The Impact of Research on the Future of Dental Education: How Research and Innovation Shape Dental Education and the Dental Profession

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Abstract: Scientific inquiry and discovery are the fuel for education, research, technology, and health care in all the health professions: dentistry, medicine, nursing, pharmacy, and allied health sciences. The progression of discoveries from basic or fundamental to clinical research is followed by the progression from clinical to implementation and improved health outcomes and processes. Generally, implementation science is the scientific study of methods to promote the systematic uptake of research findings (e.g., basic, translational, behavioral, socioeconomic, and clinical) as well as other related evidence-based practices into standards of care, thereby improving the quality, effectiveness, and cost benefits of health care services. There is little doubt that science has and will continue to provide the essential fuel for innovations that lead to new and improved technologies for risk assessment, prevention, diagnosis, treatments and therapeutics, and implementation for addressing oral and craniofacial diseases and disorders. The history of the U.S. dental profession reviewed in this article gives testimony to the continued need for investments in scientific inquiry that accelerate progress in comprehensive health care for all people. This article was written as part of the project "Advancing Dental Education in the 21st Century."

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History teaches that a look into the past of dentistry will inform appreciation of our legacy and will enable a clearer view of future opportunities and challenges in education, research, and patient care. Fortunately, excellent resources provide many insights into the establishment of dentistry, dental education, science, oral health industries, and patient oral health care in the U.S.[1-16] Our country's discovery of the critical need for federal government support for biomedical research and public health is a narrative of advocacy, cooperation, collaborations, and coalitions. As the nation developed and enlarged following the Civil War, organized dentistry also developed and became an advocate for federally sponsored public health, scientific inquiry to improve health, and the need for an independent dental research institute. Thereafter, scientific research and the establishment of standards in education and training emerged that translated into remarkable improvements in the health of America. Investments in the biological and digital revolutions of the 20th century are providing returns in the early 21st century and will do so into the future.[1,8-10] The American Dental Association (ADA), American Dental Education Association (ADEA), American Association for Dental Research (AADR), and National Institute for Dental and Craniofacial Research (NIDCR) each evolved from infancy to childhood, to adolescence, to mature and significant institutions.

Today, opportunities as well as challenges are related to the acquisition and management of a rapidly accelerating knowledge base for the biomedical, behavioral, and health-related sciences. This knowledge base is impacting academia, government, industry, and health care in the U.S. and beyond. For clinicians, educators, scientists, related industries, and the population, the best is yet to come. This article intends to provide an overview of the development of the U.S. dental profession and dental education and the essential role of science and research in that history. The article was written as part of the project "Advancing Dental Education in the 21st Century."

Development of Dentistry as a Profession

In the 20th century, the human lifespan in the U.S. doubled, with reduced infant mortality and reduced morbidity, accompanied by enormous advances in quality of life.[1] Now in the early 21st century, Americans live longer, have fewer cavities, and keep their teeth longer than their forebears. This statement rings true for most, yet there remain profound health disparities in more than 20% of the population. The shared goal of the dental profession continues: how to ensure health care access, quality, and affordability for all people.

The progress in oral health was made possible by an aligned coalition of disparate components: the nation's dentists, dental hygienists, organized professional societies, academic and government scientists, industry scientists, foundations, and federal and state public health officials played significant roles in advocacy and bringing about such remarkable advances.[4] Their mission has been and remains to improve the oral health of not just Americans but people all over the world. Scientific advances have profoundly changed society and dentistry in ways no one could have imagined during the decades before and after the Civil War, at the beginning of the 20th century, or even just a few years ago. Dentistry was an empirical endeavor when the ADA was founded almost 160 years ago.[14] The founders of U.S. dentistry were not aware of the lack of a scientific basis, yet they worked towards improvement of the standards and quality of the profession through scientific and technical investigations and applications and sustained advocacy.

Dentistry started modestly in the American colonies. In the third decade of the 17th century, William Dinley, a dentist, came from England to serve the Plymouth colony.[11-13] Dinley provided empirical oral health care for the nearly 2,000 people living in the colony. The chief complaint was toothaches, and treatment was often extraction. Although George Washington and other early leaders used the services of dentists, neither Washington nor his scientifically inclined 18th- and early 19th-century successors found a place for scientific research in the young, forming federal government.[12,13] In the first 100 years of the United States, Congress showed chronic reluctance to allocate public funds for scientific purposes.[5,11-14] In those early years, it was assumed that doing scientific research was not the province of government, but rather an "undisputed domain of private citizens, or of state and municipal governments."[13]

From the Babylonian savants of 5,000 BC to the 17th and early 18th centuries, it was assumed that "worms" were the cause of toothaches and bleeding gums.[11-14] In 1728, Pierre Fauchard, the father of modern dentistry, published *Le Chirurgien Dentiste ou Traite des Dents,* which included theory and principles of clinical practice as well as a chapter on the relationship among the oral cavity, teeth, and systemic diseases.[4,5] Another milestone was the work of John Hunter, a Scottish anatomist, who investigated the effects of various diets on the enamel and dentine of animal teeth and then published *The Natural History of the Human Teeth* in 1771. This publication contains an exquisite vocabulary to describe the anatomy for the craniofacial-oral-dental complex. Meanwhile, French chemists began to use ceramic porcelain for dental applications, and an English chemist named Joseph Priestley discovered nitrous oxide for the management of pain during dental surgery.[13] At that time, European countries were the center for scientific discoveries in chemistry, physics, mathematics, natural history, and medicine, as well as dentistry.[8-10]

As the New World's population of European settlers grew, increasing numbers of European immigrants with health professions credentials came to America with energy, creativity, innovations, and a sense of scientific discovery. In 1790, James Gardette, a Philadelphian dentist trained in Europe, published one of the earliest American publications on tooth decay and periodontal disease, "Remarks on the Diseases of the Teeth," in the *American Museum Magazine*.[4,5] After the War of 1812, Charles Ballard observed that the majority of dentists lacked adequate professional education and training—a comment that served as an early benchmark for the emergence of more formal education and training for U.S. dentists. This development was supported by Vermont-born Levi Spear Parmly, who conducted experiments on extracted human teeth and concluded "that caries universally commences externally" when stagnated food debris penetrated through minute apertures formed in enamel. By 1819, Parmly was promoting oral hygiene practices to prevent the process of tooth decay.

John and Chapin Harris started the dental school movement in the U.S.[13] John Harris used his home in Bainbridge, Ohio, for the first school of dentistry and dental surgery in North America. His brother, Chapin, graduated from that school and in 1840 joined Horace Hayden and two physicians, Thomas Bond and H. Willis Baxley, to found the first dental college in North America, the Baltimore College of Dental Surgery. In 1844, Horace Wells demonstrated the efficacy of nitrous oxide in managing pain during tooth extraction. Thereafter, several dentists established the *American Journal of Dental Science.* In 1840, the Chapin Harris group also formally organized the American Society of Dental Surgeons. Harris and his dental colleagues led the way for a convergence of theory and practice, science, education, and criteria for standards of oral health care.

After a few failed attempts, the ADA was formed in 1859 and drafted a code of ethics.[14] Further, it encouraged a formal curriculum and education for all dentists. In 1870, only 1,305 (15%) of the 7,839 dentists in the country held dental school diplomas. This low percentage stimulated hundreds of dentists to work to create a sufficient number of dental schools with education and research faculty to meet the oral health demands of the growing society.[5,13] By 1884, ten of the nation's 22 dental schools formed the National Association of Dental Faculties, designed to develop national standards for education and to raise admission requirements. By 1913, Alfred Fones started the first dental hygienist school in Connecticut.[13]

During this time in U.S. history, global as well as domestic issues increased immigration of Europeans to the U.S. by the thousands, including many physicians, dentists, and physical and chemical scientists.[13] This immigration during the Industrial Revolution brought highly educated professionals to the young country who rapidly influenced the art and science of the dental profession entering the 20th century. At the same time, a number of U.S. dentists travelled to Europe to learn from highly accomplished scientists in France, England, and Germany. For example, Willoughby D. Miller, a U.S.-trained dentist, studied with the famous German bacteriologist Robert Koch at the University of Berlin and with Louis Pasteur in France.[15] The British, French, and German governments saw the support of fundamental scientific research as being in their national interest, and such federal policies fostered a robust scientific community. These European policies did not go unnoticed by the emerging U.S. government.[5] Further, the mentored experiences coupled with ambitious experimentation resulted in 20 years of research, experimentation, and numerous publications. Miller convincingly demonstrated that bacteria produced lactic acid from fermenting starch and sugar particles adherent to tooth enamel surfaces resulting in tooth decay.[4,5,15] He deduced that dental caries occurred in stages (decalcification, infection, and putrefaction of the remaining organic matrix) and provided the first evidence that tooth decay was an infectious disease.[5,15]

As the 19th century evolved into the 20th, European and North American countries were fully engaged in scientific discoveries and accepted the assumption that science and technology informs health care and improves the human condition.[13] By the mid-19th century, the U.S. was considered by many Europeans to be the epicenter of innovations in dentistry, based primarily on applied clinical research rather than the more basic biological, chemical, and physical sciences that flourished in Europe. In no small measure, politics, economics, and growing optimism fueled North American innovations.

Examples of U.S. innovations in dentistry included Charles Goodyear, who patented the rubber vulcanite process in 1844, a discovery that became the rubber base for false teeth and denture fabrication.[4,5] James Morrison invented the first dental foot engine for drilling cavities and preparing teeth for restorations from crown and bridge procedures. Wilhelm Roentgen discovered x-rays in Germany in 1895, and Edmund Kells and J.W. Morton were among the first U.S. dentists to promote the use of dental x-rays. William Taggart of Chicago advanced the use of gold casting to fabricate dental restorations.

Greene Vardiman Black was one of the most distinguished dental scientists of the 19th and early 20th centuries.[4] Among his intellectual gifts was the ability to understand and synthesize complex information and to communicate his thinking and analyses through writings such as *A Descriptive Anatomy of Human Teeth* and *Operative Dentistry and Dental Pathology.* A gifted clinician, dental scientist, and educator, Black became in 1897 the dean of Northwestern University School of Dentistry. Also in the U.S., innovations were introduced in oral and maxillofacial surgery by Simon Hullihen, the characterization of oral deformities and their correction by Norman Kingsley, the classification of malocclusion by Edward Angle, surgical procedures for the closure of cleft lip and/or cleft palate by Truman Brophy, and the use of radiographs to detect anatomical and pathological conditions associated with teeth by C. Edmund Kells. These and many other contributions enabled dentistry to rapidly grow in the late 19th and early 20th centuries.[4-10]

Rise of Dental Public Health and Dental Science

The earliest federal government recognition of dentistry came soon after the Civil War.[5] The war illuminated such public health issues as water and air pollution, rampant bacterial infections, dietary issues, health literacy, public transportation, irrigation for food production, and much more. It was becoming apparent that the federal government needed scientific advice and innovations to improve the public's health. It was Lt. Gen. John Shaw Billings, a physician, who acknowledged the importance of publications on dentistry, dental science, and medicine. His keen appreciation for scientific and technological literature related to health issues served to eventually catalyze the National Library of the National Institutes of Health (NIH). While he built a national medical and dental library, Billings also appreciated the value of American industry, and he worked closely with Samuel S. White of the S.S. White Dental Supply Company to share literature and discoveries.[4,5] Furthermore, he brokered conferences with the American Medical Association (AMA) and the emerging American Public Health Association (APHA) in the late 19th and early 20th centuries. These and other advocacy activities, collaborations, and coalition building led Billings to become a spokesperson for creation of a national public health entity that enabled a convergence of bacteriology, acute bacterial infections in humans, and fundamental scientific research in medicine and dentistry. By 1885, the ADA and AMA were funding and encouraging biological research for the public good.[5]

Despite scurvy and bleeding gums (vitamin C deficiency), toothaches, "bad teeth," and yellow fever and cholera epidemics, the federal government did not recognize the association between the practice of dentistry and scientific research until the early 1900s.[5] This recognition evolved due to significant leadership in the private sector. Thomas W. Evans supported a museum and dental research institute in Philadelphia, which was integrated into the University of Pennsylvania Dental School in 1912. At Harvard, a saliva analysis research program was funded in the Department of Chemistry. Philanthropists such as the Forsyth brothers in Boston, George Eastman and Henry Lomb in Rochester, New York, and others provided private funding for public health programs focused on children and studies of bacteria related to dental caries and periodontal disease. In the last decades of the 19th century, numerous foundations and philanthropies were established that generously supported the oral health needs of children throughout the U.S.

The early 20th century was a unique time for the emergence of epidemiology of many diseases that affected the dentition and oral mucosa.[5,16] From a dental public health perspective, the following question was asked by W.G. Ebersole, a dentist, physician, and chair of the Oral Hygiene Committee of the National Dental Association (NDA): "What programs might be created to prevent tooth decay in children?"[5] Surveys in Ohio in 1910, for example, had shown that 97% of children presented "defective mouths." By 1912, the U.S. Public Health Service (USPHS) was established and authorized by Congress "to study and investigate the diseases of man and conditions influencing the propagation thereof." In 1913, the federal government organized the Indian Health Service (IHS) in the Bureau of Indian Affairs since the use of public health metrics with demographics had illuminated the desperate plight of American Indian populations. Comparable efforts appeared across the nation such as those in Illinois, North Carolina, Kansas, Massachusetts, Washington, DC, and Virginia. The statistics gained from municipalities, states, and regions served as the foundation for future dental research as well as advances in dental education and clinical practice.

Science and Research Become Core of Modern Dentistry

After the turn of the 20th century, detailed knowledge of the dental problems of U.S. soldiers in the Spanish-American War informed the federal government's decision to recruit and support dentists in the armed forces.[4,5] It was assumed that healthy teeth and mouths in soldiers were in the national interest, so support of healthy teeth became a factor in national defense.[5] Thereafter, the Navy, IHS, and USPHS employed dentists. Following World War I, leadership emerged from the private sector of science in industry and academics, as well as dental and medical organizations, that called for more emphasis on scientific research. The stage was set for a major advancement for dental education, science, research, and clinical practice.

Dental science and education in the 20th century evolved from the crucible of William J. Gies, a professor of biological science at Columbia University, who convinced the Carnegie Foundation to support an analysis of these fields in the U.S. and Canada.[3,4] He provided leadership for more emphasis on education and research in accredited universities and dental schools. He founded the *Journal of Dental Research* in 1918 and, in 1920, organized the International Association for Dental Research (IADR) designed to bring together dentists and scientists to enhance dental research. In 1926, he published a study for the Carnegie Foundation of the Advancement of Teaching that focused on dental education and research in North America.[3] The Gies report recommended that dental schools in the U.S. and Canada improve their curricula by employing well-trained, full-time teachers, encouraging and conducting research, and providing adequate libraries. Each recommendation corresponded to what was recommended in the 1921 Flexner report on medical education.

The Gies report made five major recommendations: "1) within universities, dental education should be perceived and supported like medical education; 2) teaching and research in dental schools should be as effectual as the best in the university and the status of the dental faculty should be raised accordingly; 3) the preparatory education and admissions requirements for dental education should be identical to those for medical education; 4) the dental curriculum should result in a general practitioner within three years; and 5) dental education should provide an optional full-year graduate curriculum, separate or combined, including dispensary and hospital experience as well as an opportunity and encouragement for research, and should be provided for all types of specialization in oral science and art, especially those of practice, public health administration, teaching, and investigation."[3] In Chapter XII (General Views and Conclusions), Gies further argued: "The dental graduate should be the peer of the medical graduate in all important personal attributes and in professional capability. Dental faculties should show the need in medical schools for integrated instruction in the general principles of clinical dentistry and in its correlations with clinical medicine and should also cooperate in teaching stomatology to medical students and in conducting effectual dental service in hospitals and dispenseries."

Carnegie Foundation philanthropy coupled with leadership from the private and academic sectors championed the cause for major revisions in dental and medical education.[2-5] In 1923, the American Association of Dental Schools (AADS; now ADEA) was founded as a nonprofit association representing academic dentistry and located in Washington, DC. Through professional networks of that era, the ADA, AADS, National Bureau of Standards (NBS), and USPHS made many efforts to communicate, cooperate, and coordinate their impact on the dental profession. For example, the ADA Research Commission on research grants aligned with the Carnegie Foundation and awarded $85,000 to the University of California Dental School "to undertake, through the cooperation of a number of men in different fields of science, a joint study of pyorrhea and its possible relation to other human maladies."[5]

Following World War I, many dentists encouraged the director of the NBS to develop standards and specifications for dental materials since proprietary control of dental products was the norm.[4] This was a time without federal or state regulation of dental materials or therapeutics. Thereafter, Wilmer Souder, G.V. Black, and Louis Weinstein provided the profession with new information on the composition, physical and chemical properties, and techniques for the proper use of a large number of dental materials. The ADA Research Commission enhanced the mission of the NBS and recruited George C. Paffenbarger as the first dentist to work at the NBS. In 1928, the Paffenbarger Research Center was established to serve as the research unit of the ADA and to actively collaborate with the NBS and National Institute of Standards and Technology (NIST) to create new science-based dental materials.[4,5,17] This remarkable asset has endured and resulted in technologies that became hallmarks of dentistry such as high-speed handpieces, rhodium-coated front-surface mirrors, panoramic radiography, dental sealants, tooth-colored resin-based composite restorative materials, calcium phosphate remineralization, and calcium-phosphate bone cements. This research center continues today, now named the Volpe Research Center in honor of Anthony Volpe, who served as scientific director of Colgate for many years. NIST continues to invest in innovation, measurement, and analyses that lead to new solutions to complex problems for oral health care.

Establishing Dental Research at the NIH

A significant advocate for federally sponsored dental research was Clinton T. Messner, who graduated from Indiana Dental College in 1908 and entered the USPHS in 1921, then assigned to Washington, DC.[5] His assigned role was to supervise field hospital dentistry around the nation. Messner's cordial, intelligent, and relaxed style focused on an idea to create an independent dental section that could coordinate dental health activities[4,5,10-17] and conduct research on dental caries as "the most prevalent disease" facing humans.[4]

Meanwhile, the ADA formed a coalition for advocacy with Messner in 1923 to apply pressure supporting federally sponsored dental research.[4] C. Willard Camalier, a dentist from Washington, DC, and Homer C. Brown, a dentist from Columbia, Ohio, joined with Messner on behalf of the ADA Legislative Committee to encourage the U.S. Senate to include a separate dental research section in the emerging NIH (previously known as the Hygiene Laboratory). On May 26, 1930, President Herbert Hoover signed legislation (Public Law 251) authorizing creation of the NIH with the mission to investigate human disease and a budget of $750,000 to build buildings, equip laboratories, and provide scientific staffing. At its July 1930 meeting, the ADA enthusiastically endorsed the NIH to conduct dental research. Overall, it seems that dental research was added to federally sponsored research for two reasons: tooth decay in children as observed by physicians, and the persistent and successful lobbying and advocacy by Messner and his colleagues.[4,5,11-14]

Role of Fluoride Research in 1930s and '40s

As the new NIH started operations in the 1930s, the leading American dental disease scientists were conducting research in a handful of academic institutions, and there were no dentists doing scientific research within the federal enterprise.[5,8] At that time, a new phase of research was emerging based on earlier reports of a strange dental disorder of disfiguring tooth discoloration near Colorado Springs reported by Fredrick S. McKay.[4,5] McKay, who graduated in 1900 from the University of Pennsylvania Dental School, discovered that many of his patients in Colorado Springs were afflicted with permanent stained teeth that he termed "mottled enamel."[5] G.V. Black doubted that the Colorado water was the cause, but McKay insisted that an ingredient in the drinking water supply caused the staining in enamel.[5] Similar observations were reported by Fernando Rodriguez, a field dentist in the IHS, based on his observations of the Pima Indians on their reservation in Arizona.[18]

By 1925, McKay had requested the USPHS to analyze the water supplies of communities in nine states, from Idaho to Arizona, where mottled enamel teeth of schoolchildren had been reported.[5,18] McKay was one of the first to identify the extreme condition among the Pima Indians of Arizona as well as along the border of Mexico with respect to diabetes, hypertension, and periodontal disease with tooth loss. His observations highlighted health disparities based on behavior choices, alcoholism, and poverty.

Testing the water in those nine states found analyses varying from 13 ppm of fluoride in Arkansas to 6 ppm in Colorado Springs.[4] Uncompromising advocacy by the ADA, the USPHS, and the creators of the NIH eventually led to the hiring of a senior USPHS dentist, 38-year-old Henry Trendley Dean, to become the first dental scientist to conduct the first study of mottled enamel in the U.S. in 1931.[4,5,16] Dean held the rank of dental surgeon, with extensive clinical experiences while stationed in Boston, New York, St. Louis, and Washington, DC. The mottled enamel study led to the NIH's embracing epidemiology and a close professional collaboration between Dean and McKay.[5,18]

Despite difficulties during the Great Depression, including limited resources for doing scientific research of any type, attention to the mottled enamel problem continued, and Dean suggested that McKay had observed "fluorosis" resulting from water fluoride levels above 1 ppm as the most likely cause.[5,18] Less than six months into the study and analyses, Dean discovered an association among children with tooth decay, children with mottled enamel, and fluoride levels in the drinking water.[5] His untiring efforts, focus, and advocacy reached across federal agencies, organized dentistry, industry and government scientists, and academics. He was also keen to support development of highly accurate instruments for the reproducible detection and measurement of constituents in drinking water, which led to his advocacy for 1 ppm fluoride or less in drinking water as a national priority. His article "Endemic Fluorosis and Its Relation to Dental Caries" launched a new era in U.S. dentistry, bringing together education, scientific research, and clinical care.[4,5,8] By 1939, he had recruited a group of highly talented dentist scientists to pursue the epidemiology of fluorosis, fluoride effects on oral microbiology, and prevention of tooth decay from drinking fluoridated water at optimal levels of 1 ppm.[4,5,12-14,19]

Thereafter, through the World War II years, Dean and his team persisted, and by January 25, 1945, the first fluoride was added to the drinking water of Grand Rapids, Michigan, initiating a remarkable clinical trial that established clinical efficacy and soon became one of the most significant public health advances of the 20th century.[1-10,17] This remarkable success—based on investigations spanning a good part of the late 19th and first half of the 20th centuries—served as an indelible scientific accomplishment for the dental profession and public health and led to the realization that science informs prevention of the number one chronic disease of children as well as advances in clinical dental practice.

Postwar Focus on Science and Establishment of NIDR

After the war, achievements in education and research advanced in a broader social, political, and cultural context. Political leadership and the dreadful legacy from World War II motivated international and domestic economic, educational, and social changes of great magnitude.[8-10] Establishment of the United Nations with the World Health Organization (WHO), legislation for building land grant universities, the GI Bill, interstate highways, the Marshall Plan to rebuild Europe, the rebuilding of Japan, and significant immigration of outstanding scientists and clinical scholars from Europe to the U.S. prior to and following the war—each of these developments served as discrete yet synergistic factors that increased federal government, foundation, and industry support for biomedical, physical, chemical, and behavioral scientific research.

Near the end of the war, President Franklin Roosevelt appointed Vannevar Bush to serve as director of the Office of Science and Technology.[4] Bush was an American engineer, inventor, academic leader, and national science administrator. He had joined the faculty of the Massachusetts Institute of Technology (MIT) in 1919 and founded the company Raytheon in 1922. One of his significant innovations was to create digital circuit design theory. He became vice president of MIT and dean of the MIT School of Engineering in 1932 and president of the Carnegie Institution of Washington in 1938, the same year he was appointed to the National Advisory Committee for Aeronautics and soon became its chair. President Roosevelt appointed Bush to serve as chair of the National Defense Research Committee. He served through the development of essentially all military R&D that was carried out during World War II, and he coordinated the activities of some 6,000 U.S. scientists in the application of science to warfare. Before the war ended, Roosevelt asked Bush in 1944 to further serve as an architect to design the nation's science and technology plan for the postwar era. Bush's 1945 plan "The Endless Frontier" included creation of the National Science Foundation (NSF) and introduction of basic, translational, and clinical science and technology to the Department of Defense mission. He also designed the formal establishment of the NIH.

The NIH plan was realized in 1948 with establishment of the National Institute for Dental Research (NIDR), National Cancer Institute (NCI), and National Heart Institute (NHI), the only three NIH institutes at the time.[5,8-10,20] The Bush plan also set national standards for secondary and post-secondary education in mathematics and the biological, chemical, and physical sciences. At that time, education and research became national priorities for the nation's defense. The plan emphasized the need to gain a scientific understanding to prevent and treat victims of trauma and infection by advancing imaging such as sonography that led to ultrasound and the national realization that healthy teeth are in the national defense interest.[20]

At the same time, physics, engineering, computations, and communications were accelerated through major investments from industry, government (Departments of Defense, Energy, and Agriculture as well as the NSF), and not-for-profit foundations.[8-10,16,19-21] These significant investments rapidly translated into increased numbers of engineers, scientists, health care professionals, and associated health care support industries (manufacturing, distribution, insurance, and technology support). Increasingly, public and private universities focused on government-funded research in academia, which included research-intensive dental schools.

In this environment of growth and optimism, President Harry Truman signed HR 6726 "National Dental Research Act" establishing the NIDR on June 24, 1948.[5,8] He signed the bill surrounded by key advocates including C. Willard Camalier (director, ADA Washington office), Rep. Walter E. Brehm (Ohio) who authored the bill, H.B. Washburn (president, ADA), Bruce D. Forsyth (chief dental officer, PHS), Carl O. Flagstad (chair, ADA Legislative Committee), Daniel F. Lynch (past-president, District of Columbia Dental Society), and H. Trendley Dean (dental director of the NIH, who became the first NIDR director). This monumental effort resulted in a mission for the NIDR to provide national leadership in dental research.[4,5] Prior to this historic event, the dental research effort was known as the Dental Research Section of the Experimental Biology and Medicine Institute of the NIH and included staff members Dean along with Edwin Short, Frank McClure, Francis Arnold, Stanley Ruzika, David Scott, William Poole, and Bertha Blue.[5] (See Table 1 for timeline of NIDR/NIDCR directors and major accomplishments from its founding to the present.)

The original strategy for the NIDR in Vannevar Bush's plan was to invest federal funds to address societal needs (defined as in the national defense or enlightened self-interest) to understand, diagnose, treat, manage, and eventually prevent craniofacial-oral-dental diseases and disorders.[4,5,9,19-21] The legislation signed by President Truman clearly outlined the institute's five responsibilities: 1) Conducting and fostering research on the cause, prevention, methods of diagnosis, and treatment of dental diseases and conditions; 2) Promoting coordination of institute research with that of other agencies, organizations, and individuals; 3) Obtaining expert consultants from the U.S. and abroad; 4) Cooperating with state health agencies in prevention and control of dental diseases and conditions; and 5) Providing training and instruction within and outside the institute on "matters relating to the diagnosis, prevention, and treatment of dental diseases and conditions."[5] In particular, the fifth responsibility translated into the creation of training programs designed to produce independent principal investigators for biomedical research in dental and medical schools around the country. This activity utilized mentoring, apprenticeship, and inquiry-based scientific investigations, which were thus infused into the teaching environments of U.S. dental schools.

The increasing federal investment enabled the dental profession to rapidly evolve from an apprenticeship into a sophisticated health profession with a robust scientific basis provided from academic and industry research.[2-10] Scientific advances fueled technology and public health in many ways, including the retention of teeth for a lifetime, reduced tooth decay and associated tooth loss, and many innovations to diagnose hard and soft tissue lesions in the oral cavity.[4,5,8] Dentists gained public respect as professionals, and dental schools became increasingly aligned with the mission of their parent institutions as research-intensive. The efforts of a number of key dental and medical public health leaders, at the right time and the right place, created a coalition that gained Congressional, academic, and industry support that profoundly accelerated the depth and breadth of dental science for the public good of America.

Federal-University Research Partnerships

Following World War II, federal investments focused on the nation's infrastructure with legislation requiring the building of land grant universities around the nation, while creating a national dental and medical scientific research workforce through training grants and fellowships.[5,8-10] Investments were required to rapidly build facilities and infrastructure in the NIDR Intramural Program as well as for the national Extramural Program communities (universities, foundations, research institutes, and industries).[2-5] Many extramural institutions were funded in order to create a national dental research and training infrastructure: funds supported buildings, laboratories and clinics, research equipment, research animal facilities, and training funds for dentists and non-dentists to pursue research on craniofacial-oral-dental problems. In addition, the ADA and AMA provided recruitment support and funding for science staff fellows to learn and work at the three NIH institutes (NCI, NHI, and NIDR). Over several decades, a sophisticated cluster of dental and medical schools in research-intensive universities was also established. The first major accomplishment, derived from chemistry, demonstrated in clinical trials that fluoride in drinking water produced a significant reduction in tooth decay.[4,5-11,13,16,17] Thereafter, those discoveries became major public health tools to improve public oral health. In spite of successes like these, the recruitment of dental graduates into careers in biomedical research has continued to be a challenge for achieving the full realization of dental research.[8,9,19,21]

Numerous investments followed, such as creation of the Intramural Genetics Branch on the NIH campus in 1957 to address genetic diseases of the craniofacial-oral-dental complex led by Carl Witkop.[4,5,8-10] Witkop, who held a DDS and an MS in oral pathology, had interests focused primarily on hereditary abnormalities of teeth (e.g., amelogenesis imperfect, dentinogenesis imperfect, and osteogen-

Table 1. NIDR (1948-98) and NIDCR (1998-present) directors and their accomplishments

H. Trendley Dean, 1948-53. Provided first leadership for dental research at National Institutes of Health (NIH) (1931); appointed director of Dental Research Section (1945); became first director of National Institute of Dental Research (NIDR) (1948); provided for oversight by National Advisory Dental Research Council; awarded first extramural dental research grants and fellowships; supported research on mottled enamel and fluoride, fluorosis, and prevention of dental caries by fluoride and water fluoridation; established intramural research units for basic and clinical science; created an intramural section for epidemiology and biometry; advocated for integration of dental health into mainstream medical research.

Francis A. Arnold Jr., 1953-66. With H. Trendley Dean, led Grand Rapids, MI, fluoridation study that established water fluoridation as a safe, effective, and economical way to prevent dental caries; established first Board of Scientific Counselors to provide advice to the director for intramural research program; established intramural Laboratory of Biochemistry; provided oversight for intramural building and laboratory facilities of intramural research program; encouraged U.S. dental faculty members to apply for research grants; expanded NIDR research to dental materials, human genetics, and oral medicine; funded first multidisciplinary cleft palate study.

Seymour J. Kreshover, 1966-75. Previously served as scientific director of NIDR's intramural research program; enhanced grants in the neurosciences, pain research, caries prevention through National Caries Program (a merger of both intramural and extramural programs), and craniofacial research and cleft palate reconstruction; enabled formation of intramural Laboratory of Oral Medicine, Laboratory of Microbiology, and expanded research investments in periodontal diseases, autoimmune diseases. and allergic disorders; expanded intramural research and grants to include pain research and anesthesiology, as well as behavioral sciences.

Clair L. Gardner (Acting), 1975.

David B. Scott, 1976-81. Expanded extramurally supported research in periodontal diseases and oral and pharyngeal cancer; enhanced both intramural and extramural capacity to conduct clinical studies; stimulated expansion of grants in behavioral and social sciences; established intramural Diagnostic Systems Branch to study noninvasive diagnostic techniques; established intramural Clinical Investigations and Patient Care branch to coordinate and integrate patient treatment with clinical research conducted elsewhere in NIDR and NIH; supported first consensus development conference on dental implants.

Harald Loe, 1983-94. Established Epidemiology and Oral Disease Prevention Program to include periodontal and other diseases of the oral cavity; established Dental Scientist Award program to enhance clinical research; expanded extramural dental research to include research centers in collective fields of oral biology, oral and craniofacial diseases and disorders, and minority oral health; initiated first national surveys of U.S. adult oral health and children's caries; initiated programs of continuing dental education and public information to translate research findings; established World Health Organization Collaborating Center for Dental Research and Training.

Dushanka V. Kleinman (Acting), 1994-95.

Harold C. Slavkin, 1995-2000. Engineered renaming NIDR as National Institute of Dental and Craniofacial Research (NIDCR) to reflect expanded research mission; promoted research in developmental biology, genetics, oral complications of HIV/AIDS, and oral health needs of minority and vulnerable populations; encouraged scientists outside of dentistry to focus on structure and function of oral and craniofacial area; reached out to dental profession, patients' groups, and the public to promote communication of NIDCR research findings; facilitated NIDCR leadership in *Oral Health in America: A Report of the Surgeon General,* the first of its kind dedicated solely to oral health.

Lawrence A. Tabak, 2000-10. Increased support for research on oral health disparities, neuroscience of chronic pain, head and neck cancer, Phase III clinical trials, genomics (including genome-wide association studies), systems biology of salivary glands and diagnostic potential of saliva; supported creation of dental practice-based research network and a formal Dentist Scientist Training Program for concomitant Doctor of Dental Surgery/Doctor of Philosophy degree training; fostered interdisciplinary research as co-chair of NIH Roadmap program on Research Teams of the Future; helped lead NIH initiative to enhance peer review; served as acting deputy director of NIH (November 2008-spring 2009).

A. Isabel Garcia (Acting), 2010-11.

Martha J. Somerman, 2011-present. Provides leadership for NIH Pain Consortium; enhances quality for practice-based research network; renovated the NIDCR Dental Clinic; provided leadership for NIDCR Strategic Planning 2014-19; provides advocacy for biomedical research workforce panel, precision medicine and dentistry initiative, issues related to health literacy and health disparities, and increasing budget to over $400 million per year.

Sources of information: Guttman JL. The evolution of America's scientific advancements in dentistry in the past 150 years. J Am Dent Assoc 2009;140(9 Suppl):8S-15S; Harris RR. Dental science in a new age: a history of the National Institute of Dental Research. Rockville, MD: Montrose Press, 1989; and Slavkin HC. Birth of a discipline: craniofacial biology. Newtown, PA: Aegis Communications, 2012.

esis imperfecta), pigment metabolism abnormalities, and oral manifestations of hereditary dermatological conditions.[8-10] During the same period, federal funding increased for investigator-initiated, hypothesis-driven research (basic, translational, and clinical) related to dental caries and periodontal diseases, congenital and acquired craniofacial malformations, autoimmune diseases, tooth and bone diseases, soft and hard tissue infectious diseases and disorders, acute and chronic craniofacial-oral-dental pain, and human behavior.[7,12,16,18-23] Basic research investigations were undertaken of neoplastic diseases, cell migrations, extracellular matrix molecules (e.g., collagens, laminins, fibronectins, proteoglycans), mechanisms of invertebrate as well as vertebrate biomineralization, genetic mechanisms that control growth and development, oral mucosal immunology, oral microbiology (viruses, bacteria, yeast), saliva as an informative diagnostic fluid, genomics of specific pathogens, the oral microbiome, and *FaceBase* for craniofacial dysmorphogenesis.[4,5,8-10,21-31]

More recently, investments have been made in gene therapy associated with the production of saliva, saliva as an informative fluid for diagnostics, biomimetic studies for tooth and root regeneration, oral microbiology (viruses, bacteria, and yeast) and related gene-targeted therapy, the structure and function of biofilms and host immune responses, acute and chronic pain mechanisms, oral health disparities, and more.[1,5-10,16-31] Collectively, this federal investment has profoundly improved the oral health of the American people (and beyond), and there is much yet to be accomplished in the future. In particular, there are current efforts to reduce or eliminate craniofacial-oral-dental health disparities; reduce or eliminate tooth decay; reduce the burden of oral cancers, periodontal diseases, temporomandibular disorders (TMD), Sjogren's diseases, and neurological diseases and disorders (e.g., Bell's Palsy, trigeminal neuralgia, chronic facial neuropathies); and improve management of chronic facial pain.[1,4,5,8-10,16-31]

The Role of Genomics

Human and microbial genomics were derived from the many decades of research focused on the structure and function of deoxyribonucleic acid (DNA), the genetic code, discovery of transcription, translation, post-translational modifications of proteins, secretory mechanism, cell surface and extracellular matrix molecules and their functions, bacterial and mammalian genetics, and bioinformatics.[8-10,17-26] Many of the NIH intramural programs of various institutes and centers, along with universities, foundations, and industry scientists, advanced the fundamental knowledge of microbial (microbiome) and human biology (human biome). The period from 1948 through the 1990s was exceptionally productive.

The following highlights a few selected examples from applications derived from the Human Genome Project in the post-genomic era to oral health care in a new era (2004-14). Genetic factors are at the root cause of most human diseases and disorders,[8-10,21-31] including congenital non-syndromic (e.g., cleft lip and cleft palate) and syndromic craniofacial anomalies (e.g., craniosynostosis, ectodermal dysplasia), dental anomalies (e.g., number, shape, timing of eruption and tooth replacement, amelogenesis imperfecta, and molecular biology of enamel gene products), periodontal diseases (inherited single gene Mendelian as well as complex human multi-gene, gene-environment diseases), tooth decay (dental caries), and oropharyngeal cancer.[1,5,8-10,17,22-45] Genome-derived information has been found to enable a more comprehensive understanding of disease etiology and permits earlier diagnosis, allowing for preventive measures prior to disease onset and progression.[1,8,9,25-28,31-40] Genetic mutations in polarizing signals (Shh, BMPs, Wnt5a, Smad2-4), growth factors and their cognate receptors (Egf and Egfr, Fgfs and Fgfrs), transcriptional factors (Dlx, Hox, Pitx2, Tbx22), cell cycle regulation factors (e.g., p53), cell adhesion molecules (E-cadherin, Connexin43), and extracellular matrix molecules (e.g., Col2A1, Mmp2, Timp1-3, laminins, fibronectins) are implicated in the genetic variances that cause human diseases and disorders.[9,10,23-28,31-45] These examples provide "proof of principle" for personalized oral medicine and provide rapid determination of risk and precise personal diagnostics.[9,24,28,29,31,35,37,38]

Diseases with Gene-Gene/ Gene-Environment Interactions

Human diseases such as childhood obesity, periodontal diseases, tooth decay, head and neck cancers, cardiovascular diseases, cerebrovascular diseases, type 2 diabetes, chronic obstructive pulmonary disorders, autism spectrum disorders, schizophrenia, and dementias (including Alzheimer's disease) demonstrate complex multi-gene inheritance patterns that will require sophisticated analysis of "big data."[36,39] The completion of the Human Genome Project that revealed 21,000 genes and 19,000 pseudo-genes in the human genome, along with advances in DNA sequencing so that a complete patient genome can be done for less than $1,000, now enables very rapid progress towards understanding when and how multiple gene-gene and gene-environment interactions produce disease and disorders. For example, metabolic syndrome diseases (MetS) are a global pandemic of enormous health, economic, and social concern that affects a significant portion of the world's population.[45-54] MetS includes abdominal obesity, hyperglycemia, hypertriglyceridemia, low high-density lipoprotein cholesterol, hypertension, periodontal diseases, and type 2 diabetes mellitus.[46] However, geography and ethnicity provide further genetic variations among African, Hispanic, and/or Asian populations; for example, type 2 diabetes has a unique gene mutation found in Hispanic people.[47,48]

Genomics of Periodontal Diseases

Periodontal diseases represent complex human diseases of the oral cavity.[45] They are characterized by host inflammatory responses associated with hard and soft tissues in the periodontium, modulated by multiple genes, in response to commensal and pathogenic oral microorganisms (oral microbiome). These conditions are associated with a number of systemic associations along with macro- and micro-environmental factors (e.g., age, gender, ethnicity, family health history, obesity, cardiovascular disease, type 2 diabetes, chronic kidney disease, pregnancy, smoking, diet, hygiene habits).[1,5-8,24-28,44-54] In addition to the cardinal signs of inflammation, periodontal diseases present other phenotypes including gingival pocket formation, clinical attachment loss (measured in millimeters), bleeding on probing examination, and loss of tooth-supporting alveolar bone as assessed by radiographic examination and tooth mobility.[45,48-50] As the disease progresses, tooth mobility and chronic destruction of soft and hard tissue are readily apparent. Periodontal diseases are present in 40% of the adult U.S. population and are considered the primary cause of tooth loss among adults.[49,50] However, we still lack a comprehensive understanding of the role of chronic oral microbial infections associated with aging and an array of chronic systemic diseases and disorders (e.g., chronic microbial infections with tooth loss and dementia or with cardiovascular disease or type 2 diabetes).

I am using the word "diseases" advisedly and emphasize that critical observations, documentations, and assessments of clinical phenotypes are profoundly important towards correlation of phenotype with genotype (e.g., phenomics).[23,24,26-29,31,36-38,45-55] This is particularly important when considering periodontal diseases as related to age, gender, ethnicity, composition of biofilms, and systemic diseases (e.g., type 2 diabetes, insulin levels, gonadotrophic hormone levels, puberty, pregnancy, and obesity).[27-34,39,45,49-54]

For example, epidemiologic studies found that biofilm-induced gingival inflammation was universal in children and adolescents without any evidence of gingival tissue or alveolar bone destruction.[39,52-54] This condition is typically called gingivitis (without periodontal disease). However, children and adolescents can present the signs and symptoms of chronic destructive periodontal disease with soft tissue and bone loss. These children and adolescents present with rapid, destructive bone loss localized to permanent incisors and first molar teeth—termed localized aggressive periodontitis. Another observation was made in children and adolescents with more teeth associated with destructive bone loss; this is termed generalized aggressive periodontitis. Each example demonstrates an association with age, gender, and ethnicity as well as systemic disease associations and hormonal levels associated with puberty. Each would be considered non-Mendelian inheritance (single gene mutation) but rather as a complex human disease (multiple gene variance with gene-environment interactions). Significant research opportunities arise with respect to genome-wide association studies to identify multiple gene variance correlated with specific clinical phenotypes.

Meanwhile, Papillon-Lefevre syndrome (PLS) is an autosomal recessive disorder characterized by palmoplantar hyperkeratosis and severe early onset generalized aggressive periodontitis that results in premature loss of the primary and secondary dentitions.[32,33] A major gene locus for PLS is mapped to a 2.8-centaMorgan interval on chromosome 11q14. This region contains six known genes including the lysosomal protease cathepsin C gene (CTSC).[32,35,54] Significant research opportunities arise related to understanding the functions of CTSC as related to periodontal disease susceptibility in complex diseases. What regulates tissue-specific gene expression of cathepsin C? In addition to the cardinal features of PLS, PLS patients are reported to present increased susceptibility to infection, which may reflect additional effects of specific cathepsin C mutations or epigenetic effects from other gene loci. Further complications arise in that all PLS patients do not show CTSC mutations, yet their phenotype aligns well with ectodermal dysplasias.

In these examples, let me emphasize that genotyping is critically dependent upon astute clinical observations that enable understanding of how gene variance results correlate with phenotype in health or disease. Genome-wide association studies identify hundreds of genetic variants associated with complex human diseases and traits.[36,39,48,52-56] However, most genetic variants so far confer small increments in risk and explain a small portion of familial clustering. This inevitably leads to questions about how to explain "missing" heritability. A study published in 2010 reported that 45% of genetic variance can be explained by considering all single nucleotide polymorphisms (SNPs) simultaneously.[56] The emerging approach to complex human diseases is to consider incomplete linkage disequilibrium between causal variants and genotyped SNPs and to employ stringent significance tests to large data sets.[52-57]

Genomics of Tooth Decay

The number one chronic disease of children and adults is tooth decay or dental caries.[17] Available information has shown that tooth decay is a chronic disease caused by a colony of discrete bacteria species organized in three-dimensional biofilms, specific or unique microorganisms found in the oral microbiome, excessive carbohydrates derived from the diet, host genomics as well as microbial genomics, and environmental factors. The heritability of dental caries has been estimated to be from 30% to 60%.[17,58-60] This condition is a classic example of a complex human disease reflecting gene-gene and gene-environment interactions.

Genome-wide association scans identified a number of genes associated with risk for tooth decay in children and adults.[60] Projected or anticipated research related to the elimination or reduction of tooth decay will require scientific teams that enable linkages to well-developed theoretical frameworks in many disciplines (social, economic, behavioral, chemical, physical, environmental, nutritional, and other areas). Of course, this approach will also require academic institutions to provide support, incentives, and promotions to science team members. Interprofessional or multidisciplinary science teams are a rapidly growing component of the scientific workforce across the industrial nations of the world.

Genomics of Head and Neck Cancers

Relatively common head and neck cancer phenotypes include melanoma, basal cell carcinoma, and squamous cell carcinoma.[1,36,39] Oral squamous cell carcinoma (OSCC) is a major cause of morbidity and mortality worldwide, with presentation of more than 275,000 new cases and over 120,000 deaths each year. OSCC is the sixth most common neoplastic disease in the developed world. OSCC-associated morbidity and mortality remain high and have not improved in over four decades.[61-64] One explanation for the lack of improvement relates to tumor size: lymph node involvement and stage (I to IV) do not provide guidance for clinical outcome. Apart from tobacco, alcohol, and direct sunlight, human papilloma virus (HPV) infection is another known risk factor for OSCC.[64]

OSCC results from progressive genetic mutations leading to malignancy in a multistep process.[64] Current progress in the discovery of genetic biomarkers is rapidly advancing (Table 2). At this point in the journey, it is clear that one biomarker for head and neck cancers will not materialize. Rather, multiple gene-based markers associated with cell cycle regulation or tumor suppression correlated to specific causes in specific ethnic groups can eventually become the foundation for diagnosis and therapeutics.

Table 2. Progress in genomics of head and neck squamous cell carcinoma (HNSCC)

- TP53 is most common gene in HNSCC—a gene that encodes p53 protein known to regulate the cell cycle, programmed cell death, DNA repair, and transcriptional control.
- NOTCH1 is second most common gene mutation in HNSCC and functions in blood cancer acute lymphoblastic leukemia.
- CDKN2A, PIK3CA, HRAS, and FBXW7 are other gene mutations found in HNSCC tumors and represent part of the neoplastic signature.
- Exome is the complete set of exons, or protein-encoding sequences, found in the human nuclear genome and which represent about 1% of the total DNA.

Genomics of Chronic Craniofacial-Oral-Dental Pain

Migraine headaches, TMD, and muscle disorders are the most common causes of chronic craniofacial-oral-dental pain. In 2011, the Institute of Medicine (IOM) published a report on the public impact of chronic pain entitled *Relieving Pain in America.*[65] This report noted that 25% of adult Americans experience chronic pain and that women experience pain much more often than men yet their accounts of pain are often dismissed by male health care professionals. Genes have been discovered that are associated with chronic facial pain (e.g., orofacial myalgia), and additional genes have been discovered that influence or modulate nociception—the neuronal process of encoding and processing noxious mechanical, thermal, and chemical stimuli vis-à-vis nerve endings called nociceptors located in skin, periodontium, periosteum, joint surfaces, and muscles of mastication and facial expression.[65-69] These advances enable improved correlations between phenotype and genotype and improved and more precise diagnostics and selection of therapeutics based on genomics.[65]

Broader Dental Research Contributions

In the last half of the 20th century, remarkable contributions towards understanding complex human diseases and disorders beyond the mouth and teeth were made by dental research scientists and clinical scholars. From its origins as an institute in 1948, dental scientists on the NIDR/NIDCR intramural research staff have made significant contributions to understanding the molecular composition of extracellular matrices throughout the body (e.g., types of collagen, fibronectins, laminins, proteoglycans), fundamental principles of immunity, discovery of unique bacteria and viruses, biofilm composition and formation, key principles of craniofacial developmental biology, major molecular aspects of head and neck cancers, and fundamental discoveries related to mechanisms of acute and chronic pain and the management of chronic pain.[5,8-10]

Beyond NIDR/NIDCR intramural research activities, extramural dentists or dental scientists have contributed to complex biomedical problem areas.[8-10] For example, Norman Simmons, a Harvard dental graduate, pursued postdoctoral studies with Rosalind Franklin towards his goal of isolating and purifying DNA from adenoviral particles. His preparations of DNA were ideal for the first x-ray diffraction studies of DNA in the early 1950s at King's College, London. His studies with Franklin were noted by James Watson, Francis Crick, and Maurice Wilkins as leading to the structural models of DNA showing base pairing and the form of a double helix.[70,71]

Robert Ledley, another example, was one of the first dental scientists to envision using mathematics and computers to create "a mathematized biology" that enhanced computerized medical (and dental) diagnoses.[8,10,72,73] Ledley recruited Margaret Oakley Dayhoff to join him at the National Biomedical Research Foundation at Georgetown University Medical Center in 1960. Dayhoff was the first to establish a computer-based biological database. By 1962, these two gifted individuals had collaborated to develop the field of bioinformatics. Their computer programs aided in the experimental determination of protein sequences based on the genetic code for each amino acid as found in messenger and unique transfer RNAs. Thereafter, hundreds of discrete discoveries with computer programs, instrumentation, and high throughput gene and protein sequencing resulted in biology experiencing many of the same changes that revolutionized physics and chemistry in the 20th century. Imagine biology before computers, polymerase chain reactions, rapid sequencing of DNA and RNA, genomics, pharmacogenomics, bioinformatics, and the enormous opportunities for government and venture capital funding with unlimited applications for improving human lives.

Another example is Russell Ross, a dentist at the University of Washington who had specialty training in periodontics and a PhD in experimental pathology.[8,10,74,75] His curiosity and enormous talents led him to discover and describe the biological mechanisms leading to cardiovascular disease from the pathogenesis of athrosclerosis. Another dentist who pioneered the genetic foundations for head and neck birth defects, especially those included in craniofacial dysmorphogenesis, was Robert Gorlin.[8-10,76] From his home base at the University of Minnesota, Gorlin travelled the world with his remarkable intellect and encyclopedic memory to become the father of modern craniofacial genetics.

Role of Research and Innovation in Dental Education

Scientific research is the essential fuel for the engines of technology and health care, clearly including oral health care aligned and integrated within comprehensive health care for all people. Oral microbiology offered the curious scientist enormous opportunities to observe, define, and eventually explain acute and chronic infectious disease as well as host immune responses in the oral cavity. Fundamental and applied dental research provided the discoveries that led to the educational content to prepare dental and medical clinicians to understand the common issues relative to chronic infectious diseases throughout the human body. Moreover, science informs clinical care on many levels: risk assessment, prevention, diagnostics, treatments, therapeutics, and implementation from bench to chairside and bedside.

Research is also the fuel for health professions education and beyond. Health professions education is not only content in a curriculum but also how critical thinking is gained through a process of active inquiry. Further, the "half-life" of biomedical information and knowledge is becoming shorter and shorter as we evolve from the 19th through the 21st century. With rapid advances in all fields, there is a critical need for educators to reinvent themselves in terms of skills and knowledge several times in their careers in order to provide students, residents, and colleagues with currently significant and accurate "ways of knowing." Further, cognitive neuroscience studies have found that passive learning from lecture formats needs to be transformed into a different model, featuring small-group, inquiry-based processes such as case-based and problem-based learning.[77-80] Inquiry-based learning generally leads to critical thinking, which is especially valuable in the health sciences. This approach is directly applicable to clinical as well as research education and training. Anything less might be considered "educator malpractice."

What is taught (content) couples with how people learn (inquiry-based learning approaches) to help learners gain critical thinking skills.[81,82] In this context, faculty members function as facilitators, coaches, and models of inquiry-based learning. Doing scientific research can be considered a model for how adults learn, and it provides evidence for a reasonable merger of research and education for predoctoral as well as doctoral and postdoctoral learning. Clinical case-based, problem-based, and inquiry-based learning can lead to both critical thinking and advances in health professions.

As we anticipate the near future in the 21st century, major revisions in health professions education must be advanced.[77,81-89] In part, the digital and biological revolutions of the last century offer a sense of the future. For example, artificial intelligence derived from the digital revolution is already impacting health care on many levels. In addition, the completion of the Human Genome Project in 2003, derived in the biological revolution, has introduced "omics" and applications to the system biology of the human condition, including oral health and oral medicine.[8-10,22-28,31,36,37]

Of even greater significance is the emerging realization that societal issues and problems must guide and inform curricula and educator preparations required for world-class dental education in the 21st century.[67,71] The major challenges to society today and in the near future include prenatal care, early childhood development, food choices and behaviors, autism, obesity, learning disabilities, physical exercise and behavioral choices, substance and drug abuse, chronic diseases and disorders, quality of life issues, and life expectancy. Are we preparing future dentists with the skills and tools needed to engage in 21st-century practice?

Future Opportunities and Challenges

Genomic information, knowledge, and technology continue to illuminate our understanding of craniofacial-oral-dental diseases and disorders as well as the oral microbiome. Increasingly, these scientific discoveries are informing clinical practice towards "personalized oral health care."[78-92] It is becoming increasingly evident that the knowledge from human as well as microbial genomics ("the human biome") have and will continue to yield predictive genetic tests for dozens if not hundreds of conditions, reduce risk through various interventions, routinely be used for pre-implantation genetic diagnosis, provide guidelines for translating pharmacogenomics knowledge to bedside and chairside applications (especially related to drugs used for oncology, autoimmune diseases and disorders, inflammation, periodontal diseases, and chronic pain management), and be utilized by primary care health professionals (in dentistry, medicine, nursing, pharmacy, and the allied health professions).

Despite the promise of precision or personalized medicine, dentistry, and general health care, implementation in standards of care will require a national vision and strategy developed among government, academia, industry, and the larger society. Implementation science can accelerate the translation of basic and clinical genomic research findings by assessing how health care professionals and organizations behave and then applying that knowledge to the process of changing routine clinical practice. A recent workshop report sponsored by the National Academy of Medicine (previously the IOM), *Applying an Implementation Science Approach to Genomic Medicine,* embraced this vision.[93] The report provides a blueprint for implementation of genomics into clinical practices of dentistry, medicine, nursing, pharmacy, and the allied health professions. Here is yet another opportunity for dental and medical education, research, and professionalism.

Technologies for genome-wide sequence interrogation profoundly advance identification of informative gene loci associated with infectious and complex human diseases. Since the authorization of the Human Genome Project in the late 1980s, the cost for sequencing nucleic acids declined from $2 million to complete one single human genome in 2007 and 2009 to $1,000 per patient in 2014 and continues to decline.[36] One enormous challenge is the gap between correlations and causality. We have a limited theoretical framework derived from Mendelian genetics for complex human diseases and disorders and an incomplete molecular understanding of biofilm-based oral microbial infectious diseases as well as host chronic diseases and their individual pathophysiology. Mapping the epigenome will provide significant information for each cell type during embryogenesis and subsequent postnatal growth and development in health and disease. Specifically, when, where, and how do epigenetic factors such as acetylation and methylation regulate gene expression and function?

For many decades, clinical scholars have been advocates for human and microbial genetics, and more recently genomics and pharmacogenomics, to be an integral component of the preclinical and clinical education and training of oral health professionals.[36] One example of implementation is in interprofessional education and patient care in oncology using integrative network modeling approaches to personalized cancer dentistry and medicine. However, despite formal recommendations, very modest progress has as yet been made.

In addition, the standards in virtually every state in the U.S. have failed to keep pace with changes in the biological sciences, especially genomics, including omitting concepts related to genetic complexity, the importance of environment to phenotype variation, differential gene expression, and the differences between inherited and somatic genetic diseases.[22,26-28,32-39,55-63,78-84] A multidisciplinary analysis of primary health care recommends that medical, dental, pharmacy, and nursing professional education must be revised and aligned to address interprofessional clinical care approaches to prevention as well as diseases and disorders found in the greater society.[82-84] In addition, making significant improvement in the public's craniofacial-oral-dental health will require major revisions in dental education.[81-93]

To address these issues as related to modern human genetics and genomics, the 2004 Macy Study report provided a detailed curriculum for genomics to enable oral health professionals to use the knowledge and practical applications for risk assessment, stratification of patients, selection of therapeutics based on pharmacogenomics, and diagnostics.[34] Moves toward interprofessional health care support adoption of the Macy curriculum and a new laboratory manual *Genetics of Complex Human Disease.*[90] We must also create practical continuing education courses that will enable practitioners to gain access to content and applications related to personalized oral medicine.[38,39] Further, we must provide essential knowledge for health care policy experts as well as leaders in the insurance, manufacturing, and distribution industries. In those ways, we will continue to experience a next-generation sequencing revolution that will influence personalized oral medicine.

Meanwhile, enabling the future of personalized oral health care requires a few significant lessons based on experiences from the last few decades. First, free and open access to human genome and microbiome data is critical for the rapid progress of the biomedical sciences. Second, accelerated innovations in technology and informatics for clinical research and development with an emphasis on interprofessional teams will continue to be a key to success. Third, phenomics or the accurate identification and alignment of genetic and phenotypic as well as environmental risk factors are a major driver of success. These efforts must also coordinate with human behaviors to achieve optimal benefits. Fourth, support for public-private partnerships is critical to advance drug development coupled with pharmacogenomics.[94-96] One example was former President Obama's initiative "Precision Medicine," announced in his January 20, 2016, State of the Union Address and for which he requested 215 million new dollars for FY 2017. Funding was announced in July 2016 for distribution of the first $55 million to begin the study of a million volunteers who give consent to have their phenotypes measured and to correlate these findings with their genotypes, a process of correlation called "phenomics." At the same time, the Food and Drug Administration produced draft guidance to regulate the path for DNA sequencing that determines risk as well as diagnosis. Framed in a different way, this initiative can provide a remarkable platform for precision health care that includes dentistry, medicine, nursing, pharmacy, and the allied health professions.

Demographers and health policy experts suggest that the U.S. population will increase by 1.5 million people per year well into the 21st century.[94] The number of adults 50 and over will reach 132 million by 2030, an increase from 2000 of more than 70%. In 2030, one of five Americans will be 65 or older. Demographers project that, from 2012 to 2060, the number of individuals aged 65 years and older will increase from 43.1 million to 92 million. Further, it is now well documented that, as adults age, their risk for developing chronic diseases and disorders increases. As a nation, we face the sobering reality of needing to control health care costs for a large aging population.[94-96] Major reforms have increased access to care for millions of people but have not realized reductions in cost with increases in quality of care for all Americans.[96]

Today, seven out of ten deaths result from chronic diseases and disorders, each with oral complications; and, of the ten most commonly prescribed medications, six are used to treat chronic diseases with oral complications.[95] The seven most common chronic diseases faced by older adults are arthritis (associated with TMD, xerostomia, and bleeding); cancers (chemotherapy and radiation therapy are associated with oral mucositis, candidiasis, and xerostomia); chronic obstructive pulmonary disorders (associated with oral leukoplakia, erythroplakia, squamous cell carcinoma, xerostomia, and candidiasis); type 2 diabetes (associated with periodontal disease, candidiasis, neuropathy, oral mucosal ulcerations, "poor" healing, compromised inflammatory response, and xerostomia resulting from medications); heart diseases (with possible hematoma, excessive bleeding, taste changes, and xerostomia); hypertension (associated with lichenoid drug reactions, gingival overgrowth, xerostomia, and taste changes); and mental health diseases and disorders (associated with excessive biofilm formations, lichenoid reactions, tooth decay, gingivitis, periodontal disease, and xerostomia). As specified, all of these have oral complications.

According to Truffer et al., oral health care expenses in 2009 reached $101 billion for the treatment of two-thirds of the U.S. population using only 7% from public funds.[94] That same year, oral health conditions treated in the medical care system (head and neck birth defects, oropharyngeal cancers, and trauma) cost $95.9 billion. Total health care that year reached $2.5 trillion. Truffer et al. projected that health care expenses will reach $4.5 trillion by 2019 or 19.3% of the GDP. The U.S. spends more than all major industrial nations combined on health care, yet receives much less as measured by morbidity and mortality across the lifespan.[94-96] Another driver for transforming health professions education and health care delivery is economic, including rising costs, insufficient electronic records technology, and the balance between federal and private insurance coverage.

Studies have reported gaps or disconnects between societal needs and formal health professions education.[77-84] Over the last five decades, there have been calls to include human genetic education, including genomic and pharmacogenomics, in the curricula of North American dental education.[9,10,19-31,34,36,37,39,54,56-60,62,63,65,78-84,87,90-93] Despite these efforts, little has been accomplished. In the 21st century, a need continues to exist for human genomics and personalized health care to be integrated into health professions education. Education in "-omics" (genomics, transcriptomics, proteomics, metabolomics, phenomics, epigenomics) as a major derivative from the biological revolution should become an integral part of health professions education and practice. The human genome and microbiome enable systems biology investigations that focus on complex and multiple functions of individual molecules in important pathways for prokaryotic and eukaryotic cells. Future opportunities include pursuing definitions of the specific role of a special microorganism in a biofilm and developing methods to eliminate that bacterial species without compromising benefits from the oral biofilm. Such an approach might lead to precision-guided antimicrobial peptides as targeted

Table 3. Online information and databases to assist educators and clinicians in risk assessment, differential diagnosis, or candidate-gene identification for syndromic disorders

Free Access
www.NIDCR.NIH.Gov
www.ADEA.org
www.ADA.org
www.NDA.org
www.NHDA.org
www.ADHA.org
Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr)
HuGE Navigator (hugenavigator.net/HuGENavigator)
Human Gene Mutation Database (www.biobase-international.com/product/hgmd)
Online Mendelian Inheritance in Man (www.omim.org)
Phenomizer (compbio.charite.de/phenomizer)
SimulConsult (www.simulconsult.com)
Entrez (National Center for Biotechnology Information) (www.ncbi.nlm.nih.gov/gquery/gquery.fcgi)
Subscription or Fee Required for Access
Isabel (www.isabelhealthcare.com/home/default)
London Medical Databases (lmdatabases.com)
POSSUM (www.possum.net.au)

modulators of human microbial ecology in biofilms.[97] A provocative and potentially significant cariogenic bacterial species, one of the 700 species found in the human oral cavity, is *Streptococcus mutans*, considered primary to the initiation of tooth decay.[98-103]

I encourage readers to visit important educational and research websites (Table 3) and to review publications that address the opportunity and challenges for present and future health professions research and education.[2,3,5-10,19,20,22-31,33,35-42,54-56,75,82-105] Remarkable advances in the biomedical sciences have made it possible to correlate patient and microbial phenotype with a complete genotype (genome and microbiome) and achieve significant accuracy for risk assessment, diagnostics, pharmacogenomics (which drug can target a specific mutation), metabolomics, and much more.[21-31,33-38,51,54-58,62,75-82,97-105] The fact that the craniofacial-oral-dental complex is connected to the rest of the body, including the oral microbiome, further supports the imperative to align and integrate primary care with mental, vision, hearing, and oral health.[1-3,6-10,68-70,97-105]

Conclusion

The opportunity and challenge of dentistry reside in our priority as a profession to address the needs and issues of society and to create a renewable profession that evolves and adapts to advances in the biomedical and behavioral sciences. Can we align the content and processes of education, learning, and research? Can we reconsider what we learn and how we learn? Can we assess critical thinking in our students and in ourselves? The future is replete with opportunities to advance the profession of dentistry.

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REFERENCES

1. Oral health in America: a report of the surgeon general. Rockville, MD: U.S. Department of Health and Human Services, National Institute of Dental and Craniofacial Research, National Institutes of Health, 2000.

2. Field MJ, ed. Dental education at the crossroads: challenges and change. An Institute of Medicine Report. Washington, DC: National Academies Press, 1995.
3. Gies WJ. Dental education in the United States and Canada: a report to the Carnegie Foundation for the Advancement of Teaching. New York: Carnegie Foundation, 1926.
4. Guttman JL. The evolution of America's scientific advancements in dentistry in the past 150 years. J Am Dent Assoc 2009;140(9 Suppl):8S-15S.
5. Harris RR. Dental science in a new age: a history of the National Institute of Dental Research. Rockville, MD: Montrose Press, 1989.
6. Improving access to oral health care for vulnerable and underserved populations. An Institute of Medicine Report. Washington, DC: National Academies Press, 2011.
7. Advancing oral health in America. An Institute of Medicine Report. Washington, DC: National Academies Press, 2011.
8. Slavkin HC. The evolution of the scientific basis for dentistry: 1936 to now and its impact on dental education. J Dent Educ 2012;76(1):28-35.
9. Slavkin HC. Birth of a discipline: craniofacial biology. Newtown, PA: Aegis Communications, 2012.
10. Snead ML, Slavkin HC. Science is the fuel for the engine of technology and clinical practice. J Am Dent Assoc 2009;140(9 Suppl):17s-24s.
11. Prinz H. Dental chronology. a record of the more important historic events in the evolution of dentistry. Philadelphia: Lea & Febiger, 1945.
12. Guerini V. History of dentistry from the most ancient times until the end of the 18th century. New York: Lea & Febiger, 1909.
13. Weinberger H. History of dentistry in America. New York: Lea & Febiger, 1948.
14. McCluggage RW. A history of the American Dental Association. Chicago: ADA Press, 1959.
15. Miller WD. Original investigations concerning pyorrhea alveolaris: the micro-organisms of the human mouth. Philadelphia: S.S. White Dental Mfg., 1890.
16. Bremner MDK. The story of dentistry from the dawn of civilization to the present, with special emphasis on the American scene. New York: Dental Items of Interest Publishing Company, 1954.
17. Zero DT, Fontana M, Martinez-Mier EA, et al. The biology, prevention, diagnosis, and treatment of dental caries: scientific advances in the United States. J Am Dent Assoc 2009;140(9 Suppl):25S-34S.
18. McKay FS. Investigation of mottled teeth. PHR 1916;31:2915-8.
19. Dean HT. The personnel problem in dental research: with some comments on USPHS research fellowships. J Am Coll Dent 1948;15:52-3.
20. Scott DB. The support of research by the American College of Dentists. J Am Coll Dent 1970;37:201-5.
21. Wong DTW. Salivaomics. J Am Dent Assoc 2012;143(10 Suppl):19s-24s.
22. Glick M. Expanding the dentist's role in health care delivery: is it time to discard the Procrustean bed? J Am Dent Assoc 2009;140:1340-2.
23. Garcia I, Tabak LA. A view of the future: dentistry and oral health in America. J Am Dent Assoc 2009;140:44s-48s.
24. Garcia I, Kuska, Somerman M. Expanding the foundation for personalized medicine: implications and challenges for dentistry. J Dent Res 2013;92(Suppl 1):3s-10s.
25. Collins FS, Tabak LA. A call for increased education in genetics for dental health professionals. J Dent Educ 2004;68(6):807-8.
26. Giannobile WV, Kornman KS, Williams RC. Personalized medicine enters dentistry: what might this mean for clinical practice? J Am Dent Assoc 2013;144:874-6.
27. Kornman KS, Duff GW. Personalized medicine: will dentistry ride the wave or watch from the beach? J Dent Res 2012;91(7 Suppl):8S-11S.
28. Slavkin HC. From phenotype to genotype: enter genomics and transformation of primary health care around the world. J Dent Res 2014;93(7 Suppl):3s-6s.
29. NIDCR strategic plan, 2014-19. At: www.nidcr.nih.gov. Accessed 10 Oct. 2014.
30. Kleinman DV. The future of the dental profession: perspectives from oral health in America, a report of the surgeon general. J Am Coll Dent 2002;69(3):6-10.
31. Giannobile WV, Braun TM, Caplis AK, et al. Patient stratification for preventive care in dentistry. J Dent Res 2013;92:694-701.
32. Hart TC, Hart PS, Bowden DW, et al. Mutations of the cathepsin C gene are responsible for Papillon-Lefevre syndrome. J Med Genet 1999;36:881-7.
33. Hart TC, Hart PS, Michalec MD, et al. Haim-Munk syndrome and Papillon-Lefevre syndrome are allelic mutations in cathepsin C. J Med Genet 2000;37:88-9.
34. Johnson L, Genco RJ, Damsky C, et al. Genetics and its implications for clinical dental practice and education: report of panel 3 of the Macy study. J Dent Educ 2004;72(2 Suppl):86-94.
35. Epstein CJ, Erickson RP, Wynshaw-Boris A, eds. Inborn errors of development. 2nd ed. New York: Oxford University Press, 2008.
36. Slavkin HC, Navazesh M, Patel P. Basic principles of human genetics: a primer for oral medicine. In: Glick M, ed. Burket's oral medicine. 12th ed. Shelton, CT: People's Medical Publishing House-USA, 2015:625-52.
37. Slavkin HC. The future of research in craniofacial biology and what this will mean for oral health professional education and clinical practice. Aust Dent J 2014;59(1 Suppl):1S-5S.
38. Slavkin HC, Santa Fe Group. Revising the scope of practice for oral health professionals. J Am Dent Assoc 2014;145:228-30.
39. Polverini PJ. A curriculum for the new dental practitioner: preparing dentists for a prospective oral health care environment. Am J Public Health 2012;102(2):e1-3.
40. Slavkin HC. The surgeon general's report and special needs patients: a framework for action for children and their caregivers. Spec Care Dent 2001;21(3):88-94.
41. Slavkin HC. Expanding the boundaries: enhancing dentistry's contribution to overall health and well-being of children. J Dent Educ 2001;65(12):1323-34.
42. Crall JJ. Oral health policy development since the surgeon general's report on oral health. Acad Pediatr 2009;9(6):476-82.

43. Lewis CW. Dental care and children with special needs: a population perspective. Acad Pediatr 2009;9(6): 420-6.
44. Petersen PE. Global policy for improvement of oral health in the 21st century: implications for oral health research of World Health Assembly 2007, World Health Organization. Community Dent Oral Epidemiol 2009;37(1):1-8.
45. Armitage GC, Robertson PB. The biology, prevention, diagnosis, and treatment of periodontal diseases: scientific advances in the United States. J Am Dent Assoc 2014;50:36s-44s.
46. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Med 2011;9:48-62.
47. Shimazaki Y, Saito T, Yonemoto K, et al. Relationship of metabolic syndrome to periodontal disease in Japanese women: the Hisayama study. J Dent Res 2007;86(3): 271-5.
48. SIGMA Type 2 Diabetes Genetics Consortium. A low frequency variant in HNF1A has a large effect on type 2 diabetes risk in a Latino population. JAMA, June 11, 2014.
49. Loe H, Brown LJ. Early onset periodontitis in the United States of America. J Periodontol 1991;62:608-16.
50. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005;366:1809-20.
51. Van Dyke TE, Serhan CN. Resolution of inflammation: a new paradigm for the pathogenesis of periodontal diseases. J Dent Res 2003;82(2):82-90.
52. Vaithilingam RD, Safii SH, Baharuddin NA, et al. Moving into a new era of periodontal genetic studies: relevance of large case-control samples using severe phenotypes for genome-wide association studies. J Periodontal Res, Feb. 17, 2014.
53. Rhodin K, Divaris K, North KE, et al. Chronic periodontitis genome-wide association studies. J Dent Res 2014;93(9):882-90.
54. Divaris K, Monda KL, North KE, et al. Exploring the genetic basis of chronic periodontitis: a genome-wide association study. Hum Mol Genet 2013;22(11):2312-24.
55. Houle D, Govindaraju DR, Omholt S. Phenomics: the next challenge. Nature Rev Genet 2010;11:855-63.
56. Yang J, Benyamin B, McEvoy BP, et al. Common SNPs explain a large proportion of the heritability for human height. Nature Genet 2010;42:565-9.
57. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature, Oct. 8, 2009.
58. Shuler CF. Inherited risks for susceptibility to dental caries. J Dent Educ 2001;65(10):1038-45.
59. Wang X, Willing MC, Marazita ML, et al. Genetics and environmental factors associated with dental caries in children: the Iowa fluoride study. Caries Res 2012;46(3): 177-84.
60. Shaffer JR, Feingold FE, Wang X, et al. Heritable patterns of tooth decay in the permanent dentition: principal components and factor analyses. BMC Oral Health, March 9, 2012.
61. Warnakulasuriya KAAS, Harris CK, Scarrott DM, et al. An alarming lack of public awareness towards oral cancer. Br Dent J 1999;187(6):319-22.
62. Slavkin HC. The human genome, implications for oral health and disease, and dental education. J Dent Educ 2001;65(5):463-79.
63. Cohen RL, Settleman J. From cancer genomics to precision oncology: tissue's still an issue. Cell 2014;157: 1509-13.
64. Osazuwa-Peters N. Human papillomavirus (HPV), HPV-associated oropharyngeal cancer, HPV vaccine in the United States: do we need a broader vaccine policy? Vaccine 2013;31(47):5500-5.
65. Committee on Advancing Pain Research, Care, and Education. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. An Institute of Medicine Report. Washington, DC: National Academies Press, 2011.
66. Dao TT, LeResche L. Gender differences in pain. J Orofac Pain 2000;14:169-84.
67. Sato H, Droney J, Ross J, et al. Gender, variation in opioid receptor genes, and sensitivity to experimental pain. Mol Pain 2013;9:48-57.
68. James S. Human pain and genetics: some basics. Br J Pain 2013;7(4):171-8.
69. Slavkin HC. Distinguishing Mars from Venus: emergence of gender biology in health and disease. J Am Dent Assoc 1998;129:357-61.
70. Simmons NS, Blout ER. The structure of tobacco mosaic virus and its components: ultraviolet optical rotary dispersion. Biophys J 1960;1(1):55-62.
71. Wilkins MHF. The molecular configuration of nucleic acids. Nobel Lecture, December 11, 1962. At: cmbi.bjmu.edu.cn/news/report/2003/DNA50/source/wilkinslecture.pdf. Accessed 12 Jan. 2017.
72. Ledley RS, Ayers WR. Computerized medical imaging and graphics evolves from computerized tomography. Comput Med Imaging Graph 1988;12(1):v-xviii.
73. Ledley RS. Innovation and creativeness in scientific research: my experiences in developing computerized axial tomography. Comput Biol Med 1974;4(2):133-6.
74. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999;340(2):115-26.
75. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993;362(6423):801-9.
76. Cohen MM Jr. Robert Gorlin, 1923-2006: a remembrance. Am J Med Genet A 2006;140(23):2516-20.
77. Frenk J, Chen L, Bhutta ZA, et al. Health professionals for a new century: transforming education to strengthen health systems in an interdependent world. Lancet 2010;376:1923-58.
78. Kopel H, ed. The teaching of human genetics in dental education. Los Angeles: University of Southern California Press, 1979.
79. Sanger R, ed. Guidelines for the teaching of human genetics in dental education. Denver: University of Colorado Press, 1979.
80. Salinas CF, Jorgenson RJ, eds. Dentistry in the interdisciplinary treatment of genetic diseases. New York: Alan R. Liss, Inc., 1980.
81. Kohn LT, ed. Academic health centers: leading change in the 21st century. An Institute of Medicine Report. Washington, DC: National Academy of Sciences, 2003.

82. DePaola D, Slavkin HC. Reforming dental health professions education: a white paper. J Dent Educ 2004;48(11):1139-50.
83. Hendricson WD, Cohen PA. Oral health care in the 21st century: implications for dental and medical education. Acad Med 2001;76(12):1181-206.
84. Slavkin HC, Sanchez-Lara P, Chai Y, Urata M. A model for interprofessional health care: lessons learned from craniofacial teams. J Calif Dent Assoc 2014;42(9):637-44.
85. Agundez JAG, Esguevillas G, Amo G, Garcia-Martin E. Clinical practice guidelines for translating pharmacogenomics knowledge to bedside: focus on anticancer drugs. Front Pharmacol 2014;5(188):1-4.
86. Chakravarti A, Clark AG, Mootha VK. Distilling pathophysiology from complex disease genetics. Cell 2013;155:21-6.
87. Rivera CM, Ren B. Mapping human epigenomes. Cell 2013;155:39-55.
88. Dougherty MJ, Pleasants C, Solow L, et al. A comprehensive analysis of high school genetics standards: are states keeping pace with modern genetics? CBE Life Sci Educ 2011;10:318-27.
89. Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. N Engl J Med 2011;364(12):1144-53.
90. Al-Chalabi A. Genetics of complex human disease: a laboratory manual. New York: Cold Spring Harbor Laboratory Press, 2014.
91. Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. N Engl J Med 2014;370(25):2418-25.
92. Slavkin HC. The answer lies in the genome. Global Health Nexus 2012;14:6-15.
93. National Academies of Sciences, Engineering, and Medicine. Applying an implementation science approach to genomic medicine: workshop summary. Washington, DC: National Academies Press, 2016.
94. Truffer CJ, Keehan S, Smith S, et al. Health spending projections through 2019: the recession's impact continues. Health Aff 2010;29(3):522-9.
95. Kronenfeld JJ, Kronenfeld M. Health care reform in America. 2nd ed. Santa Barbara, CA: ABC-CLIO, 2015.
96. Obama B. United States health care reform progress to date and next steps. JAMA 2016;316(5):525-32.
97. Guo L, McLean JS, Yang Y, et al. Precision-guided antimicrobial peptide as a targeted modulator of human microbial ecology. PNAS 2015;112(24):7569-74.
98. Dewhirst FE. The human oral microbiome. J Bacteriol 2010;19(19):5002-17.
99. Kuramitsu HK, He X, Lux R, et al. Interspecies interactions within oral microbial communities. Microbiol Mol Biol Rev 2007;71(4):653-70.
100. Hamada S, Slade HD. Biology, immunology, and cariogenicity of Streptococcus mutans. Microbiol Rev 1980;44(2):331-84.
101. Rickard AH, Gilbert P, High NJ, et al. Bacterial coaggregation: an integral process in the development of multi-species biofilms. Trends Microbiol 2003;11(2):94-100.
102. Polverini PJ, ed. Personalized oral health care: from concept design to clinical practice. Geneva, Switzerland: Springer International Publishing, 2015.
103. Wright JT. Genomics of dental caries and caries risk assessment. In: Polverini PJ, ed. Personalized oral health care: from concept design to clinical practice. Geneva, Switzerland: Springer International Publishing, 2015: 87-98.
104. Garaicoa-Pazmino C, Decker AM, Polverini PJ. Personalized medicine approaches to the prevention, diagnosis, and treatment of chronic periodontitis. In: Polverini PJ, ed. Personalized oral health care: from concept design to clinical practice. Geneva, Switzerland: Springer International Publishing, 2015:99-112.
105. Slavkin HC. Personalized oral medicine and the contemporary health care environment. In: Polverini PJ, ed. Personalized oral health care: from concept design to clinical practice. Geneva, Switzerland: Springer International Publishing, 2015:1-18.