REVIEW ARTICLE

Biomaterials and Biomechanics of Oral and Maxillofacial Implants: Current Status and Future Developments

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Major advances have occurred over the last 3 decades in the clinical use of oral and maxillofacial implants. Statistics on the use of dental implants bear this out; about 100,000 to 300,000 dental implants are placed per year,[1] which approximates the numbers of artificial hip and knee joints placed per year.[2] Implants are currently used to replace missing teeth, rebuild the craniofacial skeleton, provide anchorage during orthodontic treatments, and even to help form new bone in the process of distraction osteogenesis.

Despite the impressive clinical accomplishments with oral and maxillofacial implants—and the undisputed fact that implants have improved the lives of millions of patients—it is nevertheless disquieting that key information is still missing about fundamental principles underlying their design and clinical use. With some important exceptions, the design and use of oral and maxillofacial implants has often been driven by an aggressive, "copycat" marketing environment, rather than by basic advances in biomaterials, biomechanics, or bone biology.

A wide variety of implants now exists for use in many clinical indications, with over 50 companies listed by the United States Food and Drug Administration (FDA) as being involved in the manufacture, marketing, and distribution of dental implants. While this situation is not necessarily a problem, in many instances new companies have entered the dental implant market by simply copying or making minor, incremental changes to the sizes, shapes, materials, and surfaces of competitors' products, while exaggerating the new product's effectiveness. In addition, busy clinicians, not always equipped to discern the difference between marketing hype and scientific advance, yet wanting to help their patients sooner rather than later, have often been too eager to use new implants in new clinical situations before these new indications have been fully researched from the clinical or basic science viewpoint. For better or for worse, the current state of the oral implant field is such that a myriad of different types of implants are now being used in a very wide variety of clinical indications, under largely undocumented loading conditions in different quantities and qualities of bone that has healed to varying extents. It is a fertile but complicated state of affairs.

Given this situation and the many variables that can affect the performance of oral implants, it is sometimes difficult to separate fact from fiction and make reliable predictions for the future. However, a helpful starting point is to appreciate that the use of oral implants—and the key role of biomaterials and biomechanics—is an excellent example of a multifaceted design problem.

TREATMENT PLANNING WITH ORAL IMPLANTS AS A DESIGN PROBLEM: AN OFTEN-IGNORED PERSPECTIVE

A guiding perspective is that the clinical use of implants is a design problem in the true sense of the word. Two key characteristics distinguish design problems.[3] First, design problems are open-ended, which means that they typically have more than one possible solution: "The quality of uniqueness, so important in many mathematics and analysis problems, simply does not apply."[3] Second, design problems are ill-structured, which means that "their

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solutions cannot normally be found by routinely applying a mathematical formula in a structured way."[3] Moreover, design is a process typically characterized by a series of steps leading toward a solution of the problem[4]:

- Identification of a need
- Definition of the problem
- Setting design objectives
- Searching for background information and data
- Developing a design rationale
- Devising alternative solutions
- Evaluating alternative solutions
- Decision-making and communication of solutions

To help clarify the above characteristics of design as applied to oral implants,[5] consider the following questions, which are often asked by clinicians: What is the best implant system? What is the best implant biomaterial? What is the best surface for an implant? What implant surface gives the best bone-implant contact? Which grade of commercially pure titanium is the best? What is the best implant shape?

While each of these questions seems meaningful, they all miss the point in the context of design. First, without defining the word "best," it is impossible to answer each question properly. This is because each question essentially begs another question, namely, "What do we mean by 'best'?" Second, each question seems to have the implicit assumption that the answer to that question alone will define the full merit of an implant, and by extension, the full merit of the implant in all clinical situations in which it is used.

An example illustrates the short-sightedness of the above thinking. To the untrained eye—and as often implied in advertisements—it might seem that a dental implant with the largest percentage of bone-implant contact must be the "best" implant. But some thought suggests a reason why this is not necessarily true. One could have a short, cylindric implant with a relatively small diameter that develops 100% bone-implant contact. While 100% contact may be desirable, it alone does not guarantee that the implant will work at the clinical level. For example, it could turn out that, because of that implant's small diameter and length, it would be inadequate in total surface area to support the in vivo loads, even though it has 100% bone contact. On the other hand, one could use the same length implant as above but select a larger diameter plus a screw-shaped or macro-rough geometry for 2 reasons: *(1)* it might be known ahead of time that, for whatever reason, this implant will achieve 70% bone-implant contact in the same bony environment; and *(2)* this 70% contact is known to be sufficient for the expected in vivo loads (because of the larger net surface area of the implant via the larger diameter and screw shape).

An analogous example could be developed involving the intrinsic strength properties of titanium, such as yield or ultimate tensile strength. Here it might be known that there is a difference between the intrinsic strength properties of different commercial grades of titanium and its alloys, such as titanium-aluminum-vanadium (Ti-6Al-4V). However, a designer would appreciate that this difference in strength properties could be important but is not necessarily paramount in a particular application; instead, what is critical is the overall strength of an implant structure made of one sort of titanium versus another. In general, a good designer might realize that it might be possible, with proper engineering, to design a successful implant from a range of implant materials, given due consideration to the expected loadings and the intrinsic properties of the material in the design of the restoration.

The above examples make the point that the problem with the original questions taken one at a time is that they focus on the implant per se rather than the entire clinical problem to be solved—which is in general a multifaceted design problem. Another limitation with these questions taken in isolation is that they do not seem to admit the possibility that more than one implant might "work" equally well in treating a patient, just as different automobiles serve different people equally well, provided the total design satisfies the design objectives.

Therefore, the relevance of each of the questions listed above depends on the design objectives for the clinical situation. Oral and maxillofacial implants are chosen, placed, and restored in a patient to achieve certain design objectives. The design objective is not necessarily to have the most bone around a dental implant, although this may help. Instead, the goal is to treat the patient. While at one level the objectives for this might be stated in a generalized manner—for example, "to improve the patient's quality of life"—eventually the design objectives should be defined more specifically. For example, eventually one has to decide on the type, location, and number of implants; the type of prosthesis; the nature of the expected loading, ie, whether the restoration will undergo immediate or delayed loading; costs of the treatment; and the amount of bone that may be expected to form around the implant. A key point involving most dental implants is that there are usually several ways to accomplish a treatment in the same patient.

Indeed, this is why such problems are in fact design problems. The existence of alternative solutions makes treatment planning quite similar to design in conventional engineering, as in the design of a house, a car, a laptop computer, or a computer operating system, each of which can be designed in a variety of ways, depending on the objectives. Depending on the available technology, one has to identify the different possible solutions and review them in light of the design objectives, which could include such factors as cost, simplicity, and speed. However, the bottom line is that the determination of which design solution is "best" depends on how one prioritizes different objectives.

A final example may emphasize the aforementioned message. Suppose that the most important clinical design objective is to provide a patient with implants and a final prosthesis on the same day as surgery. For example, this goal is implicit in the new Brånemark Novum System (Nobel Biocare, Göteborg, Sweden).[6] But if this is the goal, then one has to face the problem of designing all of the aspects of the situation—including the number, type, and biomaterial of the implant; the surgical procedures; and the prosthesis—with this goal in mind. Moreover, it would be useful to abandon, or at least re-examine, any preconceived notions that an implant designed for delayed loading is automatically suitable for use in immediate loading. And indeed, in the Novum System, differences exist between the new implants and those used in the more conventional 2-stage Brånemark System. The point is that implant size, shape, material, abutment connection, etc, are but a few of the many factors that must be identified and considered in light of the design objectives. This theme resurfaces repeatedly when considering the role of biomaterials and biomechanics in oral implant design.

BIOMATERIALS

A goal of biomaterials research has been, and continues to be, the development of implant materials that induce predictable, controlled, guided, and rapid healing of the interfacial tissues, both hard and soft. The premise is that such biomaterials will add to the arsenal of available tools enabling the design of improved implant systems. In addition to an ability to positively affect normal wound healing phenomena, it would be ideal if endosseous implants could also fulfill a design objective of forming a characteristic interfacial layer and bone matrix with adequate biomechanical properties over the long term.

To achieve biomechanical and biologic objectives, however, a better understanding of events at the interface is needed, and of the effects that biomaterials have on bone and bone cells. Such knowledge is essential for developing strategies to optimally control the phenomena that have been collectively used as a description of the often-used but still somewhat undefined term *osseointegration*. These outcomes would allow not only faster recuperation for the patient, but also stable fixation between bone and implant that would perhaps permit clinically reliable immediate or early loading of the implant. This latter type of treatment has great potential impact in terms of decreased patient morbidity, improved patient psychology, and decreased health care costs. To achieve these goals, however, a better understanding is needed of fundamental events surrounding tissue healing.

Events leading to integration of an implant into bone, and hence to the clinical performance of the restoration under loading, take place largely at the tissue-implant interface. Development of this interface is complex and involves numerous factors. These include not only implant-related factors, such as material, shape, topography, and surface chemistry, but also mechanical loading, surgical technique, and patient variables such as bone quantity and quality. This section of the paper reviews current knowledge of the bone-biomaterial interface and new methods being investigated for controlling this interface. Because of their predominant use as load-bearing implants, emphasis is placed on metallic biomaterials, although most of the noted work also applies to ceramic implant materials.

Events at the Bone-Implant Interface

The performance of biomaterials can be classified in terms of: *(1)* the response of the host to the implant, and *(2)* the behavior of the material in the host.[7] Although this section emphasizes the host response, a brief review of material response is also given.

Material Response. The event that occurs almost immediately upon implantation of metals, as with other biomaterials, is adsorption of proteins.[8,9] These proteins come first from blood and tissue fluids at the wound site and later from cellular activity in the interfacial region. Once on the surface, proteins can desorb (undenatured or denatured, intact or fragmented) or remain to mediate tissue-implant interactions. In fact, the nature of this "conditioning film" deposited on biomaterials, along with the biomechanical conditions surrounding the implantation, can be a major determinant of the host response, as discussed further in the section of this paper on biomechanics.

In addition to protein adsorption on the implant's surface, significant changes also occur in the material's surface. There is ample literature that describes oxidation of metallic implants both in vivo and in vitro.[10,11] Although metallic implant biomaterials were originally selected because of their stable oxide films, it is appreciated that the oxide surfaces still undergo electrochemical changes in the physiologic environment. For example, depending on the method of sterilization, commercially pure titanium (cp Ti) implants have an oxide thickness of 2 to 6 nm before implantation.[12] However, films on implants retrieved from human tissues are 2 to 3 times thicker.[10,12,13] Furthermore, surface analytic studies show that the chemical composition of the oxide film has also changed by incorporating calcium, phosphorus, and sulfur.[12,13] Continued oxide growth reflects ongoing electrochemical events at the tissue-implant interface. Another consequence of these events is the release of metallic species into tissues.[14] These corrosion by-products accumulate locally but may also be spread systemically. Significantly elevated metal contents have been measured both in periprosthetic tissues[15,16] and in the serum and urine of patients with orthopedic implants.[17–19] For example, metal levels of up to 21 ppm titanium, 10.5 ppm aluminum, and 1 ppm vanadium around Ti-6Al-4V and up to 2 ppm cobalt, 12.5 ppm chromium, and 1.5 ppm molybdenum around cobalt-chromium-molybdenum (CoCrMo) have been measured in the fibrous membrane encapsulating hip implants.[15,16] The tissue may include some particulate metal, but the ratios do not reflect the bulk composition of the alloys. Trace metals are essential for health, but they can also be toxic[20] or cause hypersensitivity reactions.[21] In vitro studies have revealed that metal ions, even at sublethal doses, interfere with differentiation of osteoblasts and osteoclasts.[22–24] It remains to be determined whether these effects on bone cells also occur in vivo. It is also unclear whether such effects are seen with oral and maxillofacial implants, which in general have much less surface area in tissues than orthopedic implants.

Host Response. The host response to implants placed in bone involves a series of cell and matrix events, ideally culminating in tissue healing that is as normal as possible and that ultimately leads to intimate apposition of bone to the biomaterial, ie, an operative definition of osseointegration. For this intimate contact to occur, gaps that initially exist between bone and implant at surgery must be filled initially by a blood clot, and bone damaged during preparation of the implant site must be repaired. During this time, unfavorable conditions, eg, micromotion (a biomechanical factor discussed later), will disrupt the newly forming tissue, leading to formation of a fibrous capsule.[25–27]

Morphologic studies have revealed the heterogeneity of the typical bone-implant interface. One feature often reported is the presence of an afibrillar interfacial zone, comparable to cement lines and laminae limitans.[28–31] Although its thickness and appearance vary, this zone forms regardless of the type of biomaterial implanted, including cp Ti, stainless steel, and hydroxyapatite.[32] Early reports indicated that the interface was rich in glycosaminoglycans.[28] However, more recent high-resolution immunocytochemical studies demonstrated that the electron-dense interfacial layer contains noncollagenous bone matrix proteins, such as osteopontin (OPN) and bone sialoprotein (BSP).[32,33] The absence or relative paucity of serum proteins, such as albumin, indicates a selective accumulation/deposition of molecules at the interface.[32] Because they contain arginine-glycine-aspartic acid (Arg-Gly-Asp) and polyacidic sequences, OPN and BSP are believed to play roles in cell adhesion and binding of mineral.[34–36] This interfacial zone might be the source of whatever mechanism of "bonding" exists between natural hard tissue and biomaterial, as discussed further in the biomechanics section of this article. However, the inherent weakness of cement lines argues against this level of bonding being stronger than a few MPa (while, for example, the ultimate tensile strength of fully mineralized compact bone is on the order of 100 to 150 MPa).[37]

Osteoblasts, osteoid, and mineralized matrix have been observed adjacent to the lamina limitans,[28–31] suggesting that bone can be deposited directly on the surface of the implant, extending outward from the biomaterial. Thus, bone formation in the periprosthetic region occurs in 2 directions: not only does the healing bone approach the biomaterial, but bone also extends from the implant toward the healing bone.

Understandably, because of the complexities of the in vivo environment, the bone-implant interface has not yet been fully characterized. The heterogeneity and patchy immunolabeling observed in morphologic studies suggest that, even though several biomolecules have been identified at the interface, they are likely not the only ones present. These other biomolecules may have essential roles in directing bone response to the implant, and further work is needed to identify them and determine their functions at the interface. It must be noted that cement lines are still present on OPN-knockout mice, suggesting that there are likely other yet-unidentified constituents in cement lines.[38]

In Vitro Studies. Bone cell culture models are employed increasingly often to study bone-biomaterial interactions. Most of the cultures have utilized osteoblastic cells (reviewed by Cooper et al[39]), with only a few using osteoclastic cells.[24,40] Primary and passaged cells from several species and anatomic locations have been used, as well as several osteosarcoma, clonal, and immortalized cell lines. Substrate-dependent differences have been reported, but the variety of models used makes it difficult to draw consensus conclusions.

Whether the different bone cell models would be expected to give comparable results is still a subject of debate. There are few side-by-side comparisons of different bone cell culture models on the same biomaterial substrates. It is known that bone from different sites, developmental ages, and types shows variabilities.[41,42] Taking into account the different microenvironments from which the cells come, there is no a priori reason to expect that all "osteoblastic" cells, eg, those derived from bone marrow or calvaria, would behave the same, at least during the initial phases of culture. In fact, unpublished observations from Puleo and Nanci indicate differences in adhesiveness of bone marrow– and calvaria-derived osteogenic cells on certain substrates. Nonetheless, in vitro models have the potential to help elucidate events at the bone-implant interface (as reviewed by Davies[43]) by providing morphologic, biochemical, and molecular information regarding osteoblastic development and synthesis of matrix at the interface with various biomaterials. An important consideration, however, is that the information obtained can indeed reflect in vivo events. For example, in vitro and in vivo models have shown formation of a cement line–like layer (described earlier) and appropriate organization of mineralized matrix during culture on various substrates.[36,44,45]

Controlling the Bone-Implant Interface by Biomaterials Selection and Modification

Different approaches are being used in an effort to obtain desired outcomes at the bone-implant interface. Many would accept the premise that an ideal implant biomaterial should present a surface that will not disrupt, and that may even enhance, the general processes of bone healing, regardless of implantation site, bone quantity, bone quality, etc. As Kasemo and Lausmaa,[46] among others, have described, biologic tissues interact mainly with the outermost atomic layers of an implant. Although secondary and other by-product reactions will occur, the "primary interaction zone" is generally only about 0.1 to 1 nm thick. Consequently, much effort has been devoted to methods of modifying surfaces of existing biomaterials to achieve desired biologic responses. As described by Ito et al[47] with respect to polymers, the approaches can be classified as physicochemical, morphologic, or biochemical.

Physicochemical Methods. Surface energy, surface charge, and surface composition are among the physicochemical characteristics that have been altered with the aim of improving the bone-implant interface. Glow discharge has been used to increase surface free energy so as to improve tissue adhesion.[48,49] Considering the role of electrostatic interactions in many biologic events, charged surfaces have been proposed as being conducive to tissue integration.[50,51] Calcium phosphate coatings have been extensively investigated because of their chemical similarity to bone mineral.[52,53] Each approach, however, has drawbacks. Increased surface energy does not selectively increase the adhesion of particular cells or tissues, and it has not been shown to increase bone-implant interfacial strength.[54] Contradictory results with charged materials in bone have been reported; indeed, both positively[50] and negatively[51] charged surfaces were observed to allow bone formation. Although short-term clinical results have been encouraging,[53,55] dissolution of coatings as well as cracking and separation from metallic substrates remain a concern with hydroxyapatite coatings.[56,57]

Morphologic Methods. Alterations in biomaterial surface morphology and roughness have been used to influence cell and tissue responses to implants. Porous coatings were originally developed with the rationale that, because of mechanical interlocking, bone ingrowth would increase fixation and stability of the implant. Many animal studies support the rather obvious idea that bone ingrowth into macrorough surfaces enhances the interfacial tensile and shear strengths (as determined from certain tests) compared to smooth surfaces (as discussed further in the section on biomechanics). However, data from retrieval studies of porous orthopedic implants indicate that only a relatively small portion of the available pore volume is filled with bone.[58–60] In addition to providing mechanical interlocking, surfaces with specially contoured grooves can induce "contact guidance," whereby the direction of cell movement is affected by the morphology of the substrate.[61] This phenomenon has applications in preventing epithelial downgrowth on dental implants and directing bone formation along particular regions of an implant. Mineral deposits in bone cell cultures can also be altered by surfaces with pits and grooves.[62]

Concerning surface roughness and its effects, there is a large but inconclusive literature on the biologic and clinical effects. Using in vitro cell culture systems, not all authors have come to the same conclusions about a role for surface roughness. Cochran et al[63] reported that human fibroblast and epithelial cell attachment and proliferation in vitro were affected by surface characteristics of titanium. Martin et al[64] used osteoblast-like cells (MG63) and noted that surface roughness of titanium altered osteoblast proliferation, differentiation, and matrix production. Using the same cell line, Boyan et al[65] found that titanium surface roughness affected the responsiveness of cells to hormones such as 1α,25-dihydroxy-vitamin D_3. On the other hand, Castellani et al,[66] who worked with titanium surfaces of differing roughness exposed to rat bone marrow cells, "could not clearly confirm the effect of surface roughness on the proliferation, differentiation, and calcification of rat bone marrow cells."[66p369] Likewise, Sauberlich et al[67] studied human gingival fibroblasts on surfaces of titanium subjected to different surface treatments and concluded that "a marked correlation between the cellular compatibility of the modified titanium and the surface modification made did not become apparent."[67p379]

In vivo studies also create an inconclusive picture of the role of surface texture. For example, Buser et al[68] placed titanium implants with 6 different surfaces into the metaphyses of the tibiae and femora of miniature pigs for 3 and 6 weeks. Surface treatments of the Ti included electropolishing (E), sandblasting with medium grit (0.12 to 0.25 μm) and acid pickling (hydrofluoric acid/nitric acid) (SMP), sandblasting with large grit (0.25 to 0.50 μm) (SL), sandblasting with large grit and acid attack with hydrochloric acid/sulfuric acid (SLA), titanium flame-spraying (TPS), and hydroxyapatite (HA) flame-spraying. These surfaces had not only different roughnesses, but also different surface compositions; the SL surface had some of the grit-blasted particles embedded in the "highly distorted" metal surface. A key finding of the study was that all the implants revealed "direct bone-implant contact," but with differing percentages of bone contact in the cancellous bone. The highest bone-implant contact was in the SLA and HA cases, with contact percentages of 50 to 60% (SLA) and 60 to 70% (HA). The authors reported that "the extent of the bone-implant interface is positively correlated with an increasing roughness of the implant surface."

Chehroudi et al[62] worked with titanium-coated epoxy replicas of 19 different micromachined grooved or pitted surfaces in the parietal bones of rats and reported that "surface topography influenced the frequency and amount of bone deposited adjacent to the implants." Wong et al[69] examined bone reaction to press-fit cylindric implants made of 3 materials and given different surface treatments in trabecular bone sites in knees of mature miniature pigs. After 12 weeks of implantation time, HA-coated implants had the highest push-out loads and the largest surface coverage by bone, ie, 79.9% versus a mean of 38.5% for the all-metal groups (cp Ti, Ti-6Al-4V, and titaninum-aluminum-niobium [Ti-6Al-7Nb]). Notably (see the section on biomechanics), there was an "excellent correlation . . . between the average roughness of the implant surface and pushout failure load." Ericsson et al[70] made a histomorphometric comparison in dog maxillae of screw-shaped dental implants with surfaces characterized as "machine-prepared" versus roughened by blasting with titanium oxide. At 2 months, both types of implants had a mean bone-implant contact percentage of about 40%. However, at 4 months, the roughened implants had a mean contact percentage of 65.1% (± 17.3%), which was greater ($P < .05$) than the contact for the standard machined implant surfaces, 42.9% (± 31.2%). Wennerberg et al[71] studied screw-shaped implants with 3 different surfaces in rabbit bone: blasted with 25-μm titanium oxide (TiO_2), blasted with 75-μm aluminum oxide, and a "turned" surface (as-machined). After 12 weeks, there was a higher percentage of bone-metal contact for implants with the 25-μm TiO_2-blasting. However, there was a greater surface area of bone in threads for the turned implants compared with the TiO_2-blasted implants. Based on this short-term study, there was better fixation using implants with greater roughness.

In contrast with the foregoing studies, other work has not revealed a major effect of roughness in vivo. Jansen et al[72] tested cylindric plugs of 3 different titanium alloys (cp Ti with 0.2 wt% palladium, Ti-6Al-4V, and titanium-aluminum-iron [Ti-5Al-2.5Fe]) and HA-coated Ti-6Al-4V alloy in rabbit tibiae for 6 and 16 weeks. The materials did not have identical roughness. After measuring the amount of bone apposition and other aspects of the bone reaction to the implants, the authors noted that "the results demonstrated no marked differences in bony reaction to the different implant materials" and that "the HA coatings showed a loss of thickness." Caulier et al[73] tested the response of "low-density" bone to threaded, uncoated, commercially pure titanium implants as well as the same metal plasma-sprayed with 3 different types of calcium/phosphorus–containing materials (fluoroapatite, HA, and heat-treated HA). After implantation times of 3 to 6 months in the maxillae of goats, no

differences were found in the histomorphometric measurements that were made. The authors found no significant differences "in the bone reaction among the various implant materials," although all coatings showed some decrease in thickness.

Moving to clinical studies with implants of different surface textures or roughnesses, few long-term comparisons are available of various implant surfaces in prospective trials. Helsingen and Lyberg[74] compared the surface composition and microstructure of 4 titanium implants that were identical in external shape (ie, screw-shaped "clones") but made by 4 different manufacturers: Nobel Biocare; Core-Vent (Los Angeles, CA); 3i (West Palm Beach, FL); and Osseodent (Palo Alto, CA). The study found no "substantial qualitative differences as regards chemical composition" and noted that only the Core-Vent implant's surface was different ("more irregular"). In their clinical pilot study involving 22 patients who received Brånemark implants on one side of the jaw and 1 of the 3 other implant types contralaterally, there were no significant differences in the success rate and marginal bone level 1 to 2 years after implant loading. In a recent study in humans, Iamoni et al[75] placed special screw-shaped implants that were half-coated (longitudinally) with plasma-sprayed HA. Each of 4 subjects received 2 implants in the retromolar area. Bone cores were excised at 1, 3, 6, and 12 months and analyzed histologically. The study reported a "tendency toward a higher percentage of bone contact at each healing period" for the HA-coated implants, although the number of specimens did not allow definitive conclusions.

Overall, these in vitro, animal, and clinical studies as yet do not yield compelling conclusions about the role of surface composition and texture with respect to bone response at the interface. Research continues in this area, for example, to formulate hypotheses and experiments about the role of specific geometric and size-related aspects of the surface and their role in the strength of the bone-implant interface.[76] Davies,[77] for example, hypothesizes that rough surfaces can capture the fibrin clot more readily than smooth surfaces and thereby positively affect the initial stages of integration. It is likely that future work will continue to formulate and test cellular-level hypotheses involving the role of surface texture and composition on the basic biology of cell and tissue interactions.

Biochemical Methods. Biochemical methods of surface modification offer an alternative or adjunct to physicochemical and morphologic methods. Biochemical surface modification endeavors to utilize current understanding of the biology and biochemistry of cellular function and differentiation. Much has been learned about the mechanisms by which cells adhere to substrate,[78] and major advances have been made in understanding the role of biomolecules in regulating differentiation and remodeling of cells and tissues, respectively.[79] The goal of biochemical surface modification is to immobilize proteins, enzymes, or peptides on biomaterials for the purpose of inducing specific cell and tissue responses, or, in other words, to control the tissue-implant interface with molecules delivered directly to the interface.

Although there are several reports of biochemical surface modification for modulating tissue responses to cardiovascular materials,[80–83] this approach has received comparatively little, but increasing, consideration for orthopedic and dental applications.[84–88] This methodology has great potential for controlling initial bone-implant interactions. In contrast to calcium phosphate coatings, biochemical surface modification utilizes critical organic components of bone to affect tissue response.

One approach for controlling cell-biomaterial interactions utilizes cell adhesion molecules. Since identification of the Arg-Gly-Asp (RGD) sequence as a mediator of attachment of cells to several plasma and extracellular matrix proteins, including fibronectin, vitronectin, Type I collagen, osteopontin, and bone sialoprotein,[89] researchers have been depositing RGD-containing peptides on biomaterials to promote cell attachment. Cell surface receptors in the integrin superfamily recognize the RGD sequence and mediate attachment.[79] Because of redundancy in the affinity of integrins for adhesive proteins and because a variety of cells possess the same integrins, nonspecific attachment of cells to RGD-modified surfaces is a concern. Some groups are attempting to circumvent this problem by using longer peptides with a particular conformation, rather than using short tetra-, penta-, or hexapeptides.[90] Others are examining non-RGD peptides that may be more specific for bone cells.[91,92] Furthermore, a combination of immobilized peptide and soluble growth factor(s) might be needed to elicit specific responses.[93] Presently, more studies are needed to develop surfaces, modified with bioactive molecules, that are selective for only osteoblastic cells.

A second approach to biochemical surface modification uses biomolecules with demonstrated osteotropic effects. A wealth of information has been obtained about the biomolecules involved in bone development and fracture healing. Many growth factors have been cloned and are recombinantly expressed. They have effects ranging from mitogenicity (eg, interleukin growth factor-1, FGF-2,

and platelet-derived growth factor-BB) to increasing activity of bone cells (eg, transforming growth factor-β1 [TGF-β1] enhances collagen synthesis) to osteoinduction (eg, bone morphogenetic proteins [BMPs]).[94,95] By delivering one or more of these molecules—which normally play essential roles in osteogenesis—directly to the tissue-implant interface, it is possible that bone formation may be promoted in implant applications.

Two considerations about delivering biomolecules to the tissue-implant interface are: *(1)* local cell populations must interact with the biomolecules for a period of time to initiate cellular events, and *(2)* concentrations of biomolecules must exceed certain threshold levels for cellular activity.[96] However, data regarding the duration of exposure or concentration needed for optimal activity of osteotropic biomolecules are lacking.

To control exposure and concentration, it is possible to alter retention and/or release of biomolecules from implant surfaces by using different methods, such as adsorption, covalent immobilization, and release from coatings. The simplest way to deliver biomolecules to the tissue-implant interface is by dipping the implant in a solution of protein before placing it. In orthopedic model systems, studies using simple adsorption indicate that delivery of TGF-β to the tissue-implant interface can improve bone formation in the periprosthetic gap[97,98] and can enhance bone ingrowth into porous coatings.[86] Using a similar approach, alkaline phosphatase adsorbed on titanium implants enhanced periprosthetic bone formation.[99]

Besides the fact that it is difficult to control the amounts adsorbed during dipping, another drawback to the adsorption method is that it provides little control over the delivery of molecules, including release/retention and orientation. Proteins are initially retained on the surface by weak physisorption forces. Thereafter, depending on the implant micro-environment, which varies between anatomic sites and between patients, the proteins desorb from the surface in an uncontrolled manner to initiate desired responses. Considering the necessity of specific receptor-ligand interactions for activity of many relevant biomolecules, appropriate presentation of protein may also be needed. Although positive responses have been observed using this simple approach, there is no indication that they are optimal for clinical applications. There is also a potential problem with diffusion of osteogenic factors and formation of mineral at undesired sites.

Bonding biomolecules to implants is an alternate way of delivering them to the tissue-implant interface, although in this case the protein will not be released. This approach is more complicated than adsorption because of the chemistry involved, but the activity of molecules immobilized on plastics has been shown to equal or exceed that of soluble protein.[100–102] For orthopedic and dental applications, metal surfaces possess a relative paucity of the functional groups needed for immobilizing molecules. The passivating oxide film on these materials does, however, have surface hydroxyl groups that provide locations for bonding using silane chemistry. This approach has been used to immobilize peptides, enzymes, and adhesive proteins on different biomaterials, including Co-Cr-Mo, Ti-6Al-4V, Ti, and nickel-titanium (NiTi).[88,89,103,104] Depending on the particular silane, experimental conditions, and substrate used, biologically active molecules can be retained on biomaterial surfaces for several days under simulated physiologic conditions.[89,105] Methods to circumvent the problem of lack of functional group diversity on metals include use of plasma treatments, etching, and deposition of self-assembled monolayers (SAMs). Plasma treatment can be used not only to increase the number of hydroxyl groups, but also to deposit reactive amino and carboxyl groups on the surface; this offers greater versatility for binding biomolecules using different immobilization chemistries. Preliminary results demonstrate ultrathin plasma-deposited films that are stable and tightly bind bioactive molecules.[105,106] Stable SAMs can be formed by depositing silanes with different terminal functional groups on model substrates, eg, thiol on gold.[107,108] However, formation of SAMs on the imperfect surfaces of real polycrystalline metals has not been demonstrated. Even deposition of gold on metallic biomaterials will likely reflect many of the defects of these surfaces. Another potential benefit of the immobilization approach is that it could be used to control presentation/orientation of biomolecules to cells. Although this has not been adequately explored, it is conceivable that, using specific binding sites on proteins (eg, protecting all but the terminal amino groups), biomolecules could be immobilized in a particular orientation on the surface.

Coatings incorporating biomolecules are also being explored for delivering biomolecules to the tissue-implant interface. In light of the dependence of cell and tissue responses on the duration of exposure and concentration of biomolecules, this approach is attractive because it can be used to control their release. Ethylene vinyl acetate (EVAc),[109] poly(lactide-co-glycolide) (PLGA),[110] and collagen[111] are among the coating materials being pursued. The continued presence of a non-bioerodible hydrophobic polymer, eg, EVAc, at the tissue-implant

interface after exhaustion of biomolecule, however, is cause for concern. On the other hand, bioerodible polymeric coatings, such as PLGA, can be used to release protein for long periods, although there is no evidence that sustained release is required for optimal implant integration. Because they mimic the way many biomolecules are normally retained in bone matrix, collagen coatings incorporating proteins have also been investigated. Furthermore, cooperative interactions between BMPs and collagen have been reported.[112–114] In addition to an initial release over 1 to 4 days that can initiate cell and tissue responses, biomolecules are retained in the collagen matrix coatings and would be available for later release to sustain responses.[111] The amounts of protein released and retained can be controlled by the amounts of collagen and/or biomolecule. Additionally, collagen coatings will be turned over in vivo and replaced with new tissue during the healing response.

Recently developed injectable, absorbable calcium phosphate cements may also be useful for biochemically modifying the tissue-implant interface.[115,116] These materials solidify in situ to temporarily stabilize the implant and allow early loading, while providing an osteoconductive environment as the cement is replaced with bone. A further development of the cements would be to use them as a medium for the delivery of bioactive agents to the bone-implant interface.

BIOMECHANICS

All oral and maxillofacial implants are meant to support forces in vivo, so it is obvious that biomechanics plays a major role in implant design. The following biomechanical issues are among the most important:

- What are the in vivo loadings that dental implants must be designed to resist?
- What factors are most important in controlling how the in vivo loads are transmitted to interfacial tissues? What are the stress and strain states in bone around the implant, and how can they be controlled?
- What are safe versus dangerous levels of stress and strain in interfacial bone? What biomechanical factors contribute most to implant success or failure?

Bite Forces and In Vivo Loading of Implants

Bite Forces in the Normal Dentition. In the normal dentition without implants, mean maximal vertical (axial) bite force magnitudes in humans can be 469 ± 85 N at the region of the canines, 583 ± 99 N at the second premolar region, and 723 ± 138 N at the second molar.[117] (A vertical force is defined as the force component acting perpendicular to the occlusal plane.) Raadsheer et al[118] measured biting forces with a triaxial piezoelectric transducer and reported average values of the "maximal voluntary bite forces" as 545.7 N in men (n = 58) and 383.6 N in women (n = 61). The maximum force measured in each group was 888 N in men and 576 N in women. The angle between the resultant bite force and the z-axis (perpendicular to the occlusal plane) was typically 3.9 degrees. The x and y components of the force were much smaller than the z component (1 to 49 N).

It is interesting to compare the above data with the vertical bite forces in other mammalian species, if only because many different animal models have been used for dental implant research without much data on the actual loadings in those species. For example, maximal bite forces were 550 N at posterior locations in a Labrador dog[119] and 1,712 N at posterior locations in orangutans.[120] Unfortunately, for parafunctional activities in humans, such as bruxism, few data exist on bite forces in human subjects,[121] even though it is believed that such habits contribute to some of the problems that can develop with implant loading.

For lateral bite forces in the normal human dentition, the data are less definitive. Some estimates put the values on the order of 20 N,[122] which is probably a conservative estimate, although Raadsheer et al's data[118] are comparable. In the incisal region, the direction of maximum incisal bite force is about 12 degrees to the frontal plane,[123] which suggests that the lateral components of force on an anterior implant could be appreciable.

Bite Forces After Implant Treatment. It has been suggested that the general features of mastication in patients with normal and implant-restored dentitions are approximately the same.[124] However, Carr and Laney[125] reported a significant improvement in both maximum and mean biting forces in a group of 14 patients who started with conventional complete dentures but then received mandibular tissue-integrated prostheses opposing a complete maxillary denture. For example, the mean maximal force was 59.6 N in the case of conventional dentures and 112.9 N for tissue-integrated prostheses. Carr and Laney also summarized other workers' data on the same subject and noted forces on dentures ranging from 57 to 120 N and forces on tissue-integrated prostheses from 137 to 190 N. Mericske-Stern and Zarb[126] explored maximum occlusal force and oral tactile sensibility in: *(1)* a group of partially edentulous patients restored with ITI implants supporting

fixed prostheses or single crowns, and *(2)* a control group of fully dentate subjects with healthy natural teeth. They found the highest maximal occlusal force in fully dentate subjects on the second premolars (mean 450 N). For fixed prostheses supported by implants, the average value of maximal occlusal force was lower—about 200 N for first premolars and molars and 300 N for second molars. In their data, the range of forces measured in the various subjects included values as large as 1,100 N in the molar region.

In Vivo Measurements of Bite Forces and Moments on Implants. For implants used as single-tooth implants, in vivo forces ought to replicate the forces exerted on natural teeth. This is expected because in both cases, the biting would be delivered to single, stand-alone crowns. However, factors such as the width of the crown occlusal table, the height of the abutment above the bone level, and the angulation of the implant with respect to the occlusal plane will affect the value of the moment on the implant. Also, it is self-evident that the forces and moments on an implant depend on exactly how the crown is built into an occlusal scheme. Moreover, it is also likely, but not necessarily clinically significant, that the nature of the occlusal surface material—eg, porcelain or acrylic—influences the dynamic character of the forces transmitted to the implant.[127]

However, it is necessary to go beyond the above factors for free-standing implants when trying to understand the loadings on several implants linked together by the prosthesis. Under these conditions, leverage effects exist because of geometric factors relating to restorations linking the implants, such as the existence of distal cantilevers in a full-arch restoration. Such factors cause the implants to be subjected to increased bending moments as well as axial forces that can be tensile and compressive. These facts are demonstrated in a number of representative experimental studies (and in theoretical work discussed shortly).

For example, Glantz et al[128] used strain-gauged abutments in vivo to measure the loading of implants supporting fixed prostheses retained by osseointegrated implants in 1 patient. Typical in vivo loading of the implants during chewing of celery, apples, and bread included axial force components from –20 N to + 25 N, with – meaning compression and + meaning tension. At the same time, there were bending moments in vivo up to about 20 N·cm. (These data are for bending moments about mesiodistal and buccolingual axes. No data were provided concerning the moments about the central axis of the implant.) Moreover, when biting occurred at the cantilever location of a prosthesis supported by 5 implants, axial forces on some of the implants were as much as twice the biting force on the prosthesis, a result that can be predicted from theoretical models discussed shortly.

Rangert et al[129] used the same methods for in vivo measurements of the vertical load distribution and bending moments on a 3-unit prosthesis supported by a natural tooth and a single Brånemark implant. In 5 patients, they demonstrated that the vertical loads were distributed between the natural tooth and the implant. For relatively large forces on the prosthesis (greater than 100 N), the bending moments on the implant were 10 to 15 N·cm, which was below the acceptable limit for the mechanical components of the system (50 to 60 N·cm for the screw joints).

Mericske-Stern et al[130] used piezoelectric transducers to measure forces on implants that supported overdentures. The overdentures were attached to the implants by 3 different attachment systems: U-shaped bar, round clip bar, and single telescopes. They found that the vertical component of the force depended on the nature of the attachments, and that the transverse (lateral) components were 10 to 50% of the vertical force components. These workers also noted that "rigid bars contribute to load sharing and stress distribution onto the implants."

Fontijn-Tekamp et al[131] used bite forks and transducers of special design to record the biting forces during closure on mandibular overdentures supported in different ways by implants. They reported that the differences in support of the mandibular overdenture were not reflected in bite force capabilities of the patients. Typical data for patients with implants showed maximal unilateral bite forces in men and women ranging from about 50 to 400 N in the molar regions and 25 to 170 N in the incisal regions.

For fixed prostheses, Mericske-Stern and Zarb[126] measured maximal occlusal force and oral tactile sensibility in 21 patients wearing complete maxillary dentures and mandibular fixed prostheses supported by Brånemark implants. The maximal occlusal force ranged from 35 to 330 N, with the largest values at the second premolar region. The detection threshold of minimal pressure was 330 g in the horizontal and 388 g in the vertical direction.

Gunne et al[132] measured axial forces and bending moments in vivo on freestanding and connected implants supporting 3-unit mandibular prostheses that opposed complete dentures. Each of 5 patients had 2 prostheses, one supported by 2 implants and the other supported by 1 implant and 1 natural tooth. The study found "no major difference in

functional load magnitudes related to the support type." Also, the study reported that "the distribution of load between the abutments was influenced more by the prosthesis geometry and implant placement than by the difference in load characteristics of tooth and implant,"[132p335] although this conclusion was "limited to [the case of] one implant connected to a tooth." Bending moments on implants ranged from 0 to 25 N·cm. An especially noteworthy finding in the study was the fact that implants could be connected with teeth in these patients without causing any detrimental clinical sequelae—an idea that has often been debated over the years. Also, axial forces on an implant could be tensile or compressive, depending on their location when supporting a 3-unit prosthesis, and that the axial loading on an implant could sometimes be twice as large as the bite force on the prosthesis because of cantilever extensions.

Richter[133] used a strain-gauged abutment to measure in vivo horizontal bending moments on IMZ implants in the molar area in humans. The author reported maximum bending moments and the corresponding transverse force when the patients chewed various types of food, including sticky confections (jelly beans), sausage, carrots, and crackers. The magnitudes of the bending moments ranged from less than 10 N·cm to slightly more than 20 N·cm. The corresponding transverse forces in buccal and oral directions were always less than 30 N.

Biomechanical Models for Predicting Implant Loading. Many investigators have tried to gain insight into implant loading by performing tests using experimental, analytic, and computer-based simulations of systems of implants supporting various types of prostheses. The biomechanical modeling of implant systems is a large literature in its own right, and only a few highlights are reviewed below.

Popular experimental methods have included the use of strain-gauged abutments (designed like those used in vivo by Glantz et al[128] and Gunne et al[132]) and photoelastic models.[134] Theoretical approaches have ranged from the simple to the relatively complex (Table 1). Monteith[135] presented a computerized version of the 1983 Skalak model so that clinicians might use it more readily in case planning. More complex computer models have ranged from 2D finite element (FE) idealizations to full 3D FE stress analysis with anisotropic material properties for the bone, and bonded versus nonbonded boundary conditions for the bone-implant interface. The main assumptions underlying the analytic and computer studies are summarized and discussed recently in Brunski and Skalak.[136]

From the above literature, the first key result is that when more than 1 implant is used to support a prosthesis, the forces on the supporting implants can sometimes exceed the forces applied to the prosthesis. This seemingly paradoxical result is explained by the mechanics of multi-unit prostheses supported by 2 or more abutments in various geometric arrangements. A second key finding from the literature is that both forces and moments can be produced on dental implants, which was illustrated by some of the in vivo studies reviewed previously. Third, even though bite forces are typically viewed as acting downward, toward the apex of natural teeth, thereby tending to compress the teeth into their alveolar sockets, it is a fact that implants can be exposed not only to compressive forces but also tensile forces (in addition to moments), depending on how the implants are arranged relative to where the bite force is applied to the prosthesis. Again, this fact emerges when more than 1 implant supports a loaded prosthesis.

The above 3 results are demonstrated by typical results of experimental studies and theoretical models noted in the following. Table 1 outlines similarities and differences among the analytic models.

One problem with the models in Table 1 is that none of them has been thoroughly checked against results from in vivo measurements. Qualitatively, the various studies of in vivo loads on implants suggest that typical predictions from the models are correct, at least in broad terms. For instance, it is clear that: *(1)* both tensile and compressive axial loads can occur on implants, *(2)* long cantilevers exacerbate the axial loading and bending moments, and *(3)* significant bending moments can exist on implants in vivo. However, detailed validation of the analytic models in view of in vivo data would be a useful topic for future work, to allow evaluation and greater confidence in the predictive power of the models.

Another specific issue that needs to be investigated in all of these analytic models (except for one of the models discussed by Morgan[142]) is the assumption of an infinitely rigid bridge. Actual prostheses are probably not infinitely rigid in the sense used in these models. For example, recent tests of actual prostheses[143] indicate that the rigid-bridge assumption of the 1983 Skalak model[138] leads to somewhat inaccurate results when trying to predict the forces and moments on abutments supporting metal-backed versus all–acrylic resin prostheses used by Balshi and Wolfinger[144] in immediate loading via conversion prostheses. This study involved in vitro experiments with metal-backed and acrylic resin prostheses supported by strain-gauged abutments and implants imbedded in plaster. In contrast to

Table 1 Summary of Analytic Models for Predicting Implant Loading

Model	Idealization of prosthesis: rigid or flexible	Nature of the connection between prosthesis and abutments	Stiffness of the abutments	Axial and lateral force components on the abutments?	Moments supported by the prosthesis-abutment connection?
"See-saw" (Rangert et al[137])	Rigid prosthesis (supported by no more than 2 abutments)	Ball-and-socket	Same stiffness for both abutments	No, only axial	No
Skalak[138]	Rigid	Ball-and-socket	Same for all	Yes	No
Skalak et al[139]	Rigid	Ball-and-socket	Different stiffnesses allowed for each abutment	Yes	No
Morgan and James[140]	Rigid	Built-in-joint	Same for all	Yes	Yes
Brunski and Hurley[141]	Rigid	Built-in-joint	Different for all abutments	Yes	Yes

what would be predicted by Skalak's 1983 theory, the data showed that more of the loading was concentrated on the implants nearest to the point where bite force was applied to the prosthesis. Notably, this same trend was seen in the experiments on abutment loading described in recent textbooks.[145,146] Overall, it remains to be determined whether the prostheses used in actual in vivo cases are well described by the assumption of a rigid bridge. Interestingly, the prosthesis design for immediate loading in the Novum System by Brånemark et al[6] is shaped more like an I-beam; perhaps because of this shape, this prosthesis will behave more like a rigid structure, but experiments will be needed to confirm this.

A second validation topic for the analytic models is the extent to which it is realistic to assume that all of the abutments/implants have the same stiffness in bone. It is understood from the analytic models that the stiffness of an implant—which is further defined and discussed in the references cited initially in this section—influences the load distribution among the abutments. For example, the Skalak-Brunski-Mendelson (SBM) theory,[139] which was the first to allow for different axial and lateral stiffness values among the abutments, demonstrated that the load distribution deviates appreciably from that predicted by a model having identical stiffnesses for each abutment (eg, the 1983 Skalak model[138]). And to a large extent, the SBM theory has been successfully validated in benchtop testing with a collection of abutments having known but different stiffnesses. However, when it comes to actual in vivo situations, there have been no definitive validation studies of this model.

A third factor that needs to be validated before confidently applying analytic models to clinical reality is the nature of the connections between prostheses and implants in actual patients. All of the models in Table 1 except the Morgan-James (MJ) and Brunski-Hurley (BH) models assume ball-and-socket connections between each abutment and the rigid bridge. In reality, it is of course known that prostheses are commonly attached to abutments by screw joints or cemented joints, neither of which is correctly idealized as a ball-and-socket joint. Hence, the MJ and BH models are probably the most realistic, especially the BH model, which also allows for different stiffnesses of the abutments. However, it remains to check these models against actual results from clinical situations, and to see whether the simpler models predict the results well enough for clinical purposes.

It should be noted that it is also possible to use the BH and MJ analytic models to analyze partially edentulous patients[141] as well as overdenture subjects.[147] For instance, a 2-implant patient was analyzed by Brunski and Skalak,[136] and a 3-implant subject has been analyzed.[148] The latter study addresses the specific problem of whether an in-line versus staggered arrangement of 3 implants is preferred when supporting a 3-unit partial prosthesis. The main result from that work is that a staggered arrangement is generally preferred because the implants tend to develop lower bending moments when arranged in a staggered fashion. Daellenbach et al[149] conducted an FE study of straight versus staggered implants with essentially the same conclusions. Renouard and Rangert[148] have collected a number of these ideas and clinical guidelines about implant loading and risk factors in a recent textbook.

Several computer models for predicting loading on implants have appeared over the last 2 decades. While many FE models have more commonly been used to analyze the stress and strain states in bone around implants, only a few have been used to predict the loadings on the implants.

What appears to be the first 3D FE model to predict forces and moments on implants supporting full-arch cases was based on Mailath et al.[151] This model was formulated to predict 3 force components and 3 moment components at the junction between each implant and the loaded prosthesis. A similar model by Mailath-Pokorny and Solar[146] compared axial loading of 4 or 6 implants supporting a prosthesis. This work showed data consistent with the trend noted earlier about the role of bridge rigidity—namely, that if the bridge is not perfectly rigid, there tends to be a concentration of more load (relative to the predictions of the original Skalak model) on those abutments nearest the loading point on the bridge.

An FE model by Benzing et al[152] concluded that a more "spread out" arrangement of the implants across the arch gave a "more favorable" distribution of bone stresses around the implants. This model also pointed out that the prosthesis material and design (shape) affected the stress distribution as well. Lewinstein et al[153] developed a unique "IL" system for supporting the distal extension of a cantilevered prosthesis; the system used a short implant and a special ball-type attachment that provided a distal stop when the cantilever displaced downward under loading. The results of the study did not focus on the implant loadings per se, but did discuss the stresses in the bone around the implants, which were lower when the IL system was employed. Sertgöz[154] used a 3D FE model to study the effect of the superstructure material and occlusal surface material on the stress distribution in an implant-supported fixed prosthesis. The work reported that using a superstructure material with a lower modulus did not lead to substantial differences in the stresses in any of the parts of the model (eg, prosthesis, screws, implants, surrounding bone), although the lower-modulus material did tend to concentrate stresses in the retaining screws.

Overall, the main advantage of FE models versus the analytic models is that they can more accurately simulate the many geometric and material complexities that exist in real patients. Such complexities include the 3-dimensional nature of the problem; the differing material properties of the prostheses, implants, and bone; the various boundary conditions inherent in how the mandible and maxilla are supported; and the nature of the boundary conditions between the bone and the implant, eg, whether the implant and bone are bonded together or not. However, the main disadvantage of FE models is the need for expertise in relatively complex software and hardware to formulate the problem, together with the need for expertise in the mechanical principles involved in the problem. This means that FE modeling is not a tool for the novice. Therefore, even though FE models would no doubt be valuable as a clinical treatment-planning tool, it is unlikely that such models will make their way into the clinical world anytime soon.

Misfitting Prostheses. The topic of misfitting prostheses and the biomechanics thereof is discussed in depth in a companion paper by Taylor et al in this journal.[155] Briefly, the misfit problem stems from the fact that dimensional errors exist in the fabrication of the prosthesis relative to the spacing and angulation of the abutments. Then, when the final prosthesis is attached to the abutments in spite of a misfit, this "non-passive" fit induces forces and moments on the supporting implants, even before they are loaded during mastication. The underlying mechanical principles that come into play in analyzing this problem encompass a number of topics, including the mechanics of screw joints under both ideal[156,157] and nonideal[158] conditions, as well as the properties of the structural members held together by the joint.[159]

It is interesting that even though research has demonstrated misfit in typical prostheses,[160] and even though there have been measurements showing that there can be significant loading on implants as a result,[161,162] this has not translated into significant problems at the level of the bone-implant interface.[163,164]

Orthodontic and Craniofacial Biomechanics. Orthodontic and craniofacial applications of implants involve many of the same issues discussed above. For further analysis, see other research.[165,166]

Noninvasive Assessment of the Interface Using Biomechanical Means. When loading is to begin on a given dental implant, eg, after second-stage surgery, it would be advantageous if the healing status of the bone could be measured noninvasively by some technique. Radiography can give some information, along with tests of implant "mobility," but neither approach provides fundamental information about the structure and properties of interfacial bone at the level of detail needed for biomechanical predictions. The following data are needed: *(1)* the axial and lateral stiffness of the implant-bone complex; *(2)* the level of mineralization and mechanical properties of interfacial bone (eg, woven bone, trabecular bone, or cortical bone); *(3)* the spatial extent of the bone

around the implant (eg, percent bone-implant contact and where there is bone contact); and *(4)* monocortical or bicortical anchorage. It would be possible to use this sort of data as input to various predictive biomechanical models that could then help with treatment planning—for example, the previously noted analytic or FE models for predicting forces and moments on implants.

Unfortunately, there is no current technique that provides such information. Many workers have tried to use the Periotest device as a means to assess the status of the bone-implant interface, but this only provides a number that has an unclear relationship to specific properties of the surrounding bone. For example, Caulier et al[167] found that the Periotest was "neither able to discriminate between the first thread nor between the total number of threads in contact with bone." The modal analysis technique of Elias et al,[168] which involves a small hammer with a built-in load cell and accelerometer, has the advantage of being able to discern trabecular versus cortical bone at an interface, or soft versus hard tissue, at least in vitro. The method also has a theoretical basis that helps with interpretation of the resulting data.[169] Potentially, it also could yield data that relate to the axial and lateral stiffness needed in models such as the Skalak-Brunski-Mendelson analytic model. However, although it can be further miniaturized, it has the disadvantage of being cumbersome to use in the mouth, and in any case has not been reduced to a clinically convenient device.

The so-called resonance frequency technique of Meredith and coworkers[170,171] has the significant advantage of being convenient, involving only a small vibratory element that can temporarily be screwed into the implant for in vivo tests. The signal analysis in this method allows it to distinguish, for example, changes in the mechanical properties of the interface during the polymerization of resin in which an implant is embedded. But owing to an unclear theoretical interpretation of exactly what is being tested by the device—eg, a combination of bone and implant properties, and if so, exactly what properties?—it does not produce data of direct use in biomechanical models. Overall, the field still needs a clinically reliable, sensitive, noninvasive test of the biomechanical status of the interface[172] that also provides input data for predictive models.

Biomechanics of the Bone-Implant Interface

Loaded oral and maxillofacial implants have to be supported by the interfacial bone in which they are placed; the chain of action-reaction from the prosthesis to implant to interface keeps the system in mechanical equilibrium. The interfacial bone is loaded, which produces stress and strain fields that extend for an appreciable distance away from the implant. Stress and strain are related by the constitutive equation for a material, the nature of which has to be determined for a given material, eg, woven bone as opposed to mature lamellar bone. Stress and strain are both important quantities, but whether one focuses on stress or strain depends to an extent on the goals of the analysis, which as noted earlier, depend on the design perspective.

Probably the most important reason for discussing stress and strain is that bone, like any other material, will be damaged and possibly fail if the stresses and strains become too high at a particular point in the material. Ideally, the design goal is to create an implant and its interface so that anticipated loading does not damage the implant or surrounding tissues when the implant is loaded. Second, it is important to know what stresses and strain develop at the exact region where the implant surface comes into contact with surrounding bone or other tissue. Here a relevant question becomes: Is there any sort of "bond" between the implant surface and tissue, and if so, what is its strength? This specific bone-implant contact region is only part of the interfacial zone between implant and bone, but it is a part that could be damaged if the stress and strain states are excessive. A third reason for studying stress and strain in interfacial bone is more biologic: the cells of blood and bone near a loaded implant will also be loaded and could be affected by the local stress-strain fields. Here the question is: What sorts of stress and strain states are "good" versus "bad" for the cells and biology of bone?

All 3 aspects of stress transfer above have been explored in a wealth of papers over the years. The following sections summarize that work by starting with biomechanics of the early healing stages of bone, and then ending with biomechanical issues related to loading at later times.

Biomechanical Aspects of Interfacial Bone Healing. Three major facts are clear: *(1)* drilling and cutting involved in oral implant surgery damages bone, *(2)* a cascade of wound healing events is triggered by the surgery, and *(3)* not all bone sites have the same quality and quantity of bone. It is also clear that differences inevitably exist among various implants, surgical techniques, animal models, postoperative loading protocols, graft materials, etc. Therefore, it should not be assumed a priori that immediately loaded implants, implants in grafted bone, implants in craniofacial bone, implants used with guided bone regeneration (GBR) and membranes, etc, all have identical bone healing sequences, rates, and interfaces. Also, it would be presumptuous to conclude that the load-bearing capacity or adaptability

of bone to loading will be identical in all these different situations. Moreover, the bone in various animal models is certainly not all the same and is not necessarily easily related to human bone.

In view of the foregoing, and especially with an eye toward interest in immediately loaded implants, it is relevant to review what is known about the events and timecourse of bone healing in: *(1)* gaps that inevitably exist between implant and bone at surgery, and *(2)* pre-existing bone that is damaged by surgical procedures.

Healing in Gaps, Pores, or Other Spaces that Initially Exist Between Bone and Implant. In general, perfect 3-dimensional congruity will not exist between a surgically prepared bone site and the surface of a dental implant, especially in view of the multitude of different implants that are now used. Micro- and macro-gaps will typically exist at the interface, even when the implant is supposed to have a reasonably close fit to the prepared bony site, as already alluded to by Brånemark.[173] A common feature of any gap, pore, or other defect between bone and implant is that it should (under the right conditions) fill with a blood clot soon after surgery. Then, as long as the implant is stable in the site, bone will develop in the gap.[77,174,175]

Looking at 2 extremes of healing in bone defects, Schenk and Hunziker[175] reported on intramembranous bone healing in small holes (0.6-mm diameter) drilled in rabbit cortical bone, while Schenk et al[176] studied such healing in large (approximately 10 × 10 × 7 mm) 3-wall defects in dog mandibles covered by e-PTFE membranes. These and other studies in various animals show that intramembranous bone formation proceeds through a well-defined sequence of steps, including blood clot formation, angiogenesis, osteoprogenitor cell migration, woven bone formation, compaction of woven bone by deposition of parallel-fibered and lamellar bone, and eventually secondary remodeling of the woven bone. For small (0.6-mm diameter) drill holes in rabbit tibial cortex, woven bone (compacted with parallel-fibered and lamellar bone) filled the hole by 6 weeks after surgery. Six months later, there was appreciable secondary remodeling and creation of new osteons, which were replacing the woven primary bone with secondary lamellar bone. Rahn[177] quotes reports showing that if the gap is very small, eg, a hole up to 0.2 mm in diameter, there may not be any woven bone, but rather healing by development of lamellar bone directly on the walls of the drill hole, at a rate of about 1 to 2 μm per day. (This means that a 0.1-mm hole would be filled in about 3 to 4 weeks.) In the case of Schenk et al's[176] bone healing in the large 3-wall, membrane-covered defects in the dog mandible, healing followed a sequence of steps that was similar to that in the larger-diameter holes, ie, compacted woven bone existed in the defect at 1 to 2 months, with secondary remodeling of woven bone starting at about 3 to 4 months after surgery. Similar events were reported in healing of a 1-mm-wide sham defect cut in mandibular bone.[178]

While the above studies did not have oral implants present during bone healing, the significance for implant biomechanics is that actual studies with implants confirm that the above steps do occur in various-size gaps or spaces that inevitably exist around implants. The significance of this is that, for example, in the first weeks to months after surgery, the interface will typically be comprised of new woven bone (that will eventually remodel), as well as damaged and remodeling lamellar bone; indeed, this has actually been shown in many examples in the literature (eg, Plenk and Zitter[179]). Certainly the size and location of interfacial gaps as well as the extent of remodeling in the nearby damaged bone will vary among different implant designs, bone sites, and surgical procedures.

Another significant point about the foregoing is that the biomechanical properties of the resulting composite interfacial structure are as yet unknown, yet would be needed in any detailed biomechanical analysis of interfacial biomechanics. One of the few studies to try to quantify the properties is a recent microhardness study of bone around implants in dog femoral mid-diaphyses.[180] This work documented a gradient in hardness with distance away from the implant surface. At 12 weeks after implantation, the Knoop microhardness number was about 31 at 0.2 mm from the implant. Hardness values increased to 45 at 1 mm from the implant, which essentially matched the hardness of normal cortical bone far away from the implant. Exactly how the hardness data correlate with elastic modulus is not clear, but recent work with nano-indentation of bone could provide a new technique with which to answer this question.[181]

Healing of Damaged Pre-existing Bone. Implant surgery clearly damages pre-existing bone at the implant site, which triggers innate healing responses in that bone. Hoshaw et al[182] documented the nature and extent of microdamage to bone during drilling, tapping, and placement of 3.75 × 7 mm Ti Brånemark implants in tibial diaphyses of New Zealand white rabbits. In a baseline group of 5 rabbits, they measured a mean area fraction of microdamage (eg, microcracks revealed by basic fuchsin staining) of about 12.5% ± 2% in a 1.2-mm-wide region of the interface adjacent to the screw. In a

healing group of 10 rabbits, implants in both tibiae were allowed 4 weeks of healing; this group showed an area fraction of microdamage of about 9.5% ± 2% ($P < .03$). Hoshaw et al demonstrated a correlation between microdamage at the interface and bone remodeling (A-R-F) at 4 weeks after implantation. (A-R-F stands for the cellular stages of the remodeling process: activation of osteoclastic cutter cones, resorption, and formation by osteoblasts.[182])

Hoshaw et al's observation of increased remodeling in relation to damage from surgical placement is consistent with other work suggesting that microdamage in bone stimulates bone remodeling as a reparative reaction.[183] Also, Roberts[184] reported that "about 1 millimeter of compacta adjacent to the osseous wound undergoes necrosis postoperatively despite optimal surgical technique," and noted that bone remodeling would be needed to repair this bone.

The above facts are biomechanically significant because they indicate that damaged pre-existing bone (as well as whatever newly formed woven bone might exist in gaps) around an implant would have to undergo at least 1 remodeling cycle (1 "sigma") to repair the damage. One sigma is about 1.5 months in rabbits, 3 months in dogs, and 4.25 months in humans.[185] However, it is not clear whether just 1 sigma is sufficient time to allow repair of 100% of the damage caused by surgery. It seems reasonable to suggest that the time needed for complete repair depends on the extent of the damage, the amount of remodeling that is triggered, and the size of the discrete packets of bone turned over by the A-R-F process. It seems possible that 100% repair of damaged bone by A-R-F turnover might take longer than 1 sigma in dental implant patients and experimental animals. Moreover, new bone can be deposited on old bone without prior remodeling.

This begs the question of exactly when, after surgery, the bone around an implant should be assumed to have settled back into a steady state of remodeling akin to that which existed before surgery. However, there are those who question whether interfacial bone remodeling around an implant ever returns to presurgical remodeling rates.[186,187] Garetto et al[186] have reported a highly elevated (with respect to normal) remodeling rate—on the order of 500% per year—around the threads of 2-stage implants. However, their data analysis assumes that a time of a few sigma is by definition long enough after surgery or loading for bone to have reached a new "steady state" of remodeling. But one could question the validity of this assumption; is it certain that just a few sigma are sufficient for all transients to die away after surgery and/or loading? This area of research deserves further experimentation, especially in view of the data below.

The literature indicates that, in addition to remodeling of bone that is frankly damaged by the surgery, there is heightened remodeling of cortical bone for some millimeters beyond this region of obvious, identifiable damage. For example, in a summary of bone remodeling in dog radii subjected to osteotomies, Schenk and Hunziker[175] reported that a large region of bone near the osteotomy site was undergoing remodeling via the A-R-F process; at 8 weeks after the osteotomy, 62.5% of all osteons in the entire bone's cross section were replaced or in the formative phase of renewal. This percentage of actively remodeling osteons greatly exceeded the percentage involved in remodeling in the control limb, which was 2.5%. Similarly, for 3.75 × 7 mm Brånemark screws in dog tibiae, Hoshaw et al[188] reported an increased uptake of fluorochrome bone label 5 weeks after surgery for 3 to 4 mm proximal and distal to the edges of the drill hole for the implant; 3 to 4 mm is beyond the region with noticeable microdamage from surgery. (The increased uptake of label was in comparison to uptake at a control site defined as the opposite cortex of the same tibia.) Other publications,[180] as well as schematic diagrams of bone remodeling around implants[189] and the concept of Frost's regional acceleratory phenomenon (RAP),[190] all suggest heightened remodeling activity (compared to controls) of interfacial bone over an appreciable distance of the interface. Related to this question of determining when bone has "quieted down" after being perturbed by surgery or loading, Frost has noted[191]:

> Sigma designates the earliest time after challenging the bone remodeling system when a new steady state characteristic of the treatment can exist. In practice one should allow such a system 2 or more sigmas to settle down, to avoid mistaking transients for steady-state phenomena; such unwitting mistakes arose so often in past work . . . that they represent the rule rather than the exception.

Note that implicit in all of this is the idea that bone has some sort of control system, which is a key idea discussed again in the last section of this paper.

From a biomechanical view, the facts above are significant because they suggest the considerable difficulty in knowing *(1)* when, and indeed if, bone resumes some sort of steady state of remodeling after surgery (or load-related insult); and *(2)* accurate mechanical properties of the interfacial bone, especially early after surgery. Currently there is a

lack of data about the mechanical properties of woven bone, although new work is shedding light on differences in noncollagenous proteins in the makeup of woven versus lamellar bone.[41,42] Also, the above facts lead to a second key problem in studying in vivo bone reactions during implant loading shortly after surgery. Namely, if loading starts within days, weeks, or months after surgery, it could prove difficult to distinguish biologic responses that might be triggered by load-related variables per se from biologic responses triggered by innate healing reactions per se. (This issue is further discussed by Brunski.[37]) At this point all that can be said is that for immediately loaded oral implants, the structure and properties of interfacial bone will not be identical to those that exist under conditions of delayed loading. Unfortunately, for either interface, detailed mechanical properties have not been determined.

Interfacial Micromotion and In Vivo Tissue Response. Micromotion (relative motion)—a relative displacement between an implant and surrounding tissue—has been fully discussed in recent review articles,[25–27] from which the following conclusions emerge.

First, it is not the absence of loading per se that is critical for osseointegration around implants, but rather the absence of excessive micromotion at the interface. In this statement, the term *osseointegration* might best be understood to mean simply "undisturbed bone healing around the implant."

Second, with micromotion, it is important to specify when the excessive micromotion occurs relative to the time of implantation. To date, most literature on micromotion has dealt with micromotion occurring immediately after implantation, when healing events have been triggered and implant stability depends on the implant's shape and retentive design features (or lack thereof). Under these conditions, the mechanism of the oft-reported fibrous tissue sequela of micromotion seems to be as follows. Micromotion, if excessive, is thought to damage the tissue and vascular structures that are part of the early stages of bone healing. Micromotion probably interferes with development of an adequate early scaffold from the fibrin clot. Also, micromotion probably disrupts angiogenesis and the establishment of a new vasculature for the healing tissue, which in turn interferes with the arrival of regenerative cells. Eventually, excessive micromotion will promote, in ways not fully understood, a re-routing of the healing process into repair by collagenous scar tissue instead of regeneration of bone.[192] Davies[77] has also suggested that excessive micromotion may prevent the fibrin clot from adhering to the implant surface during early healing; it has been theorized that surface roughness might help diminish the negative effects of micromotion relative to what would happen with a perfectly smooth surface.

Third, it is especially relevant that these findings about micromotion are true not only for metallic biomaterials (with either smooth or rough surfaces), but also for ceramic biomaterials such as HA.[193]

Lastly, from a design viewpoint, this research on micromotion begs a definition of "excessive" micromotion. That is: How much micromotion can be tolerated before a fibrous tissue interface will develop instead of an osseointegrated interface? The review articles noted earlier put the threshold at about 100 μm, assuming micromotion is started and maintained at this magnitude soon after surgery. However, maintaining the same amount of micromotion throughout an animal experiment can be problematic and depends on the setup. Prendergast et al[194] conducted a computer simulation of work by Søballe et al[193,195,196] in which fibrous interfaces changed cellular content over time from fibroblastic to osteoblastic, nominally under the same conditions of micromotion. However, a computer simulation suggested that the same amount of micromotion may not have occurred throughout Søballe et al's experiments; the data indicated that conditions in the experiment probably changed from motion-control to force-control because of changing tissue properties at the implant site. Thus, it might be that bone formation could occur once the micromotion decreased below the threshold level.

The biomechanical relevance of the foregoing is that in cases of immediate or early loading of oral implants, excessive micromotion at the bone-implant interface must be avoided. Obviously, it is not easy to demonstrate that this design goal is achieved at the start of a given case. A useful clinical guideline is that much will depend on the inherent stability of the implant when first placed in its site and loaded. Factors that will most likely affect stability include the shape of the implant relative to its bone site, the surface texture of the implant, the properties of the bone, the nature of the loading on the implant, and the splinting design for the implants (if used in a full-arch situation), among other factors. For example, the axial and lateral mobility of a new implant design, the Mark IV implant (Nobel Biocare), has been measured in vitro using a special system designed to measure axial and lateral stability in trabecular bone.[197]

Overall, it has been difficult to gain more detailed information about micromotion and related issues from the results of clinical studies of immediate loading, because none of these studies have actually targeted those factors in a quantitative manner.

Attachment Strength Between the Implant Surface and Bone. Given that it is detrimental to have excessive micromotion at an interface, it makes sense to direct design efforts toward developing as strong a "bond" as possible between an implant and tissue. For example, in the extreme case of an infinite-strength interfacial bond, it would be impossible to have any interfacial micromotion because the bone and implant would remain bonded together at the interface. However, as discussed below, the literature indicates that an infinite-strength bond does not occur in reality. A number of studies have centered on the exact nature and strength of the attachment that does exist, but some papers have questioned whether in fact this attachment has any appreciable physicochemical strength. That is, in the absence of mechanical interdigitation between surface asperities and bone constituents, what is the strength of attachment?

Cement Line at the Bone-Implant Interface? Recent research by a number of workers[29,31–33,43,177,198] has documented the ultrastructure of the junction between the implant surface and bone in vitro and in vivo. This work shows that biochemical and structural similarities exist between bone-biomaterial interfaces and natural interfaces in bone itself, for example the cement line between a secondary osteon and pre-existing bone. Davies[43,77] draws attention to this sort of cement line, but more generally for mineralized tissue, cement lines (reversal, resting lines) also exist and are actually about 10 times thinner than cement lines around osteons and correspond to what is seen around implants.

Cement Lines in Normal Bone. Even for normal bone there is uncertainty about the exact structure and properties of cement lines.[199] While the osteonal cement line is known to be collagen-deficient and probably hypomineralized,[200] the exact percentage of collagen, mucopolysaccharides, glycoproteins, and mineral is still under study. After reviewing the data, Martin and Burr suggested that[199]:

> . . . the cement line represents a residuum of the ground substance in osteoid, which is produced as a part of bone remodeling. Because the cement line . . . represents the remnant of the reversal phase of bone remodeling . . . the similarities in composition [with osteoid] should not be surprising.[199p51–52]

Significantly, cement lines in normal bone are generally thought of as weak points in the overall composite structure. For instance, yield and fracture testing show failures at cement lines.[201,202] Martin and Burr[199] attributed crack-stopping potential and energy dissipation to the compliant nature of cement lines during fatigue of compact bone. Burr et al[203] discussed a possible stiffness difference between bone and cement lines. Moreover, in fatigue studies of small beams of trabecular bone versus small beams cut from dense cortical bone, Choi and Goldstein[204] explained the poorer fatigue behavior of trabecular bone in terms of its "mosaic" microstructure, consisting of packets of remodeled bone separated from pre-existing bone by cement lines. However, except for these inferences that natural cement lines are weak, little data are available on the direct mechanical properties of cement lines.

Intrinsic Strength of the Bone-Biomaterial Interface. If a structure similar to a cement line exists at the bone-implant interface, it follows that this structure determines the intrinsic strength of a bone-implant interface. Here, intrinsic strength of an interface can be defined as the strength in the limit of a perfectly smooth biomaterial surface. What follows is the thinking behind this idea as well as some results relating to the shear and tensile strength of such an interface.

Steinemann et al[205] discussed interfacial bonding and distinguished between contributions to interfacial strength from surface roughness and bone-implant interlocking versus intrinsic biomaterial-biologic attachment. They pointed out that in the absence of roughness to provide interdigitation between an implant and bone, the intrinsic strength of an interface in shear or tension must be determined by the intrinsic biomaterial-biologic attachment. Now, based on more modern test data, if this attachment indeed consists of a cement line, then it follows that the intrinsic strength of the bone-implant interface will be determined by the strength of a cement line. However, in view of the structure of natural cement lines and their weakness in normal bone, as discussed below, it follows that the intrinsic strength of bone-implant interfaces will then be rather small when compared to the strength of fully mineralized bone.

In attempts to quantify interfacial strength, many investigators have devised a variety of methods. Brånemark[206] reviewed 38 so-called pull-out or push-out "shear" tests of implants placed in transcortical or intramedullary sites, 24 removal torque tests, and 18 miscellaneous tests, including tensile, crack propagation, and energy absorption. Key findings from that work were: *(1)* as roughness of the implant surface decreases, interfacial shear strength decreases; and *(2)* for tests of smooth-surfaced implants, interfacial shear strengths do not reach the full shear strength of bone (which is about

68 MPa[207]), and interfacial tensile strengths do not reach the full tensile strength of bone (which is about 100 to 150 MPa[207]).

The role of surface roughness in shear strength tests is well demonstrated in the work of Wong et al,[208] who measured shear strengths as a function of the roughness of different implant biomaterials in the same animal model. For implant surfaces with different roughness but the same implant shape, site, and implantation time, the results show a nearly linear relationship between the "pushout load to failure" and surface roughness in microns. Notably, test surfaces included commercially pure Ti, Ti-6Al-4V, Ti-6Al-7Nb, and HA, the latter having the largest roughness. Moreover, as roughness decreased to zero, the push-out force also approached zero (as would the shear strength computed in stress units, MPa, accounting for the interfacial area). The highest shear strength in the study was about 7 MPa, for HA with a surface roughness of about 6 to 7 μm.

Tensile data from a number of studies are not as complete as the shear studies of Wong et al, owing to a wide range of animal models and implant shape/size among the studies. Steinemann et al's[205] "rough" and "plasma-coated" Ti disks (roughness of about 20 μm) gave bone-implant interfacial tensile strengths of 1 to 4 MPa after 100 days of implantation in the ulnae of *Macaca speciosa*. Using disk-shaped implants of surface roughness R_a = 0.77 μm in periosteal sites in dog femora for 301 days, Taylor et al[209] reported interfacial tensile strengths of 0.27 ± 0.47 MPa for Ti-6Al-4V and 2.7 ± 0.82 MPa for HA-coated Ti-6Al-4V. Aspenberg and Skripitz[210] recently reported mean tensile strengths of 0.01 MPa for untreated cp Ti and 0.29 MPa for alkali-treated Ti in rat tibiae when the surface roughness was R_a = 0.48 μm. For dense HA disks with R_a = 0.32 μm, Edwards et al[211] reported tensile strengths of 0.15 ± 0.11 MPa at 55 days and 0.85 ± 0.55 MPa at 88 days in a rabbit tibial model. Other investigations[212,213] with dense HA polished to 400 grit (about 11 μm) reported tensile strengths of 1.32 to 1.5 MPa.

Note that in all of these tensile studies, the measured bone-implant tensile strengths were all less than about 4 MPa, which is much less than the tensile strength of fully mineralized bone (which, as noted before, is on the order of 100 to 150 MPa[207]), even for so-called bone-bonding ceramics such as HA.

While more conclusive data are not yet available on the tensile and shear strengths of a natural cement line in bone, it could be that the above-noted data are as close as can be obtained to such data for the biomaterial interface. And in any case, the biochemical makeup and structure of cement lines would seem to preclude a very large tensile or shear strength. That is, given that a cement line—naturally occurring in bone or at a bone-implant interface—consists of a thin layer of collagen-deficient, incompletely mineralized tissue between implant and bone, it is unlikely that this could confer a high tensile or shear strength at an interface, especially with the limit of a smooth implant surface. Even if somehow the cement line's attachment to the implant surface per se was strong, the strength of the material within the cement line could not be very high, given its composition and structure. While more data need to be gathered about cement lines, it is probable that its intrinsic strength would set an upper boundary for the strength to be expected at a perfectly smooth bone-implant interface. To date, there are no data suggesting that this upper boundary exceeds a few MPa at best.

The Meaning of Interfacial Strength Data in Biomechanical Models of Implants in Bone. The biomechanical relevance of data about intrinsic interface strength can be illustrated in an FE study[214] that allowed for interfacial "bond" failure according to input data from the literature about the shear and tensile strengths of bone-implant interfaces. The model used a typical value of 1 MPa for both the shear and tensile strengths of the bone-titanium interface, which was assumed to consist of a cement line of essentially zero thickness in the computer simulation. The interfacial strength values were used in a failure algorithm for the interface. As the implant was loaded incrementally from 0 to 300 N, stresses at the interface were computed and compared with the defined interface failure function involving the 1 MPa limit. The model revealed when and where the interface started to fail by debonding between implant and bone. For the test case considered, cracks started to open early in the loading, at just 30 N, forming at the thread cusps near the apical portion of the implant. As loading continued up to 300 N, the cracks widened and also started at new places along the interface, until finally at 300 N, the interface consisted of some regions remaining in (compressive) contact because of the interlocking geometry of the threads, and other regions where gaps had opened between the implant and bone after the interfacial tensile and shear strength had been exceeded.

Another relevant point from the above type of model is that the stresses and strains in bone adjacent to the interface depend strongly upon whether or not an interfacial "bond" does or does not exist. For example, compared to a bonded interface, strains were about 3 times larger in the same finite element model without bonding at the interface.[215–217]

Therefore, it should be recognized that the presence or absence of interfacial bonding influences interfacial stress and strain conditions—and potentially any bone cell reactions that might be linked somehow to the stresses and strains.

Significance of Stress and Strain in Interfacial Bone: Excessively High Strains. The motivation for studying stress and strain in interfacial tissue comes from an effort to define safe versus dangerous loading conditions in the bone. A number of studies[218–221] have reported that overload of the bone-implant interface can be a factor in marginal bone loss around implants. Typical clinical symptoms of overload include repeated prosthetic screw loosening or fracture and loss of crestal bone. A key biomechanical research question is the mechanism of overload failure of a bone-implant interface and a clarification of safe versus dangerous stress-strain states in bone.

The likelihood of a single-cycle overload failure of a bone-implant interface is not further considered here as a source of the clinically observed overload, although it is one potential type of biomechanical overload, especially for implants in poor quality cancellous bone. However, no single-cycle failures have clearly been documented in vivo as yet. Hence, it is more relevant to discuss overload failures that have been linked to cyclic loading conditions over a longer period of time. Given the literature reviewed below, there is evidence supporting the hypothesis that fatigue microdamage can occur in interfacial bone around a heavily loaded dental implant, and that this microdamage triggers bone remodeling (and possibly also modeling) that may not be able to keep pace with accumulating damage as loading continues—a situation that predisposes the bone to additional fatigue damage and, eventually, a net loss of bone and implant failure. The following explores the research relating to this hypothesis and other possibilities.

Damage to Bone. Monotonic compressive and tensile tests of both cortical and trabecular bone in the laboratory (using regular specimens) have revealed that bone can sustain various forms of mechanical damage when strains approach the yield point. For cortical bone, macroscopic evidence of yielding occurs at a strain of about 0.75%, although there is other evidence, eg, by acoustic emission, of yielding at lower strains such as 0.5%.[202,222] For trabecular bone, the yield strain is more difficult to pinpoint because the nominal strain of an entire specimen can differ from the strain fields that develop in individual trabeculae, as illustrated in computer models of trabecular bone.[223] For samples of bovine trabecular bone, Wachtel and Keaveny[224] saw transverse cracks, shear bands, parallel cracks, and complete trabecular fractures within samples tested to 2.5% strain in compression. This was 3 times more damage than was observed in the "yield group," which was tested up to 1% strain and then unloaded.

In tensile and compressive load-controlled fatigue tests of human cortical bone, Pattin et al[225] reported secant modulus degradation and increases in cyclic energy dissipation in specimens that were cycled at "critical damage strain thresholds" of 0.25% in tension and 0.4% in compression. Likewise, trabecular bone from bovine tibiae failed in fatigue when cyclically compressed for about 40,000 cycles at 0.4% strain.[226] Other reviews of the nature of damage that occurs in bone during the processes of yielding and fatigue appear elsewhere.[201,227–229] For bone, it is known that cracks, delaminations, shear bands, and other phenomena yet to be clarified comprise the nature of the microdamage seen in the microscope.

A promising new avenue of research into strain in bone comes from the work of Nicolella et al,[228,229] who used digital image correlation to measure strains at the microstructural level in laboratory specimens of bone. Significantly, while a strain gauge measured a nominal strain of about 0.15% in a bone specimen, the microstructural level strain values were as large as 3.5% at various locations in the microstructure. Note that 3.5% strain is over 20 times the nominal value measured by the strain gauge. This work emphasizes that values of nominal strain in bone—as might be calculated from sample dimensions or strain gauges—may severely underestimate actual strains occurring at the level of the bone microstructure. In other words, it is possible that damage might be occurring in bone even though routine strain analyses had estimated that the nominal strain values were "safe."

Damage, Bone Remodeling, and the Possible Relationship to "Overload." Mori and Burr[183] established that microdamage to bone stimulates repair by bone remodeling. Recent research in osteoporosis[230,231] indicates that: *(1)* microdamage can contribute to increased bone fragility and fracture risk; and *(2)* fractures can develop as the result of a vicious cycle (positive feedback mechanism) involving damage, remodeling-induced porosity, weakening of bone, further damage, and so on. That is, it is hypothesized that positive feedback occurs when bone remodeling (A-R-F) tries to repair a damaged site in bone, but in so doing, causes increased porosity and a vicious cycle of worsened strain state, more damage, more remodeling, more porosity, and so on, until failure. Conceptually, this idea could also be relevant to the bone-implant interface as follows. If porosity develops because of A-R- at a damaged

region, and loading continues on this already damaged but now remodeling region, more damage may occur in nearby bone as the result of the remodeling-induced porosity. This would then be followed by more remodeling, more porosity from the A-R-step, and so on. Although this hypothesis has not been conclusively tested and established in the context of dental implant overload, a number of clinical and animal studies support it.

An initial study[232] tried to develop an animal model in which controlled loads could be applied to osseointegrated implants as a means to study overloading and related interfacial tissue responses. This work used conventional 3.75-mm-diameter × 7-mm-long cp Ti Brånemark implants in dog bones. Implants in dog radii and mandibles were allowed to heal for 4 months (radii) and 7 months (mandibles) before loading by cyclic axial compression in the mandibular sites (square wave, amplitude 100 N, 0.5 cycles/sec, 500 cycles/day for 5 days), and cyclic axial tension of 50 to 100 N on implants in the radial sites. The results revealed no statistically significant differences between loaded and control interfaces. An explanation for the lack of a difference was probably the relatively low level of loading: subsequent finite element analyses suggested that maximum axial loads of 100 N may not have created strains larger than the yield strain over appreciable regions of interfacial bone for 7-mm Brånemark implants in these bone sites. Alternatively, it may be that the time between loading and histologic analyses (20 days) was too short relative to the time needed for bone to develop a measurable response via A-R-F; recall that sigma for A-R-F in dog bone is approximately 3 months. Third, the anatomy of mandibular and radial bone varied appreciably among the dogs, contributing to large standard deviations in histologic data.

Hoshaw et al[188] improved on the above study by using more uniform, mid-diaphyseal bone of dog tibiae; a larger axial load of 300 N (tensile); a longer healing time before loading (1 year); more detailed finite element and strain gauge analyses of the bone; and a longer time between loading and histologic analysis (ie, 3 months, which is about 1 sigma in the dog). The main finding was significantly more crestal bone loss in the loaded versus unloaded control group. The results were consistent with the following proposed mechanism: *(1)* principal strains in excess of bone's yield point (approximately 0.5%) occurred over substantial regions of interfacial crestal bone during each of the 2,500 cycles of loading at 300 N; *(2)* these large strains damaged the interfacial bone and stimulated a cycle of remodeling in the cortex and resorptive modeling on the periosteal surface; and *(3)* modeling and remodeling (and more cycles of loading) eventually created crestal bone loss that may have been exacerbated by downgrowth of periosteal soft tissues. The study could not experimentally confirm that microdamage occurred in interfacial bone because of implant loading, although this was quite likely in view of the strain values predicted by FE models (often larger than 4%) and the fact that 300 N was about 25% of the ultimate pull-out load for implants in dog tibiae.[233]

Isidor's studies[234,235] in monkeys were consistent with the above hypothesis of overload. Using 5 cp Ti screw-shaped implants per mandible in each of 4 monkeys, Isidor created supra-occlusal contact of the prostheses and "excessive occlusal load" (not otherwise quantified) in the lateral rather than the axial direction, on 2 implants per animal, starting at about 8 months after implantation and continuing for 18 months. Five of the 8 implants with excessive occlusal load "lost osseointegration" by 4.5 to 15.5 months after the loading commenced, while the other implants, with plaque accumulation but no loading, remained osseointegrated. Loss of osseointegration was attributed to "fatigue microfractures in the bone exceeding the repair potential."

In an analysis of a clinical case in which overload was suspected, Prabhu and Brunski[216,217] used FE analyses to evaluate a case in which 2 Brånemark implants supported a prosthesis in the mandibular molar region of a human with a positive history of bruxing. The implants had healed for 6 months before loading. After about 2 to 3 months of function, crestal bone loss was noted radiographically around the mesial implant, which eventually fractured. Three-dimensional FE analysis predicted high strains—in excess of 1%—at the crestal region of the mesial implant's interface, especially for the case of medium-size bite forces (eg, 250 N) on the mesial cantilever of the prosthesis. Again, these results support, but do not prove, an etiology of overload failure by the positive feedback mechanism outlined previously.

Computer Simulation of Overload at a Bone-Implant Interface. To make a more detailed microstructural examination of mechanisms of interface failure suggested by the above work, Brunski and Yang[236] did an FE simulation that allowed for bone microdamage and A-R-F. Therefore, a key feature of the model was that it allowed changes to the microstructure related to the actual process of remodeling by A-R-F. The model was set up in such a way to simulate the previously noted experiments of Hoshaw et al.[187] The model included an array of 25 osteons in healed interfacial bone. Upon implant loading, the

model computed principal strains in bone, and if strains exceeded a damage limit—set at 0.5% principal strain (for justification, see previously noted literature on bone damage)—then A-R-F was started at those sites. Since osteoclast (OC) recruitment and activation is the first step in A-R-F, it was assumed that OCs must come from a blood supply, which in this model was the Haversian canal of each osteon. As it turned out, the osteons were also frequently sites of high strain in the FE model, because of the stress-concentrating effect of the Haversian canal. Onset of A-R- was simulated in the FE model by removing bone matrix inside those osteons where strains exceeded 0.5%. This resorption created "holes" in the bone, which in turn changed the strain fields in subsequent load steps, which in turn sometimes created more regions of strain above 0.5%. This caused more damage, more A-R, more porosity, and so on. In some cases, bone eventually weakened so much as a result of the ensuing porosity that it failed completely in the next load cycle. Therefore, this FE simulation demonstrated a conceivable mechanism of overload by a positive feedback mechanism at an osseointegrated interface. A similar FE model has been developed for analysis of immediate loading.[237] It remains to be fully established whether these suggested mechanisms are in fact the in vivo mechanisms.

Significance of Stress and Strain in Interfacial Bone: "Wolff's Law"? In addition to assessment of the effects of excessively large stress and strain in bone, there is the overarching question of the biologic relevance of stress and strain. "Wolff's Law" often emerges when discussing this topic. This "law" has been translated as[238]: "Every change in the form and function of . . . bone(s) or of their function alone is followed by certain definite changes in their internal architecture, and equally definite secondary alterations in their external conformation, in accordance with mathematical laws."[238p225]

This law has been recast in various ways using modern engineering terms. For example, some presume that bone has a control system (eg, Frost's "mechanostat,"[239] analogous to a thermostat) that acts via modeling and remodeling to maintain constancy of the mechanical environment of cells when external loading conditions change. Or according to Mattheck,[240] bone is viewed as a biomechanically optimized structure, with the design being governed by "probably only one single design rule . . . the axiom of uniform stress," which "states that on average, over time, stress acts uniformly over the surface of components."

These ideas have become so intuitively reasonable, attractive, and ingrained in the literature that many researchers have tended to accept them a priori as unquestionable biologic fact to explain results of loading experiments in bone with and without implants present. However, at times, there has been a distressing disregard for confounding experimental variables or for alternative explanations for results in experiments; Bertram and Swartz's critique is excellent on this point.[241] In addition, there has also been a tendency to forget Chomsky's adage,[242] "It is a merit of a theory to be proven false," ie, theories should be crafted so that they can actually be tested. But as Currey has remarked[202]: "For many workers, it seems only necessary to show that bone is adapting, invoke Wolff's Law, and depart, conscious of a day's work well done." A full history and critique of Wolff's Law goes far beyond the scope of this paper; for additional insight see Huiskes,[243] Currey,[244] and Martin et al.[238] The more limited goal of this section is to emphasize that many workers with dental implants have tacitly accepted a Wolff's Law concept for bone around dental implants without directly addressing some conceptual difficulties inherent in this approach.

First, the key scientific challenge is to establish whether, in fact, bone has a control system to maintain mechanical homeostasis or optimal design, and if it does, to establish how it works both in normal bone and in bone around implants, specifically oral and maxillofacial implants. Among other tasks, it is necessary to identify the following: What quantity is being controlled by the control system? What are the sensors of bone's mechanical environment? If the cells are the sensors (since they are the only living things in bone), exactly what do they sense? And after having sensed something, how do the cells control the quantity that is supposed to be controlled? How quickly does this system work? A difficult problem!

An initial conceptual problem with the whole approach is that, when discussing the questions above in the context of oral (or orthopedic) implants, researchers often ignore the possibility that the answers to the questions will depend strongly on the biologic state of the bone. For example, while there seems to be little question that bone in the process of healing can be influenced by loading—evidently, an excellent example is distraction osteogenesis[245]—it does not necessarily follow that all types of bone—embryonic bone; bone in the developing skeleton; bone in the undisturbed, mature skeleton; bone around immediately loaded versus delayed loaded implants; or bone having different microstructure (eg, woven bone, plexiform bone, Haversian bone)—possess the same ability (and the same control system) to adapt to mechanical conditions. As Bertram and Swartz have aptly noted in their review[241]:

> We suggest that bone biology would benefit from an awareness that observations . . . gathered under the explanatory umbrella of Wolff's Law may reflect a plurality of effects which, in some cases, are related to the phenomenon suggested by Wolff only in their general morphological indications.[241p246]

Another problem surfaces related to stress shielding (stress protection), an idea that has arisen primarily in connection with proximal bone loss around femoral prostheses or bone plates in orthopedics.[246,247] It is hypothesized that bone loss occurs in certain regions near orthopedic implants because the local strain fields in bone become significantly lower than (or at least very different from) the values that used to exist in normal bone before the implant was placed. The idea has now been extended to dental implants.[248–253] This work suggests that crestal bone loss is possible around dental implants because of abnormally low strains and stress shielding. However, a key point in the dog studies with porous-coated implants[249] is that the bone sites in those studies were loaded immediately or very soon after implantation; some were loaded at 4 to 8 weeks after implantation. In those situations the authors themselves noted that woven bone existed at the interfaces.

The problem is that whatever bone responses might have occurred in these animal experiments, they must have occurred within an environment of active bone healing in both woven bone and damaged lamellar bone. Therefore, the bone-implant interface in this type of experiment is a highly complicated milieu, in which it would be difficult to separate out the events related to intrinsic healing from events ascribed to "stress shielding." In fact, the work by Perren et al[254] strongly disputes the entire notion that stress shielding is the reason for porosis beneath bone plates; these authors explain that impaired vascularity resulting from the surgery and plate placement is a more likely explanation. Certainly the issue of cause and effect is key.

Another potential confusion can arise in studies of stress shielding. Sometimes researchers seem to equate the idea of stress shielding, which is reputed to be something that happens in stress-shielded bone around implants, with the idea of disuse atrophy, which refers to events that happen in bone during prolonged bed rest or weightlessness during space flight.[255] It is sometimes implied that the underlying stimulus for bony change is the same in both phenomena, ie, a diminished stress-strain state in bone as compared with normal conditions. However, this implication can be questioned, because disuse atrophy evidently happens after bone starts off in a presumed steady state and is then perturbed noninvasively by removal or diminution of load, as in the examples of prolonged bed rest or space flight. On the other hand, things are quite different in bone around a recently placed implant, where the bone is assuredly not in a biologic steady state when the implant is placed and possibly also loaded. Indeed, bone around a freshly placed implant is traumatized by implant surgery and will be in an active state of healing for many months after surgery. In view of this fact, it is not obvious that bone loss from "stress shielding" and disuse atrophy have similar root causes, namely understressing of bone compared to "normal" levels.

Yet another problematic aspect of Wolff's Law as applied to bone around dental implants is the idea that bone cells can somehow "know" what strain state (or other mechanical quantity that is supposed to be controlled) is appropriate for a particular location in bone, and that if the strain state is inappropriate, the cells can change their bony environment until the "appropriate" strain (or other signal) is reestablished by the putative control system. As noted before, this same control-system concept is implicit in nearly all of the mathematical theories and computer simulations of bone adaptation to mechanical loading.[256] While the idea is intuitively appealing (and also underlies explanations of stress shielding and disuse atrophy), it is enlightening to recall what actually happens when implants are placed into bone.

Implantation surgery damages and sometimes kills bone, even when the gentlest procedures are used. Wound healing eventually produces new cells and matrix, which are indeed new to the site, having come from marrow or other nearby tissue. The woven bone that forms in gaps around an implant, as well as the damaged bone that remodels nearby, is made up of new cells and matrix that never existed exactly at that bony site before. This fact makes it difficult to envision how the new cells can somehow "know" what used to exist at that bony site, although communication with remaining cells is a possibility. Moreover, it becomes an even greater leap of faith to claim that the new bone cells in woven bone, as well as the new osteoclasts and osteoblasts in remodeling lamellar bone around an implant, somehow "know" the appropriate strains (or related quantities) for exactly that site—that is, they "know," for instance, that they are in a region that used to have natural teeth loaded in a certain way, or that they are in the anterior or posterior region of the mandible. This caution applies with even greater force to cells in bone surrounding an implant used in guided bone regeneration or in a bone-grafting procedure, in which bone from a fibula or iliac crest is grafted to

the mandible, for example. How can bone cells in the graft (if they survive) "know" that they are now in the mandible or maxilla?

For another example of difficulty in applying bone adaptation theories to in vivo tissue responses around dental implants, consider the work of Rubin and McLeod,[257] who have conducted numerous experiments on bone adaptation using the turkey ulna model and other systems. Their work focuses on regulating factors and morphologic goals of bone's adaptive process. These workers suggest that as a goal of skeletal remodeling, "minimization of strain per se not only is not achieved, but may not be desired." While they acknowledge that peak strain magnitudes are similar across animal species and bone types (eg, 0.2 to 0.35%), and that strains above the yield strain would be unsafe, Rubin and McLeod emphasize that:

> . . . it is difficult to imagine a biologic process that can quantify its proximity to deleterious strain levels, and subsequently adjust the tissue's mass to avoid them. Physiologically, it seems only reasonable that the resident cell population responsible for skeletal adaptation responds only to functionally induced strains, not the potential strain it might see should an aberrant loading event occur.[257p101–102]

Therefore, while not discounting that high strain levels can damage bone, Rubin and McLeod emphasize that bone adaptation to lower levels of strain might have to be mediated by signals other than just the strain magnitude per se. After all, strain at a point in a continuum (which raises the question of whether a continuum model of bone is even appropriate) is not a scalar quantity but rather a tensor quantity, represented by a 3×3 matrix of values. For example, Rubin and McLeod[257] have recently explored an alternative factor that might be more important in regulating bone remodeling, namely, the frequency spectrum of the dynamic strain signal. While it remains to be seen whether the frequency spectrum of the dynamic strain signal will prove more useful than factors such as strain magnitude, strain rate, strain distribution, strain gradient, etc, for understanding bone reactions around loaded and unloaded implants, it is sobering to note that the search continues for more information about the putative control system in bone.

As a final thought about implants, bone, and Wolff's Law, consider the vast array of oral and maxillofacial implants of widely different sizes, shapes, materials, surfaces, and loading histories that have been placed in various bone sites in humans over several decades. Probably the total number of implants in humans easily exceeds 1 million. What is perhaps most remarkable about the bone around these 1 million implants is what is not observed. That is, in long-term studies, there have not been widespread clinical reports of any conclusive trends in net bone formation or resorption around the many different implants in humans. Granted there have been reports about certain load-related bony reactions during the early healing period, or during the later periods, when late "overload" is observed. But apart from these reports of deleterious events such as micromotion during early bone healing, or late failure by overload (which, as noted, seems to be explainable in terms of overt damage to bone), clinicians have not consistently reported anything happening in bone relative to loading. All the more remarkable about this is the fact that the lack of conclusive findings occurs in spite of the near-certainty that 1 million differently shaped implants, under different loading conditions in a million different patients, must have produced widely different stress-strain states in interfacial bone—certainly much different than would have existed in that bone if natural teeth had remained. Of course, this is not meant to state that nothing happens in that bone in response to loading. But the reports do seem to be saying that whatever happened in the bone in response to loading, the results were not readily noticeable and reported in the general clinical experience. Therefore, for bone around oral and maxillofacial implants, it may be time to shift from a blind acceptance of Wolff's Law and move toward new, more testable, specific hypotheses. For example, maybe bone around oral implants is not sensitive to stress and strain except when it is healing.

SUMMARY

Research in biomaterials and biomechanics has fueled a large part of the significant revolution associated with osseointegrated implants. Additional key areas that may become even more important—such as guided tissue regeneration, growth factors, and tissue engineering—could not be included in this review because of space limitations. All of this work will no doubt continue unabated; indeed, it is probably even accelerating as more clinical applications are found for implant technology and related therapies. An excellent overall summary of oral biology and dental implants recently appeared in a dedicated issue of *Advances in Dental Research*.[258]

Many advances have been made in the understanding of events at the interface between bone and implants and in developing methods for controlling

these events. However, several important questions still remain. What is the relationship between tissue structure, matrix composition, and biomechanical properties of the interface? Do surface modifications alter the interfacial tissue structure and composition and the rate at which it forms? If surface modifications change the initial interface structure and composition, are these changes retained? Do surface modifications enhance biomechanical properties of the interface? As current understanding of the bone-implant interface progresses, so will development of proactive implants that can help promote desired outcomes.

However, in the midst of the excitement born out of this activity, it is necessary to remember that the needs of the patient must remain paramount. It is also worth noting another as-yet unsatisfied need. With all of the new developments, continuing education of clinicians in the expert use of all of these research advances is needed. For example, in the area of biomechanical treatment planning, there are still no well-accepted biomaterials/biomechanics "building codes" that can be passed on to clinicians. Also, there are no readily available treatment-planning tools that clinicians can use to explore "what-if" scenarios and other design calculations of the sort done in modern engineering. No doubt such approaches could be developed based on materials already in the literature, but unfortunately much of what is done now by clinicians remains empirical. A worthwhile task for the future is to find ways to more effectively deliver products of research into the hands of clinicians.

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