledge of craniofacial birth defects with clinical observation, phenotypic traits and specific genotypes. One of Gorlin's contributions was the ability to discriminate between syndromic and nonsyndromic birth defects. His memory of craniofacial anomalies was almost as extraordinary as was his clinical prowess; both dentists and physicians consulted him for his diagnostic expertise. Gorlin's diagnostic skills became known internationally through his lectures, book chapters, books and peer-reviewed publications.[16] From esoteric to mainstream diseases and disorders, he was considered an expert in diagnosing craniofacial-oral-dental birth defects. The key to his success was his ability to see, to understand and to integrate an array of seemingly disparate information: he saw the system of the

ABBREVIATION KEY. BMP: Bone morphogenetic protein. **NIDCR:** National Institute of Dental and Craniofacial Research. **3-D:** Three-dimensional. **UCLA:** University of California, Los Angeles.



DNA is a double helix formed by base pairs attached to a sugar phosphate backbone. Reprinted from the U.S. National Library of Medicine, National Institutes of Health, Bethesda, Md.[11]

Dr. Norman Simmons. Reproduced with permission of the University of Rochester Medical Center, Rochester, N.Y.[12]

body when others saw only derangements of its parts. Gorlin became one of the leading geneticists in the world and was the recipient of numerous awards, including the Award for Excellence in Human Genetics Education from the American Society for Human Genetics.[17]

By the end of the 20th century, researchers had begun to identify the specific role of genes in various oral diseases; this was, in no small measure, the result of the remarkable sensitivity and specificity derived from molecular biology for applications to clinical dentistry. For example, we have learned that Papillon-Lefèvre syndrome, an autosomal recessive disorder characterized by periodontal disease and palmoplantar keratosis and diagnosed mainly by dentists, is caused by a mutation in the cathepsin C gene.[18,19]

Another scientific discovery was the isolation, characterization and clinical application of the major gene for enamel formation: amelogenin. The collaboration of an interdisciplinary team from Baylor College of Medicine, Houston, and the University of Southern California, Los Angeles, enabled the first dental gene to be cloned.[20] Isolation of this gene to the X and Y chromosomes[21] provided a forensic tool to discriminate the corporal remains of males versus females and provided the basis for advancing our understanding of the Mendelian inheritance of enamel birth defects.[22]

Another major advance in dental genetics was the discovery that a gene on chromosome 4 generates three gene products: dentin phosphoprotein, dentin sialoprotein and dentin glycoprotein.[23,24] The molecular cloning and mapping of the gene for ameloblastin, the second most abundant enamel-forming protein, also was accomplished.[25] Furthermore, investigators have linked the human genome and proteome at the level of teeth, extending our understanding of normal and abnormal formation of the dentin and enamel tissues.[26]

Another use of genetic science is somatic cell gene therapy to treat human disease. Researchers at the National Institute of Dental and Craniofacial Research (NIDCR) are moving genes from the laboratory to chairside to treat salivary gland diseases.[27] It also may be possible to transfer genes to readily accessible salivary glands and use them as "biofactories" or as a source of proteins to treat diseases caused by deficient protein biosynthesis. As dentists, we appreciate that the mouth is readily accessible and that its tissues may provide a relatively easy route for introducing genes to prevent or treat a variety of oral and other diseases. The future holds great promise that researchers will identify the genetic basis of many diseases so that clinicians can provide specific preventive care and treatment to patients through somatic cell gene transfer therapy.

PROTEIN DISCOVERY, WOUND HEALING, TISSUE REPAIR AND STEM CELLS: EXAMPLES OF SCIENCE DRIVING CLINICAL PRACTICE

We have come a long way since osteoblasts first appeared in primitive bony fish (the ostracoderms). During this evolution, a bony armor formed around the head, leaving cavities for the organs of sight, smell and hearing and, of course, the brain. Eventually, 22 bones evolved to articulate and form the craniofacial-oral-dental complex. Bone has an essential role in supporting the teeth during mastication, but age, disease, trauma and birth defects all serve to remove bone. Today, our clinical challenge is to devise a strategy to generate bone to correct birth defects or to replace bone lost as a result of injury or disease.

In the 1960s, researchers observed that histiocytes were transformed into osteocytes by autoinduction, a process in which explanted bone induced new bone formation, often with hematopoietic bone marrow.[28,29] Huggins[30] showed the capacity of the urinary bladder to induce new bone formation when it came into contact with abdominal muscle cells, and Reddi and Huggins[31] described the biochemical sequences in the transformation of normal fibroblasts into bone cells. The extractable protein that induced new bone was termed "bone morphogenetic protein" (BMP),[32] and researchers used recombinant DNA technology to identify a complementary DNA clone for one of the BMPs, which allowed the new technology to produce therapeutic amounts of the protein.[33] The commercial availability of BMPs helped us understand how they work so that we can harness their healing powers. Overall, this research allowed this otherwise scarce protein to be manufactured in the laboratory for use at chairside and bedside.[34,35]

Efforts to examine the ability of dentin to induce bone led researchers to identify a small-molecular-weight protein isolated from dentin that induced naive cells to form cartilage and bone. Rather than a newly discovered BMP, the isolated protein is a small amelogenin protein that researchers previously thought was involved only in enamel matrix formation.[36-38]

The recovery of enamel matrix proteins, mainly amelogenin protein, led to the production of a commercial gel that can induce progenitor cells to regenerate bone and cementum in the treatment of periodontal disease.[39] Clinicians now use enamel matrix proteins and/or BMPs to recruit and direct resident stem cells to regenerate lost tissues such as periodontal ligament, acellular cementum and alveolar bone. The study of enamel matrix proteins, such as amelogenin, is continuing in the hope of discovering how they alter cells and direct their differentiation to form bone and cementum while attenuating the inflammatory response.[40,41]

Investigators working at NIDCR recovered stem cells from human primary teeth, a site that was not known previously to contain such cells.[42] In a large collaborative effort that reflects the intense research needed for progress in this field, researchers used stem cells in pigs to engineer a functioning cell-mediated root replacement, complete with a periodontal ligament.[43] Researchers also have shown that periodontal ligament stem cells,[44] as well as other sources of stem cells, modulate the immune response, offering hope for patients with autoimmune diseases such as lupus erythematosus that a new therapeutic tool can be developed.[45]

Scientists are investigating the use of implant-supported distraction osteogenesis that will prove useful for bone regeneration in craniofacial reconstruction.[46] They have shown that a unique population of cells with stemlike qualities, known as "the neural crest," responds to signals provided by members of the transforming growth factor family of molecules. The neural crest cells participate in forming the bones of the head and face, as well as contribute to the sutures that permit growth of the skull, while errors in cell signaling can result in developmental birth defects.[47,48] Collectively, this research provides insight into the molecular mechanisms that may cause craniofacial anomalies and offers great promise regarding treatment that can improve quality of life for affected patients.[49]

DIAGNOSTIC IMAGING

Previous achievements in science have fueled the creative advances in technology in the 20th century. In 1895, Roentgen accidentally discovered that human bones could be imaged, and that the images could be used for dental or medical diagnostics, resulting in the first opportunity to see inside the body without creating a surgical wound.[50] Otto Walkhoff, a dentist, obtained the first radiograph of the jaw just weeks after Roentgen's discovery.[51] A remarkable dentist, C. Edmund Kells used radiography, as well as fitted his dental operatory with electric equipment, compressed air and suction; these items, although improved, are still in use today.[52-54]

After World War II, Robert Ledley, a dentist and graduate of New York University, New York City, who worked at the precursor to the National Institute of Dental Research, revolutionized how we know what we see.[55,56] Ledley pioneered computerized tomographic scanning in the early 1950s. He took the scientific discovery of x-rays to a new level of understanding. His inventions, hardware and algorithms for software introduced a three-dimensional (3-D) approach by which x-rays were transmitted through varying tissue densities to capture 2-D and 3-D images of all parts of the human anatomy. This remarkable achievement was the precursor of modern diagnostic imaging used in both dentistry and medicine.

Dr. Robert Ledley. Courtesy of National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Md.

WOUND HEALING, TISSUE REPAIR AND ATHEROSCLEROSIS

Remarkable scientific advances have been made in tissue repair, wound healing and tissue regeneration owing to, in no small part, the genius of Russell Ross, a dentist who had a distinguished career in pathology. He served for many years as the chair of the Department of Pathology, University of Washington School of Medicine, Seattle.

Using transmission electron microscopy, a novel animal model of parabiotic mice, radiology and an exquisite knowledge of the early advances in wound immunology and pathology, Ross synthesized the essence of wound healing. In publications dating to the 1960s, he defined the timing, cytology, physiology, immunology and connective-tissue biochemistry of wound healing.[57,58] His strategy of using parabiotic mice enabled his team to trace cell origins and cell fate during various stages of wound healing. Simply stated, Ross' team provided the foundation for our modern understanding of wound healing.

During the early 1970s, Ross and his team proposed that localized injury to the lining of the arterial wall was responsible for the unusual accumulation of smooth muscle cells within the wall of the artery, thereby reducing the lumen of the vessel.[59] Ross used interdisciplinary scientific inquiry to study the problem of atherosclerosis. His team discovered a new growth factor called "platelet-derived growth factor" that stimulates proliferation of smooth muscle cells.[60,61] Curiously, these accumulated smooth muscle cells contain elaborate secretory vesicles that are filled with several types of collagen, fibronectin, metalloproteinases, proteoglycans and fatty acids that assemble into an abundant extracellular matrix associated with atherosclerosis. Ross[62,63] concluded that atherosclerosis is an inflammatory disease. These contributions are examples of how scientific advances in improving the human condition were derived from the passion and creativity of people who began their careers in dentistry.

TISSUE-DESTRUCTIVE ENZYMES

Tissue destruction was another focus of attention for dental scientists. Their efforts to understand tissue loss associated with periodontal disease led to significant advances in our understanding of enzymatic degradation of collagen, with the work of Fullmer and Gibson[64] revealing that collagenase is present in the tissues of the human host. This research had far-reaching consequences for other investigators working to understand the destructive process brought about by inflammation. Investigators identified a new class of metal-containing enzymes, the metalloproteinases, along with their endogenous inhibitory counterparts, that formed a yin and yang for homeostasis. These studies have had an impact in many areas of biomedical sciences, helping us understand such phenomena as cancer cell metastasis and angiogenesis, as well as the degradation of enamel matrix proteins during enamel biomineralization.[65-67] Knowledge about the destructive effects of inflammation also led to U.S. Food and Drug Administration approval and clinical use of collagenase-inhibiting low-dose doxycycline in the treatment of periodontal disease.[68] In addition, studies of the metabolism of the extracellular matrix led to the formulation of an artificial basement membrane, which allowed cells to be maintained in a 3-D architecture that resembled native tissue.[69]

SALIVA AS A DIAGNOSTIC FLUID

Saliva is emerging as an exciting diagnostic tool for dentists and physicians. For example, dental scientists at UCLA are investigating saliva as an aid in the diagnosis of oral cancer.[70] Many dentists have provided the foundation for using saliva as a diagnostic fluid. Dating back to at least 1960, Irwin Mandel of the School of Dental and Oral Surgery at Columbia University recognized the potential of saliva as an "informative body fluid."[71,72] His passion to understand saliva was infectious and attracted many dental scientists to this field of inquiry. Mandel's contributions to science opened up opportunities in many areas of biomedical scientific research and clinical practice with regard to the diagnosis of disease or monitoring the progression of disease or treatment by using salivary biomarkers. Mandel asserted that saliva, like blood and urine, provided informative clues about health and disease. His basic work in saliva sampling and analysis provided the framework for many contemporary salivary studies.

In the mid-1960s, dental scientists found that viral particles can be secreted through the salivary glands, thus connecting general health with the oral cavity.[73] Later, Oppenheim and colleagues[74] identified the molecular basis of the beneficial effects of saliva on the oral cavity by identifying antimicrobial properties of various salivary proteins; others provided the foundation for the use of enamel remineralization to control caries by identifying salivary proteins that modulate the maintenance of salivary calcium and phosphorous.[75,76] Other investigators[77,78] have been instrumental in characterizing the salivary proteome (that is, all of the proteins produced by the salivary gland); in doing so, they laid a foundation for the use of saliva as a diagnostic fluid, because it contains not only salivary proteins, but also proteins from other organs that can be used as surrogate markers for a variety of disease states.

While working at the University at Buffalo, The State University of New York, Michael Levine spawned several important discoveries regarding salivary proteins.[79] Levine and his colleagues identified the importance of salivary proteins as part of the framework for bacterial adherence to the teeth via bacterial proteins that interact with specific domains within salivary proteins, forming a molecular fastener similar to Velcro.[80] Other dental scientists who began their careers at the University at Buffalo contributed to our understanding of streptococci in the aggregation of human platelets and virulence factors associated with bacterial endocarditis.[81,82]

Bacterial biofilms are inherently resistant to antimicrobial agents and are associated with many infections, including caries and periodontal disease.[83] However, investigators have shown that protective immunity to caries may be achieved by ingestion of *Streptococcus mutans,* which can induce secretion of salivary immunoglobulin A.[84] These findings led other investigators to explore the possibility of producing a human vaccine to streptococci, an organism associated with dental caries, the most common infection of mankind.[85,86]

HISTORICAL PERSPECTIVE

Dental science in the 20th century evolved from the crucible of William J. Gies, a biochemist at Columbia University who convinced the Carnegie Foundation to support an analysis of dental science and education in the United States, aligned with the foundation's previous support of Flexner and Pritchett's[5] analyses for medicine. The Gies report was published in 1926, and it heralded a new age in American dentistry that would have a foundation in the biological, chemical and physical sciences, as found in major academic health science universities.[6]

In 1948, leaders of the ADA helped establish a dental institute within the National Institutes of Health in Bethesda, Md. The interdisciplinary work of so-called "dental research" blossomed and became the beacon of dental science for the world. The first major scientific achievement of the fledgling dental institute was the use of fluoridation to prevent caries, made possible by H. Trendley Dean (first director of the then National Institute of Dental Research).[87] Thereafter, the institute focused on fundamental research in many areas, such as oral microbiology and immunology, human craniofacial-oral-dental genetics, salivary glands and saliva, connective-tissue biochemistry, bone biology, craniofacial biology, microbial genomics and proteomics, oral neoplasia, and biobehavior and pain, as well as international outreach.

One essential mission of NIDCR is making scientific training available for oral health professionals, people who continue to acquire new knowledge and make discoveries and develop applications, thereby shaping what is thought and taught in our profession. Through the years, it has nurtured many scientists and clinicians to improve the health of Americans. The surgeon general's report on America's oral health in 2000 marked the new millennium by emphasizing that good general health must include good oral health,[88,89] a mission we celebrate on the 150th anniversary of the ADA.

CONCLUSIONS

Advances in the fields of genetics, developmental and stem cell biology, and many other disciplines continue to fuel innovative research findings that form the basis for new diagnostic tests, therapeutic interventions and procedures that improve patients' quality of life. Scientists are on the threshold of applying knowledge in stem cell biology to regenerative medicine and dentistry, enabling clinicians to consider using biological engineering to replace tissues and organs lost to disease or trauma. ■

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The authors thank their colleagues for the many stimulating conversations and manuscripts that formed the foundation of this brief review. They apologize for the exclusions required by space considerations. They note the passion that investigators bring to their work, that they share with their colleagues and that they instill in their students. Their traits assure us that the next century will be filled with discoveries and innovation that will improve the care of our patients.

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