Special Communication

Twenty-first Century Dental Practice and the Treatment of Nonmicrobial Genetic-based Dental Diseases

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Abstract

After W.D. Miller proved a causal relationship between microbes and dental caries and periodontitis, the repair and replacement of damaged or lost teeth resulting from microbial activity dominated 20th century dental practice. In this study, I predict that in the 21st century dental practice will shift to the treatment of those dental diseases not caused by microbes. As dentists already treat some nonmicrobial diseases, I will focus on craniofacial malformations, the group of nonmicrobial diseases usually called birth defects. Some examples include dental dysplasias, cleft lip and palate, and malocclusion. In this study, I introduce the word "dysmorphogenesis" (to replace the term birth defect) as it more appropriately ascribes this subset of nonmicrobial diseases results to mistakes during the formation of craniofacial structures. As dysmorphogenic diseases occur during gestation, their diagnosis and especially their treatment require intervention during embryogenesis. Fortunately, decades of research have shown that mutations are involved in malformations during amelogenesis, palatogenesis, and odontogenesis. Knowledge of which genes are involved, together with recent breakthroughs in Crispr gene editing, make interventions during gestation possible. Those dentists performing gene editing procedures I have previously called Biodontists, because creating the Biodontics specialty will take time. The dental profession including dental educators, dental practitioners, and dental manufacturers should begin discussions now on how best to proceed.

Keywords: Birth defects, craniofacial anomalies, crispr, dysmorphogenesis

Changes in 21st Century Dental Practice

In a previous study, I noted that most of the 20th century dental practice focused on two dental diseases: caries and periodontitis.[1] In that study, I also pointed out how W.D. Miller's research proved that microbes caused both diseases, and his chemoparasite theory dominated 20th century dental practice, as well as 20th century dental research and dental education.

In this study, I examine several changes dentists might expect in the 21st century and ask if these changes present threats or opportunities for dental practice of the future. These changes involve the who, where, and how dental services will be provided.

As for most of the dental history, dental care was provided by a variety of providers; in the 20th century, in the United States, dental care was provided by graduates of dental schools. But in the 21st century, this trend will be reversed. In 2009, dental therapists began to practice in the United States and to deliver dental care, whereas in 2021, the scope of care therapists deliver is limited, and their numbers remain small, in the foreseeable future, we can expect their scope of practice and their numbers to increase. Although it is true that in the 20th century, both hygienists and assistants assumed more responsibilities, the introduction of therapists to provide dental care means that for the first time in 100 years, dental care will be provided to the American population by nondental school graduates.

In addition to the "who," another change is the "where": Where will dental care be delivered? During the 20th century, dental care was provided for most Americans in a private

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practice setting. In the 21st century, this has already changed as corporate dentistry was introduced. Unlike a private dental practice, where the dentist owns the practice, a corporate dental practice is owned by a corporation and dental services are provided by employees of the corporation. These corporations usually open dental offices in shopping malls throughout the United States. Because of their success, the corporate model for delivery of dental care is likely to expand. One area for expansion is the delivery of dental care in chain store pharmacies.[2]

Having discussed the who and the where, I turn now to the "how." The technology for the delivery of dental care has changed. Many of these changes have been a result of the digital technology that changed everything from taking X-rays to optical impressions and include lasers and computer-aided design and computer-aided manufacturing technology and composite filling materials. One consequence of these changes is that many dental restorative procedures are easier to perform and no longer require the extensive training required for their mastery. For example, dental impressions, when fabricated with plaster of Paris, Kerr compound, or even alginate, required training, experience, and practice. The development of optical impressions has allowed the procedure to be performed by personnel with less training.

The first two decades of 21st century have changed who, where, and how dental services are provided. As a result of these changes, the public has options for obtaining dental care. As the alternative available will usually be at lower cost, traditional dental practices can expect a decline in patients and loss of income.

These changes represent an existential threat to each dentist and the dental profession. To survive in the 21st century, dentists must identify a segment of the population never treated by dentists and acquire new skill sets – new competencies ? to treat these patients. In what follows I will identify the new patients and introduce the opportunities for treating these patients.

Expanding Dental Practice: Stem-Cell Regenerative Dentistry

Before introducing the new patients let me discuss the use of stem cells and emerging field of regenerative dentistry. In the 21st century, dentists will continue to treat microbial-based diseases. Specifically, dental care will continue to include the repair or replacement of damaged or lost teeth from microbial action. However, because of recent advances in stem-cell regenerative technology, dentists should be expected to provide stem-cell-based dental care.[3] These procedures will necessitate dental schools teaching new techniques and procedures.

For a 21st century dentist to prosper, the practice must identify a new class of dental diseases and provide dental care to a patient population not previously served by dentist.

Expanding Dental Practice: Treatment of Nonmicrobial Dental Diseases

Fortunately, microbial diseases were not the only diseases treated by the dental profession in the 20th century – they also treated nonmicrobial diseases. One response to the increased competition would be for dentists to increase the number of patients with nonmicrobial-based dental diseases in their practice. However, even though the classification nonmicrobial dental diseases apply to wide range of diseases from oral cancers to sleep apnea, the number of patients in each category is insufficient to solve the problem.

In this study, I focus on a specific subset of these diseases namely congenital anomalies (birth defects) and more specifically those whose origins are linked to gene mutations. Two in this group are classified as birth defects, namely cleft palate and dental dysplasia. The third, malocclusion, is not usually considered as a birth defect. However, in a recent research, I present a rationale for its inclusion in this classification.[4]

Focusing on the congenital anomalies linked to gene mutations provides dentists with access to a population not previously treated, the emerging market of prenatal dentistry. One reason for optimism about treating diseases with underlying gene mutations is the success treating some single-gene diseases and most recently the availability of Crispr gene editing technology.[5]

In this study, I use the word "dysmorphogenic" to replace the term birth defect, a misnomer, as diseases such as cleft lip and palate do not occur during birth but are a result of abnormal tissue formation.

Expanding a Dental Practice – Gene-Editing as Treatment for Dysmorphogenic Dental Diseases

In the last several decades, significant progress has been made in understanding how the successful formation of craniofacial structures, including the teeth, requires a coordinated sequence of genetic events that begins as early as the fourth week of gestation.[6] But nature makes mistakes and when these occur, we get dysmorphogenic malformations. (As birth defects, particularly cleft palate, can result from toxic effects of pharmaceuticals, in this review, the focus will be on craniofacial malformations from mutations.)

Malocclusion – ectopic odontogenesis

Odontogenesis, the process of tooth formation during gestation, begins on the presumptive alveolar ridge, a structure composed of mesenchymal cells covered by a layer of epithelial cells. For the tooth to form, the epithelial cells must migrate into the mesenchymal tissue. The location of this initial invagination of the epithelial cells determines the location of first the primary tooth and later the secondary dentition. If the location is correctly specified in

the antero-posterior, labio-lingual, and oral-aboral axis, malocclusion would be prevented.

Malocclusion is not usually considered a birth defect. But in a previous study, I hypothesized that the malocclusion observed in an adult dentition was a result of mistakes in positioning of the tooth germ during odontogenesis. In that study, I suggested the phrase "ectopic odontogenesis" to refer to any error in placement. I also suggested malocclusion in the adult dentition might be prevented by intervening prenatally to assure odontogenesis would take place at the correct location on the embryonic alveolar ridge resulting in an ideal alignment of both primary and secondary dentition and preventing malocclusion.[4]

A great deal is known about tooth development including the activity of the genes implicated in odontogenesis, including those involved in localizing the odontogenic band and responsible for the lingual-labial and oral-aboral positioning of the presumptive tooth.[6-8]

But how to control those genes that determine the location and migration of the oral epithelial into the alveolar ridge and contact with the ridge mesenchyme is not determined. In the previous study, I suggested intervention *in utero* and acknowledged the significant technical barriers to intervention at this level.[4]

Recently, however, the discovery of the Crispr gene editing methodology to cut, edit, and insert new DNA during *in vitro* embryogenesis suggests that the use of this technology would be a more realistic approach to preventing ectopic odontogenesis. Clearly the application of Crispr technology would open new opportunities for dentists to control the expression of those genes regulating odontogenesis and prevent ectopic odontogenesis and resulting malocclusion.

Orofacial clefting — labia/palatogenesis

Clefting of lip and palate (CLP) is an example of a developmental mistake. As the causes for the mistake remain obscure, it is known that there is a strong genetic component to CLP.[9,10]

Three genes are implicated in CLP: T-box transcription factor-22 (*TBX22*), poliovirus receptor-like-1 (*PVRL1*), and interferon regulatory factor-6 (*IRF6*).[9,10] Although the nature and functions of these genes vary widely, it is not premature to consider CLP might be prevented by intervention at the genetic level. CLPs are birth defects that affect the upper lip and the roof of the mouth. CLP has a multifactorial etiology, comprising both genetic and environmental factors. In this review, we discuss the recent data on the etiology of cleft lip and palate. We conducted a search of the MEDLINE database (Entrez PubMed) from January 1986 to December 2010 using the keywords: "cleft lip," "cleft palate," "etiology," and "genetics." The etiology of CLP seems complex, with genetics playing a major role. Several genes causing syndromic CLP have been discovered. Three of them ? *TBX22*, *PVRL1*, and *IRF6* ? are responsible for causing X-linked cleft palate, cleft lip/palate–ectodermal dysplasia syndrome, and Van der Woude and popliteal pterygium syndromes, respectively; they are also implicated in nonsyndromic CLP. The nature and functions of these genes vary widely, illustrating the high vulnerability within the craniofacial developmental pathways. The etiologic complexity of nonsyndromic cleft lip and palate is also exemplified by the large number of candidate genes and loci. To conclude, although the etiology of nonsyndromic CLP is still largely unknown, mutations in candidate genes have been identified in a small proportion of cases. Determining the relative risk of CLP on the basis of genetic background and environmental influence (including smoking, alcohol use, and dietary factors) will be useful for genetic counseling and the development of future preventive measures.

Dental dysplasia — mistakes in amelogenesis

Human enamel formation is a multistep process requiring the timely expression of a multitude of genes. With so many genes involved in so many steps, it is no surprise that there are numerous conditions where dental dysplasia is a birth defect. These dysplasias affect primary and permanent dentition, enamel, and dentin mineralization and include hypoplasia and hypomineralizations and the imperfectas of both enamel and dentin. As is the case with all birth defects, diagnosis and treatment occur postnatally.

By 2021, we have a greater understanding of the genetic control for amelogenesis. We know there are a multitude of genes involved. For example, these genes control cellular differentiation, synthesis and processing of extracellular matrix proteins, modulation of cellular functions during enamel formation, regulation of movement of ions, and the regulation of acidity.[11]

With so many steps, there are many opportunities for error but also opportunities for Crispr technology to intervene.

In a recent review, it was noted that 91 conditions result in defective enamel, and of those, 71 have a known molecular etiology or linked genetic loci. This knowledge provides insight into the numerous molecular pathways required for enamel formation and could be useful targets for diagnosis and treatment of those hereditary conditions with an enamel phenotype.[11]

Mutations responsible for dentin dysplasia type II and mutations in the *DSPP* gene and for those with dentinogenesis imperfecta types II and III have been identified.[12]

In addition, amelogenesis imperfecta can result from mutations in the *AMELX*, *ENAM*, *MMP20*, and *FAM83H* genes. Because the *AMELX*, *ENAM*, and *MMP20* genes code for proteins essential for tooth development.[13]

Epilogue: A Future for Dental Practice

When contemplating what dentists will do for the remainder of the 21st century it is useful, to consider dividing dental diseases into two groups: microbial and nonmicrobial.

In the 20th century, and extending into the first two decades of the 21st century, dentists treated predominantly microbial-based dental diseases: caries and periodontitis. Dentists will continue to treat microbial-based dental diseases well into the 21st century, but the gradual increase in the number of dental therapists and the introduction of robotic-based digital technology will make restorative dentistry faster and easier. One result will be many patients will seek dental care outside of traditional dental practices. To compensate for the loss of patient and income, dentists must access alternative patient populations and the treatment of nonmicrobial dental diseases.

In this study, I argue for the dental profession to consider expanding its scope of practice into the treatment of craniofacial anomalies during embryonic development. As it is true that treatment of these diseases requires intervention in the pre-implantation embryo, recent advances in gene editing means the dental profession should begin to think about correcting these genetic mistakes.

There are obstacles to moving in this direction. Present day members of the dental profession may find it difficult to imagine future dentists performing gene editing. And even if they could, would the medical profession allow it?

But dental schools award a Doctor of Dental Medicine degree to graduates. Gradually, dentistry is shifting from a surgical specialty to a medical specialty. In fact, it may be time to revisit the formation of a new dental specialty. In 2006, I introduced Biodontics as a new dental specialty to focus on the shift from surgical dentistry to medically based dentistry.[14] It would be ideal to designate Biodontists as the specialist within dentistry to treat craniofacial anomalies using Crispr technology.

However, I recognize it will be decades before this approach enters routine dental practice. As expending dental practice into this area will require new technology, educational techniques, and training for dentists, I suggest the dental profession begin to examine this possibility.

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Conflicts of interest

There are no conflicts of interest.

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