

Dentistry in the 21st Century: A Look into the Future

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ABSTRACT

Modern dentistry and research will make possible the maintenance of comprehensive oral health by involving the use of nanomaterials, biotechnology including tissue engineering and, ultimately, dental nanorobotics (nanomedicine). Within 10 to 20 years, these devices will allow precisely controlled oral analgesia, dentition replacement therapy using biologically autologous whole replacement teeth manufactured during a single office visit, and rapid nanometer-scale precision restorative dentistry.

Tissue engineering is a novel and highly exciting field of research that aims to repair damaged tissues as well as create replacement (bioartificial) organs. A general review of the principles underlying key tissue engineering strategies are described.

PRACTICE IMPLICATIONS: Tissue engineering will have a considerable effect on dental practice during the next 25 years. The greatest effects will likely be related to the repair and replacement of mineralized tissues, the promotion of oral wound healing and the use of gene transfer adjunctively

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Key Words: Tissue regeneration, Lasers, Biomimetics, Remineralization.

J Oral Health Comm Dent 2009;3(1):9-14

We have just crossed the threshold of the 21st century, a monumental event for science and humankind. In science we are poised for discoveries and their application, which have the potential to change every aspect of how we view and address human health and disease. Within the next several years we will have a complete genetic blueprint of humans, extending the pioneering work of Watson and Crick. The impact of this information, which will be available to people of all ages on the Internet in the next few years, rivals that of Einstein's theory of relativity, the now familiar $E=mc^2$, as well as the monumental societal changes that occurred following the industrial revolution a century before that. In light of this new zeitgeist, as we review what the U.S. Public Health Service has accomplished over the past few years regarding dental amalgam and contemplate the future of research on restorative dentistry. The words of G.V. Black who, in 1897, stood on the threshold of the 20th century and observed that "...the day is surely coming...when we will be engaged in practicing preventive rather than reparative dentistry...when we will so understand the etiology and pathology of dental caries that we will be able to combat its destructive effects by systemic medication".(1)

Advances in dental materials and their future

Of all the innovative esthetic materials available today, the direct placement of resin composite has assumed the current thrust in restorative dentistry. This has been facilitated by remarkable advances in their physical and mechanical properties over the past 30 years, leading to significant improvements in their manipulation and durability.

Recently, numerous researches have taken place in the field of monomers and various anticariogenic i.e. fluoride releasing monomers have been manufactured. But the most important are the expanding monomers. The use of spiro-orthocarbonates as a component in dental resin composites resulted in a nearly volumetric neutral polymerization. The expansion on homo-polymerization was found to be 3.5% and experimental spiro-orthocarbonates, epoxy resins showed expansions between 0.1 and 0.8%. A 30 to 40% reduction in shrinkage was observed upon homo-polymerization of oxybismethacrylate monomers and oligomers compared with dimethacrylates commonly used in dental composites.(2,3)

Nano porous fillers have also been used in dental composites. Such materials attempt to allow the resin to have a greater interfacial strength with the reinforcing silica, thus increasing wear resistance.(3) The use of single crystal fibers or whiskers is becoming interesting. Pin-on-disc wear studies show that the whisker-reinforced material has comparable wear resistance to those of hybrid resin-based composites. It was also suggested that this type of composite could be applied to other resins, ceramic and metal based composite systems for biomedical applications. Ormocers have proved reduction in contraction of composites clinically, Smart composites results in a reduced demineralization and a buffering of the acid produced by caries forming microorganisms.(2)

Recently, there has been increasing interest by biomaterials community in utilizing polymers of various types as matrices and as reinforcements (especially in fiber forms) for calcium phosphate-based composites. Over the broad range of solution conditions when precipitation occurs spontaneously, Amorphous Calcium Phosphate (ACP) precedes the formation of hydroxyapatite. ACP has been shown to have high solubility in aqueous media and to undergo rapid conversion to hydroxyapatite, especially at low pH. Both of these properties suggest its use as bioactive filler in polymeric materials for the preservation or repair of enamel, dentin, cartilage and bone.(2)

Futuristic matrix for composites may be manufactured and used for dental use called as Metal-Matrix Composites (MMC) that could be used for dental restorative materials and implants or prosthesis. They can possess better wear resistance than pure metals or metal alloys, good transverse mechanical properties, reasonably high compressive and shear strength (because of good and KIC of metal matrix and good interface-bonding with filler).(4)

Dental devices and equipments

The future diagnostic techniques and tools such as ultrasonic, acoustic techniques and scanning techniques, Qualitative laser fluorescence (QLF), diagnodent, Optical coherence tomography, Confocal laser scanning microscopy (CLSM), erbium: YAG laser for detection of occlusal caries, Dye Enhanced Laser Fluorescence (DELFL), plasma arc curing lights, argon lasers etc have been incorporated recently to enhance our quality of practice and improve efficiency.

Air Abrasion for minimal invasive dentistry: This renewed interest in air abrasion is attributed to its ability to conserve tooth structure, our ability to bond tooth-colored restorations to enamel and dentin, and advances in technology that permit us to use less powder when preparing teeth and to adequately evacuate that powder. Air abrasion techniques provide for minimally invasive caries removal and tooth preparation. With

the wide range of bonded materials (including flowable composite resins) now available, these smaller preparations can be restored effectively.(5)

Air abrasion for restoration preparation removes tooth structure using a stream of aluminum oxide particles generated from compressed air or bottled carbon dioxide or nitrogen gas. The abrasive particles strike the tooth with high velocity and remove small amounts of tooth structure. Efficiency of removal is relative to the hardness of the tissue or material being removed and the operating parameters of the air abrasion device.(5)OLA

Se corporate profile

Lasers in dentistry: Dentistry is not only catching up with laser-related advancements, but is now surpassing other medical fields with a powerful product which performs a broader range of procedures than any other single laser related product has ever performed in any other specialty. The Waterlase from Biolase is a water and Er Cr YSGG laser technology designed to address the real needs of dentists and their patients with numerous proven applications.

Imagine a machine that not only performs a wide range of dental procedures better, faster and easier, it will do so with little or no anesthesia. And its full potential is just beginning to be realized. Considering the investment, a chief concern is how many every day procedures will benefit from using laser technology.(6)

In late January 2005, Biolase received the first FDA clearance for complete hard and soft tissue laser root canal therapy. The company can now market its Waterlase technology for root canal procedures for both hard and soft tissue procedures, which will broaden the applications that dentists and specialists can perform with the YSGG laser. This clearance covers all enamel, dentin, pulpal and diseased tissue removal, shaping and cleaning aspects of root canal therapy. This includes tooth preparation to obtain access to the root canal, pulpotomy, pulp extirpation, pulpotomy as an adjunct to root canal, root canal debridement and cleaning, root canal preparation including enlargement. The endodontic tips are very flexible and side cutting so you won't have to worry about 'screwing up' the apical foramen. The endo tips will allow you to remove dentin on the walls, remove all tissue in lateral canals and funnel the preparation.

Biolase has received the first ever clearance from the FDA for laser cutting, shaving, contouring and resection of oral osseous tissues (bone).

In addition to the newly approved root canal application, the

FDA bone clearance further expands the marketable, multiple uses of the Waterlase. It gives general dentists the ability to easily do procedures they would normally refer out to specialists resulting in tens of thousands of dollars of incremental revenue for their practice.(6)

The innovation of using lasers in dentistry has taken another giant step forward when the YSGG was approved by the FDA for complete hard and soft tissue laser root canal therapy. One of the most outstanding benefits is that patient's comfort level is generally much better during and after the laser procedures. This is significant in root canal therapy. A lot of the fear factor related to endodontic treatment comes from patients' anticipation of pain related to injections, drilling sounds, vibration pressure, and postoperative discomfort that may last a few days from the procedure. The YSGG in endodontics has the potential to give patients better comfort during and after the procedure. A series of specially designed laser fiber tips that are thin and flexible, can effectively clean and remove diseased tissue.(6)

Futuristic trends and approach

Imagine nationwide health promotion and disease prevention strategies that impact all children. Imagine all children with access to fluoridation, health diets, dental sealants, and empowered with ideal oral health hygiene habits. Imagine early detection of initial enamel demineralization addressed with non-invasive remineralization technology. Finally, imagine the possibility of being able to utilize the sequence of genes and their gene products to design and fabricate the enamel bio-ceramic—to replace human enamel. Even though the biological processes underlying this possibility are very complex, and the remaining steps in completing the biological issues required to produce enamel bio-ceramics are quite formidable, the biological and bioengineering communities are actually not very far from being able to realize the biomimetics of enamel bio-ceramics. For example, formation of enamel bio-ceramic involves the production of an organic template that is subsequently replaced by calcium carbonate and calcium hydroxyapatite crystals that are positioned along their c-axis resulting in the 99.6 percent inorganic enamel ceramic.(8,9)

Significantly, scientists in laboratories throughout the world, have identified and cloned the major enamel gene termed "amelogenin", which is located on the human X and Y chromosomes and which is responsible (when mutated) for X-linked inherited amelogenesis imperfecta. Subsequent research has discovered a number of other enamel-specific genes and their gene products required for the design and fabrication of human enamel including sheathlin or ameloblastin (chromosome 4), and enamelin and tufelin (chromosome 1). These genes when mutated are responsible for autosomal

amelogenesis imperfecta. At this time, the challenge for biomimetics is to learn how to make this bioceramic in an environment where the temperature is 37.5° C and the pH is 7.2, that is to say, in the mouth. The strategy is one of using molecular and nanotechnology to organize and orient, molecule by molecule, a pattern that promotes enamel crystal growth and orientation along the appropriate axis. With vision, innovation, creativity and sustained resources these possibilities can become realized and can become implemented within the diagnostic and therapeutic armamentarium of oral health professionals early in the new century.(9)

We are now on the verge of using bone morphogenic proteins to stimulate cells found in the host pulp to differentiate into odontoblasts and to produce reparative dentin that is biologically functional and integrated into the dentin extracellular matrix that remains.(5)

Other possibilities from research on Biomimetics extend beyond the treatment of diseased and destroyed tooth structure to include the development of diagnostics for subtle inflammatory processes. Imagine our ability to be able to accurately, precisely and safely assess oral health status without the use of ionizing radiation. Imagine our being able to precisely assess the extent of damage resulting from dental caries without the use of a probe.

Biomimetics provides remarkable possibilities well beyond the diagnosis and treatment of dental caries. Applications from biomimetics will play an important role in how we approach other diseases and conditions that affect the oral, dental, and craniofacial tissues of the body. The design of biologically compatible materials for the repair of temporo-mandibular joints that have been rendered useless by other treatment modalities or from the disease process itself; the treatment and prevention of inherited craniofacial diseases using our knowledge of genetics and biology; the development of new paradigms in the prevention, diagnosis and treatment of other infections of the oral cavity such as periodontal disease, opportunistic oral infections from *Candida albicans* associated with AIDS or other systemic conditions; and the development of alternatives to surgical placement of metallic implants in the treatment of edentulism using information from genetics and biology; all of these, will emerge in the 21st century from research involving biomimetics and will improve the oral health and hence the quality of life for all of our citizens.(8,9)

Tissue regeneration

Recently there has been a substantial and published scientific awareness of a relatively new field of applied biological research called *tissue engineering*. This field builds on the interface between materials science and biocompatibility and

integrates cells, natural or synthesis scaffolds and specific signals to create new tissue.(1) This field is increasingly being viewed as having enormous clinical potential.

Many strategies have evolved to engineer new tissues and organs, but virtually all combine a material with either bioactive molecules that induce tissue formation or cells grown in the laboratory. The bioactive molecules are frequently growth factor proteins that are involved in natural tissue formation and remodeling. The basis hypothesis underlying this approach is that the local delivery of an appropriate factor at a correct dose for a defined period of time can lead to the recruitment, proliferation and differentiation of a patient's cells from adjacent sites. These cells can then participate in tissue repair and/or regeneration at the required anatomic locale.(10)

The second general strategy uses cells grown in the laboratory and placed in a matrix at the site where new tissue or organ formation is desired. These transplanted cells usually are derived from a small tissue biopsy specimen and have been expanded in the laboratory to allow a large organ or tissue mass to be engineered. Typically, the new tissue will be formed in part from these transplanted cells.

With both approaches, specific materials deliver the molecules or cells to the appropriate anatomic site and provide mechanical support to the forming tissue by acting as a scaffold to guide new tissue formation. Currently, most tissue engineering efforts use biomaterials already approved for medical indications by the US Food and Drug Administration, or FDA. The most widely used synthetic materials are polymers of lactide and glycolide, since these are commonly used for biodegradable sutures. Both polymers have a long track record for human use and are considered biocompatible, and their physical properties (for example, degradation rate, and mechanical strength) can be readily manipulated. A natural polymer-type 1 collagen-is often used because of its relative biocompatibility and ability to be remodeled by cells. Other polymers familiar to dentistry, including alginate, are also being used.(10)

Tissue induction: In contrast to passive tissue formation achieved with conductive approaches, a tissue-inductive approach activates cells near the tissue with specific signals. The impetus for this approach was the discovery of defined molecules-termed growth factors-that could lead to new bone (osteogenesis) and blood vessel (angiogenesis) formation. Urist first demonstrated that new bone could be formed at a non-mineralizing site after implantation of powdered bone. This led to the isolation of the active ingredients (specific growth-factor proteins) from the bone powder, the eventual cloning of the genes encoding these proteins, and now their large-scale production by a number of companies. These proteins-termed

bone morphogenetic proteins, or BMPs-have been used in many clinical trials, including studies of non-healing long-bone fractures and periodontal tissue regeneration.(11)

Cell transplantation. The transplantation of cells grown in the laboratory provides another inductive means to engineer new tissues Cell transplantation is extremely attractive when inductive factors are not known for a specific tissue, when a large tissue mass or organ is needed, or when tissue replacement must be immediate. However, this approach requires the needed cells to be expanded in the laboratory. For some cell types (for example, acinar cells in salivary glands or islet cells in the pancreas), this is not yet possible.(11) The most successful application of cells transplantation involves the development of a tissue-engineered skin equivalent.

Gene Therapy. Generally, gene therapy is not considered to be an example of tissue engineering. However, gene transfer to well-differentiated cells arguably can be viewed as a way to engineer a tissue. Gene transfer in clinical settings has been used for about 10 years and began with the treatment of two children suffering from a severe combined immunodeficiency resulting from an inherited reduction in the enzyme adenosine deaminase, or ADA. These patients were treated with a procedure termed *ex vivo* gene therapy. The ADA gene was transferred into their own lymphocytes in the laboratory, followed by the return of these cells to the patients. To date, both patients have survived, although it is impossible to conclude that their survival was the result of gene transfer, because conventional therapy was administered along with the genetically modified cells. Indeed, there is still no published report of any clinical condition being corrected solely as a result of gene therapy.(1,10)

A look to the future of dentistry

As described above, engineered skin tissue and cartilage are becoming available for certain medical applications, and strategies to engineer bony tissues are close to receiving FDA approval. We foresee dental applications of these engineered tissues within the next few years. However, reconstruction of complex tissue defects made up of multiple cell types has not yet been attempted in the craniofacial complex, even in preclinical trials. Such a goal (for example, engineering a complete and functional salivary gland) will likely take about 10 to 15 years.(1)

Dentigenix is developing two products, DTX.21 and DTX.DR-1 to induce dentin regeneration over vital pulp exposures and thereby potentially be alternatives for up to 50% of root canal treatments (over 19 million annually in the US alone).

Dentigenix is developing DTX.41 to dramatically improve this

natural remineralization process. These products, applied to teeth by a dental professional, would remineralize the early areas of demineralization. This would enable the predictable reversal of the cavity producing process and reduce the number of teeth needing to be filled.(12,11)

Mineralized tissue defects: Tissue engineering is already being applied to the repair of periodontal defects, with the use of BMPs: the future is now. Indeed, considerable research activity is focused on applying tissue-engineering principles to dental and craniofacial structures, probably because of the ease of access to these sites and the extent and nature of the clinical problems. Many problems managed by general dentists or specialists are prime candidates for tissue engineering solutions, including fractures of bone and teeth, craniofacial skeletal defects, destruction of the pulp-dentin complex and periodontal disease.

BMPs and other growth factor-rich preparations are being applied with a variety of natural and synthetic scaffolds. The latter are particularly important considerations for many dental and craniofacial applications. Not only are biologically appropriate scaffolds required for the cells and inductive factors, but also the scaffolds should not adversely affect patient appearance. In that regard, an advantage may be gained from polymers that are allowed to flow into a defined site, rather than those that are fixed or implanted. Such polymers are currently being developed by a number of research groups.(11,1)

Gene therapy

There are several craniofacial examples of using gene therapy. The most substantial body of work uses gene-transfer techniques as either primary or adjunctive therapies for head and neck cancers. Already several early-stage clinical studies have been conducted. Most of the focus has been on squamous-cell carcinoma, and some incremental progress has been achieved. In general, the cancer gene therapy effort is enormous, representing a large proportion of all gene therapy research. In the next decade, clinicians will likely be able to use gene transfer technologies as part of their standard treatment of all neoplasias. Gene therapy also may offer a potentially novel approach to the treatment of severe chronic pain. Many studies have shown that genes can be readily transferred to cells in the central nervous system of animal models. Finegold and colleagues recently showed that viral-mediated transfer of the endorphin gene leads to effective analgesia in a rat pain model.(13)

Manufacturing concerns. For tissue engineering to help alleviate clinical problems, it is necessary for tissue-engineered products to be manufactured reliably. This need is almost self-

evident, but worthy of emphasis. The goals of successful tissue-engineering research are all commercially applicable (that is, to develop products for patient use).(13) This health-related use raises numerous concerns, including the following:

- Feasibility of scaling up from research levels to industrial output,
- Batch-to-batch repeatability in production
- Methods to achieve and maintain sterility
- Tissue procurement for cell preparations
- Optimal handling and storage methods

Ethical concerns. There is significant debate among researchers in the biomedical community about at least two major ethical concerns related to tissue-engineered products. The first, tissue procurement, also is a manufacturing concern (see “Manufacturing Concerns” above) for many tissue-engineered products (such as skin equivalents and bio-artificial organs), viable cells are an essential component. Unless a patient’s own cells can be amplified in an adequate and timely manner, enabling them to be used in the tissue-engineered device (that is, a cell auto-graft), then cells must be derived from another tissue.

Recently, researchers have called for a moratorium on research using cellular xeno-grafts, in large part because of a hypothetical risk. This risk is that an animal (in this case, porcine) virus might successfully overcome the human species barrier, perhaps mutate, and result in a serious human disease. Not surprisingly, there is no uniform agreement on this issue, although the dialogue has generally heightened awareness of ethical considerations in tissue engineering.(11,13) Thesleff I, Tummers M in 2003(10) gave prospects for regenerating tissues in dental practice. Stem cells have been discovered in many adult tissues, including teeth, and stem cells from embryos have the potential to form all adult tissues. Embryonic stem cells can now be cultured and even produced from adult cells by the nuclear transfer method.(13)

Conclusion

New technology continually has had a major impact on dental practice, from the development of high-speed handpieces to modern and biomimetics restorative materials. Tissue engineering in the broadest sense unquestionably will affect dental practice significantly within the next 25 years. The impact of tissue engineering will likely be most significant with mineralized tissues, which already is the focus of substantial research efforts. These efforts will yield numerous clinical dental benefits, including improved treatments for intra-osseous periodontal defects, enhanced maxillary and mandibular grafting procedures, perhaps more biological methods to repair teeth after carious damage and possibly even re-growing lost teeth.

In addition, we expect to see a range of other tissue engineering applications that may promote more rapid healing of oral wounds and ulcers, as well as the use of gene-transfer methods to manipulate salivary proteins and oral microbial colonization patterns. Less common, but still a treatment consideration for the dental profession, will be devices such as the artificial salivary gland and muscle (tongue) or mucosal grafts to replace tissues lost through surgery or trauma. This is an exciting time for biomedical science and its application. Clinical dental practice in 2030 will certainly be different.

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