Replacing and Renewing: Synthetic Materials, Biomimetics, and Tissue Engineering in Implant Dentistry

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Abstract: Hundreds of thousands of implantations are performed each year in dental clinical practice. Dental implants are a small fraction of the total number of synthetic materials implanted into the human body in all fields of medicine. Basically, these millions of implants going into humans function adequately. But longevity and complications still are significant issues and provide opportunities for the creation of improved devices. This manuscript briefly reviews the history of dental implant devices and the concepts surrounding the word "biocompatibility." It then contrasts the foreign body reaction with normal healing. Finally, the article describes how ideas gleaned from the study of normal wound healing can be applied to improved dental implants. In a concluding section, three scenarios for dental implants twenty years from now are envisioned.

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The inability of most tissues and organs in adult humans to regenerate after damage has been a profound frustration throughout history to physicians, dentists, and, of course, patients. Biocompatible implanted prosthetic devices have provided options in many cases helping millions (Table 1), but the reaction of the body to these devices is far from perfect. Complications include thrombosis, infection, ongoing inflammatory reaction, excessive fibrosis, impaired function, loosening, and extrusion. These complications are unfortunate for the patient and costly to the health care system. But, for biomaterials researchers and medical device specialists, these shortcomings with existing devices also represent opportunities and challenges to engineer improved therapies.

In dentistry, titanium and bioceramic implants are widely used. The phenomenon called osseointegration has become the accepted standard for success in dental implants. Yet, failure of these devices associated with impaired healing, infection, and overload are well recognized. Success is defined in terms of years of reliable service rather than a lifetime of device functionality. Other implants are used in craniofacial and oral surgery reconstruction. Varying degrees of success are seen, but problems and complications are evident, too.

This article will take an unusual direction. Modern implants will be viewed as foreign objects triggering a low-level, chronic inflammatory reaction. In the context of this critical assessment of contemporary "biocompatible" implants, what are the possibilities to turn on real regenerative healing or tissue reconstruction? Issues in normal healing will be reviewed to illustrate trends that may lead us to improved healing. The article will conclude with

Table 1. Medical device usage and complications

Device	No./yr. (U.S.)	Materials	*Complications*
Intraocular Lenses	>2,700,000/yr	PMMA, silicone	opacification
Hip and Knee Prostheses	>300,000/yr	titanium, steel, PE	loosening, inflammation, infection
Vascular Grafts	>100,000/yr	Teflon, Dacron	no healing, scarring
Heart Valves	>80,000/yr	carbon, fixed tissue	thrombosis, infection
Percutaneous Devices	>25,000/yr	titanium, silicone	no seal to skin
Dental Implants	>300,000/yr	titanium, hydroxyapatite	loosening, infection
Stimulatory Electrodes	>25,000/yr	platinum, iridium	encapsulation
Catheters	millions/yr	silicone, PVC, PEU, Teflon	thrombosis, infection
Cardiovascular Stents	1,700,000/yr	stainless steel	thrombosis, restenosis

speculation on what might be coming that will affect dental implantology practice and the use of synthetic material implants in the craniofacial region.

A Brief History of Implants in Dentistry

The well-preserved body of an individual dated to 200 AD was found in Europe a few years ago.[1] This person was found to have an iron tooth implant that by modern standards would be called osseointegrated. The Mayan civilization used nacre tooth implants around 600 AD, and again, evidence of osseointegration was noted.[2]

A more recent history of endosseous tooth implants starts sometime around 1950. Materials such as gold, tantalum, stainless steel, carbon (coating), and sapphire were applied, but only modest successes were noted. It was not until the introduction of the Brånemark tooth implant and implantation system in the early 1980s[3] that osseointegration in dental implants was "rediscovered." Such osseointegrated titanium devices, qualified by the criterion of less than 100Å between bone and titanium, greatly increased success rates and longevity for endosseous implants. Certainly, the titanium was important to the success of the Brånemark system (more will be said on titanium later in this article). However, improved surgical protocols, including low-speed drilling that minimized necrosis, were clearly important too.

For many years it has been known that hydroxyapatite will integrate with bone. This is a true bonding, in contrast to the Brånemark-type osseointegration, which is more of a mechanical interlock associated with the close apposition of nonadherent bone to titanium. The poor mechanical properties of hydroxyapatite have limited its widespread introduction into implant dentistry. Recently, strategies such as arc plasma spraying, chemical vapor deposition (CVD), or ion implantation to fuse hydroxyapatite to strong, metallic devices has led to a new generation of implants that will genuinely bond to bone.[4] Concern has been expressed about biosorption of the hydroxyapatite coating, mechanical failure in the hydroxyapatite layer, and debonding from the metal.

Other materials have seen application in craniofacial surgical repair and construction, often associated with repair of congenital defects, cancer resection, and trauma. Materials such as stainless steel, silicone rubber, titanium, and poly (methyl methacrylate) have been used to reconstruct the jaw, cranium, and orbital bony structure. In the hands of skilled reconstructive surgeons, reasonable cosmetic results have been obtained. Yet, problems persist, including infection and extrusion through the skin.

Widely publicized complications associated with implant biomaterials in the oral cavity involved temporomandibular (TMJ) joint cushions.[5] A Teflon-carbon composite, proven "biocompatible" in other implant sites, was applied in this application, where it was subjected to high compressive forces. Teflon does poorly under compression, and the breakdown debris, consisting of small particles, stimulated marked inflammatory responses and considerable pain and trauma for patients.

It is in the context of these clinical successes and clinical complications that we review ideas, mechanisms, and innovations that may affect modern dental implantology practice. The definition of biocompatibility will be examined in this assessment.

Wound Healing, Inflammation, and the Biological Reaction to Implants

A starting point is to look at the healing of today's implants and contrast it to normal wound healing. By examining normal wound healing, strategies might be developed exploiting the normal repair and reconstruction process that can be applied to synthetic implants.

Within a freshly prepared implant site one finds blood and damaged tissue. Blood is particularly important to this description. Components from damaged tissue are also influential. Consider an implant that is essentially free of leachable, cyto-reactive substances (the U.S. Food and Drug Administration would classify this as "biocompatible"—more on this subject shortly). The implant, in the biological fluid environment of the implant site, adsorbs a layer of proteins. This process, really a surface modification by proteins, takes seconds and is observed with essentially all materials.[6] Shortly after protein adsorption, neutrophils interrogate the implant (really the

adsorbed proteins at the surface of the implant). Unless bacteria or endotoxin (from bacterial cell walls) are found, the neutrophil numbers will diminish at the implant. However, by about one day, macrophages will be seen to accumulate at the implant. The macrophages will attempt to engulf and digest the implant as a foreign body. They will, of course, be unsuccessful and, apparently, in an attempt to enhance their effectiveness in the engulfment process, they will fuse to form giant cells. These will still be geometrically incapable of engulfing the implant. In a process often called frustrated phagocytosis, the giant cells will send chemical signals bringing fibroblasts to the implant site (typically at one week +). The fibroblasts will encapsulate the implant in a thin, avascular collagenous bag to isolate it from the body. This process is often called the foreign body reaction.[7] For a "biocompatible" implant, the reaction site after three to four weeks will be relatively quiescent. However, at the interface between the capsule and the implant, mildly activated macrophages and giant cells will be observed, even years after the implantation. This process is illustrated schematically in Figure 1.

If the implant leaches toxic or cell-reactive substances, a somewhat different response is observed. Stainless steel, for example, will leach ions upon extended residence in protein solutions. Stainless steel implants often have thick collagen capsules and more evidence of ongoing inflammatory processes. Gold also corrodes in biological fluids, leading to thicker, more active foreign body capsules.[8]

When a nonleaching (nontoxic) implant (for example, titanium)[8,9] is placed in a bony site, another reaction may contribute to healing. The classic foreign body reaction is triggered, leading to collagenous encapsulation of the implant. I hypothesize that the collagen formed in the bony tissue site, rich in biomineral-related ions and bone stem cells, may serve to nucleate new bone formation. In fact, collagen matrices are the substrates for the nucleation of normal bone formation. So it is not unreasonable to propose that the collagen-rich foreign body capsule serves to nucleate mineralization, leading to osseointegration. Where excessive inflammatory reaction occurs (for example, stainless steel, gold), the mineralization process is inhibited. This theory has

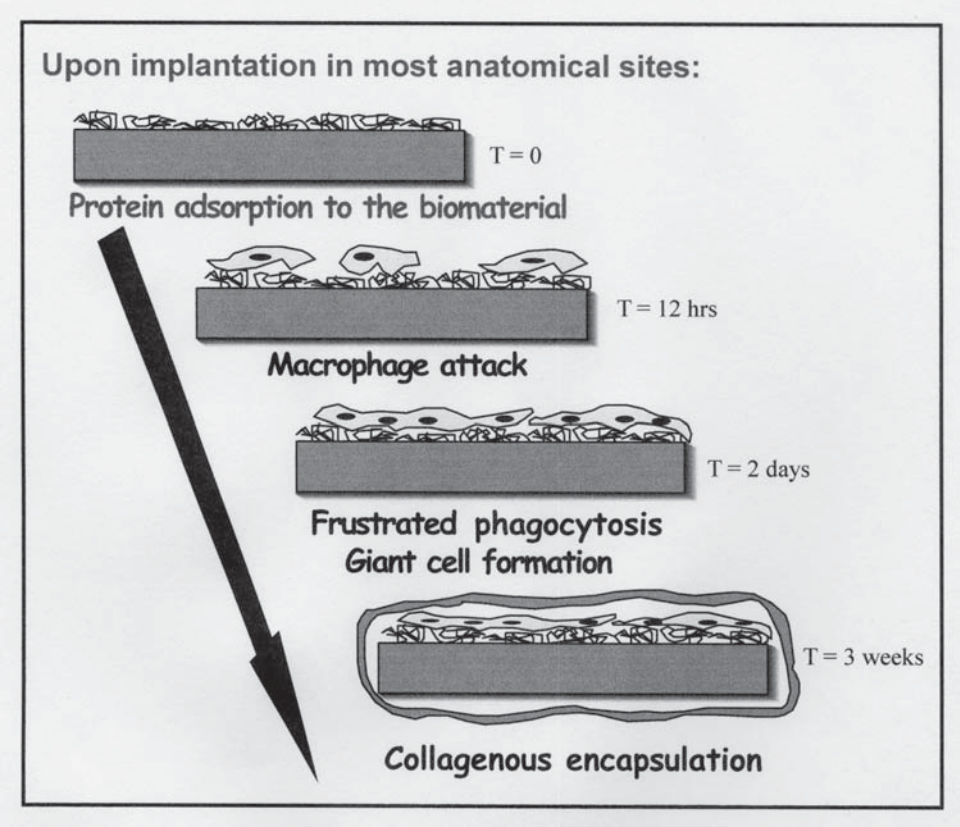

Figure 1. A schematic representation of the time course of the foreign body reaction to an implanted "biocompatible" material

been expanded upon as a chapter in a book on titanium in medicine.[10]

Finally, consider normal wound healing, in the absence of an implant.[11] In normal wound healing, neutrophils and macrophages clean the wound site of bacteria, debris, and damaged tissue. A number of proteins, referred to as matricellular molecules, including fibronectin, osteopontin, SPARC (secreted protein, acidic and rich in cysteine), and thrombospondin are found in high concentrations in the healing wound.[12-14] During the healing process, the macrophage sends signals to bring in cells that reconstruct the site. A vascularized, reconstructed tissue is left behind. When the wound is healed, the aforementioned proteins are gone from the wound site.

An understanding of the matricellular proteins involved in wound healing suggests novel surface modification approaches to improve the performance of implants, including endosseous devices. Could we immobilize to the devices proteins, such as osteopontin or SPARC, to turn on normal wound healing mechanisms[15]? Also, examination of the literature on healing of percutaneous devices intended to seal to the skin may offer insights useful for periimplant healing.[16,17]

The Definition of Biocompatibility

The most used definition of biocompatibility, "the ability of a material to perform with an appropriate host response in a specific application,"[18] though technically accurate, offers no insight into how to measure biocompatibility or how to improve it. Thus, other definitions, including those established by regulatory and standards agencies, are generally used. Table 2 lists considerations and tests associated with the 1999 standard, ISO 10993-15.

Table 2. Biological evaluation of medical devices, ISO 10993-15

- Animal welfare requirements
- Tests for genotoxicity, carcinogenicity, reproductive toxicity
- Interactions with blood
- In vitro cytotoxicity
- Local effects after implantation
- Ethyleneoxide sterilization residuals
- Degradation of materials
- Irritation and sensitivity
- Systemic toxicity
- Sample preparation
- Identification and quantification of degradation products

Current regulatory definitions of biocompatibility encompass ideas such as the absence of cyto-reactive leachables and the implant relatively quickly healing in a thin, collagenous sac with little ongoing biologic reaction at the implant site. This definition has worked reasonably well in qualifying materials for clinical use. Yet, this seems a strange definition of biocompatibility. The collagen bag is tough and avascular. It appears that the body is trying to wall itself off from this invader, the biocompatible biomaterial. These materials might be better called "biotolerated" or even "intolerable" than biocompatible. Perhaps a future definition of biocompatibility may refer to an implant that, after an appropriate healing period, is found in a vascularized tissue without capsule but with a normal collagen-based extracellular matrix, and/or biomineral. Thus, the biomaterial might trigger the normal wound repair and healing response rather than the foreign body reaction.[19,20]

Infection

An implant cannot heal properly where infection is present. Furthermore, the oral cavity is an exceptionally bacteria-rich environment. Bacteria adhere readily to implant materials and, when proliferation on those materials takes place, they secrete insoluble extracelluar polysaccharides that form a gelatinuous 3-D matrix, known as a biofilm. Bacteria living the biofilm lifestyle are phenotypically different from their free floating counterparts. They live in a gel-matrix that acts in part to protect them from the host's immune response, insulate them from antimicrobial challenges,[21] and promote the expression of genes that are unique to adherent life. The ability of an implant to heal properly in the oral cavity will be associated with the skill of the dental surgeon, bacterial counts in the oral cavity, and the rates at which the seal between implant to gingiva is made. Future biomaterials may address infection by inhibiting bacterial adhesion,[22] releasing surface localized antibiotics,[23] releasing specific metal ions, releasing molecules inhibiting biofilm formation, or perhaps enhancing the ability of neutrophils or macrophages to address surface bacteria.

Biominerals

Bone must reconstruct in the jaw to anchor an endosseous implant. How can we accelerate and use

this process? Biomimetic considerations are valuable. For example, nacre, the substance of sea shells, integrates into bone, possibly better than hydroxyapatite. Why is this so? What clues can we glean from the surface structure of bone and tooth?

Biomineralization might be viewed as a physical process (precipitation of calcium phosphate in the correct form) or a guided biological process (type I triple helical collagen is the template upon which bone forms). There are proteins that accelerate or inhibit biomineral formation. Osteopontin can turn on mineral formation or inhibit it.[14,24] There is a natural protein inhibitor of mineralization in saliva called statherin. Will biomineralization occur spontaneously if the correct protein matrix is assembled? What are the relationships between mineral formation (hydroxyapatite) and bone formation (a complex, vascularized tissue)? There is still a tremendous amount to be learned before we can reconstruct bone with precision and at will.

Evolving Ideas in Implant Dentistry

An ordered compilation of terminology associated with implant dentistry that appeared in a recent review article nicely illustrates the development of implant dentistry ideas.[4] These ideas are presented in Table 3.

The osteoinductive strategy aims at using biology to induce healing and reconstruction. Although this is a laudable concept, there are specific concerns with this approach as it is generally presented. The implants themselves have many of the problems they've always had, including possibilities for interfacial and mechanical failure. The biomolecules being explored, including the bone morphogenic proteins (BMPs), collagen, TGF-β and others, are certainly of great interest in bone healing and have shown some success *in vitro* and in animal models. However, nature never uses just one or two of these molecules in healing. During the normal wound healing process, one finds a precise, temporally staged progression of cytokines and other molecules involved in healing. The ability to deliver just one or two of these molecules seems naive compared to the elegance of nature's methods. Furthermore, these molecules are expensive, have the potential to spread viral contaminants, are of low stability, and are difficult to sterilize.

One novel method making use of synthetic materials to improve healing of the bone in the jaw that has reached clinical practice is based on the concept of guided bone regeneration.[25] The concept behind guided bone regeneration is to use a barrier membrane to separate anatomical spaces growing bony tissue from those growing soft or fibrous tissue. The rapid invasion of soft tissue into the bony site is thus inhibited. Porous Teflon membranes are commonly used. However, these do not degrade and must be removed from the implant site with a second surgical procedure. A number of biodegradable membranes are under study, including collagen and poly(lactic-glycolic acid). Modifications of the membrane material to enhance its osteoconductive nature are also under investigation. The procedure can be surgically demanding, although success rates have improved in recent years. Data in a recent study have raised questions as to whether the enhanced, early bone production from guided bone regeneration leads to enhanced survival rates after five years.[26]

Healing, Reconstruction, and Tissue Engineering

Tissue engineering, induced anatomical reconstruction, and regeneration are enticing frontiers in

Table 3. An evolution of ideas in implant dentistry

Terminology	Material	Clinical Observation	Issues
biotolerant	Stainless steel	No bone formation near the implant	Loosening, inflammation, infection
bioactive	Ceramics, bioglass	Bone bonding and osteogenesis	Fracture and mechanical problems
bioinert	Titanium	Bone in close apposition to the implant	No bone bonding, long term loosening
osteoconductive	Titanium + hydroxyapatite coating	Bone bonding and osteogenesis	Interfacial fracture, mechanics and resorption
osteoinductive	Titanium + hydroxyapatite + biological growth factors or attachment proteins	Bone bonding and enhanced bone formation	Interfacial fracture, mechanics, resorption, cost, biomolecule stability, sterilization

dentistry. Contemporary implants are "osseointegrated" in the bone of the jaw. Wolf's Law suggests they will loosen under normal loading. Teeth, of course, are not anchored directly into the jaw, but are connected by a peridontal ligament, a stress-relieving element. The ability of the peridontal anatomy to reconstruct forming a peridontal ligament has been demonstrated.[27-29] This reconstruction has even been seen with a titanium device in the implant site. A mix of cytokines has been used by Lynch et al. to stimulate this to happen. However, these cytokines are made by the macrophage. Why is the macrophage turned off from delivering these signals with implant biomaterials? What approaches are possible to stimulate this appropriate reconstruction in adult human recipients of dental implants?

Tissue engineering ideas are closely akin to regeneration concepts. In tissue engineering, a porous scaffold is used to grow cells and direct tissue. There are a few studies where tissue engineering has been applied to dentistry. For example, Mooney et al. grew fibroblasts obtained from adult human dental pulps, seeded them into a porous poly(glycolic acid) construct, and cultured them for sixty days.[30] A new tissue formed in culture with similarities to native pulp.

Speculation: Dental Implants in Twenty Years

Futurists are almost always wrong. Yet, in the context of 2001 and looking at real developments from our group at the University of Washington and from other researchers, I will make three predictions as to the nature of a dental implant in 2021 (give or take ten years).

In the first scenario, I propose that titanium implants with precision nano-machined surface textures and structures will be available for clinical use by 2021. Such engineered, geometrically precise textures will be substantially different from the stochastic, heterogeneous textures found on today's implants. It is well documented that specific textures and porosities induce unique healing in implants.[31,32] The ability to manipulate surface texture via lasers, lithography, and electrochemistry can create patterns that might couple into the spacing of mobile receptors on cell surfaces and thus modulate healing. Aspects of this idea have been expanded upon in a recent review.[33]

In the second scenario, consider a titanium implant. The device will come to the dental surgeon encapsulated in a thin gooey gel. This will serve two functions. First, it will protect the bioreactive surface from damage during implantation. Second, it will contain active molecules that can be released into the implant site. Upon implantation, the gel will dissolve within a day, liberating molecules to turn on healing. Macrophages that reach the surface of the titanium device will find biological triggers designed to turn on the healing phenotype. In this phenotype, the macrophages can rebuild the anatomical site by sending the appropriate, temporally staged sequence of healing molecules. The macrophages synthesize these molecules rapidly and cheaply. The molecules are sterile and "FDA approved." These surface-attached molecules also will facilitate the adhesion of a reforming peridontal ligament. Within two weeks, a highly functional prosthetic will be healed in place. What if, during the healing phase, infection sets in? The titanium device will have an antibiotic reservoir in its core. The dentist will apply an external pulse of ultrasound energy that will release the antibiotic right in the healing wound site and at the base of the biofilm where it will be most effective. Such ultrasound stimulated "on-off" molecular switches for drug delivery have recently been described.[34]

A third scenario draws upon tissue engineering ideas. The implant site is prepared by drilling into the jaw bone. The drilling residues are collected and placed through an affinity column that separates out stemlike cells. These cells are seeded into an anatomically appropriate porous tooth made from a biodegradable plastic. The device is placed into the implant site and covered with an artificial enamel cap. Beneath this cap, the pulp tissue regenerates, blood vessels infiltrate, tooth mineral is formed, and the peridontal ligament and jaw bone regenerates. The biodegradable plastic gradually disappears, replaced by living tooth tissue.

These three visions for endosseous prostheses of the future make use of the body's own healing and reconstructive mechanisms. They will require materials as well as concepts that are not available now. However, they are readily envisioned by extrapolating from current research efforts. Such devices that spontaneously heal and reconstruct will revolutionize implant dentistry.

Summary

In the fifty years of modern implant dentistry, great strides have been made. However, our present dental materials are foreign objects with little connection to normal biology. It is time to move beyond the present materials and concepts—we have them now, they work with varying degrees of acceptability, and they will probably not lead to large advances in performance. New ideas are emerging that should be expanded and exploited.[19,20]

There is a generality of healing in all implant sites. Although this article dealt primarily with endosseous implants, the concepts proposed here should be applicable to many biomaterial prostheses in the head and neck.

The basic theme of this article is to actively exploit healing and regeneration. What evidence do we have that this might be done? Every fetus does it casually. The potential of stem cell technology has been demonstrated. Tissue engineering as a field has taken its first small steps. The rules controlling the biology of healing are being elucidated. We may soon understand healing and regeneration at the genetic level. These developments will certainly contribute to vastly improved dental and craniofacial biomaterials in the future.

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