Enhancing Spinal Fusion

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The strategies for enhancing bone fusion are myriad. Each, in a way, uses a "trick of its own on mother nature" to improve the spine fusion environment. Such "tricks" are designed to foil the all too-often unfavorable surgical outcome of pseudarthrosis. Many of these strategies are discussed in the following pages. Each should be considered either currently or in the future, in selected circumstances or perhaps routinely. The strategies designed to enhance spinal fusion can be broken down into two separate and distinct categories: alternatives to autograft and physiology enhancement or augmentation techniques. Fundamentally, traumatized bone, whether disrupted through an overt act of trauma or through surgical intervention, heals best when bone healing-enhancing parameters are optimized. These parameters include: 1) surgical technique; 2) the use of bone graft substitutes that take the form of bone graft expanders or bone fusion enhancers through growth factors or augmentation techniques; and 3) bone physiology enhancement or augmentation strategies. Each of these strategies attempts to emulate or augment the existing attributes of autograft. Therefore, it is emphasized that autograft is the unequivocal "gold standard" strategy used for the acquisition of bone fusion. It provides the osteogenic, osteoinductive, and osteoconductive components required to achieve bone fusion. No other current strategy accomplishes such.

The bone healing process, whether it follows trauma or surgical intervention, involves multiple phases of healing (*Fig. 7.1*). First, a hematoma forms around the trauma or surgical site. An inflammatory phase associated with granulation tissue formation, fibrin matrix formation, and cellular and vascular infiltration ensues. It is the inflammatory phase that is particularly critical to the subsequent bone healing process and the acquisition of a solid arthrodesis. Of significant note, this phase is particularly sensitive to toxic extrinsic factors such as nicotine (and other factors associated with tobacco abuse), steroid use, radiation, chemotherapy, and so on. Therefore, it is emphasized that such clinical strategies should be delayed until the inflammatory phase is complete (approximately 3 weeks after trauma or surgery). The phase of callus formation follows in which cartilage and fibrous tissue (primitive woven bone) is laid down. Finally, the callus is remodeled with the deposition and resorp-

tion of lamellar bone. The latter is remodeled to achieve the final state of a solid and strong healed fracture or bone fusion.

Surgical Technique

Surgical technique obviously plays a major role in clinical outcome, but unfortunately is difficult to characterize. Regarding bony fusion, "carpentry" (e.g., the careful crafting of the bone fusion beds and the insertion of a carefully crafted graft or strut) plays a major role in enhancing and optimizing the environment for fusion. Surface area of contact optimization, the assurance of appropriate (neither excessive nor too little) loading of the fusion site, the use of carefully selected implants that do not excessively load nor "stress shield" the fusion site (*Fig. 7.2*), and the selective employment of the strategies discussed in the following pages are surgeon-dependent and often dictate the fate of a surgical procedure.[3,5]

The optimization of the surface area of contact between fusion surfaces was initially espoused by Cloward[8] and others as a strategy to enhance bony fusion. Cloward[9] suggested that a bone fusion surface area of contact that involved 80% of the surface area of the lumbar intervertebral endplate was optimal (*Fig. 7.3*). Most do not heed such advice today, and thus, many operations fail.

Bone Graft Substitutes: Alternatives to Autograft

Allograft

Allograft feebly attempts to replicate the attributes of autograft, particularly in nonweightbearing applications. With interbody weightbearing applications, in which the bone graft is in direct contact with the bone healing forces of compression,[21] allograft performs relatively well. In other words, allograft, if it is to be used as a viable standalone fusion alternative, should optimally be used in situations in which bone fusion-enhancing stresses (i.e., compression) are experienced by the graft.

Allograft performs with diminished efficacy when the graft does not acutely bear load (optimally, axial load). The most common of these is dorsal onlay fusion applications. The most common application for allograft in dorsal non-weightbearing applications is that of a bone fusion mass augmentation technique (particularly in children, in which fusion success is much more likely and autograft donor site options may be limited), in which allograft is used to augment
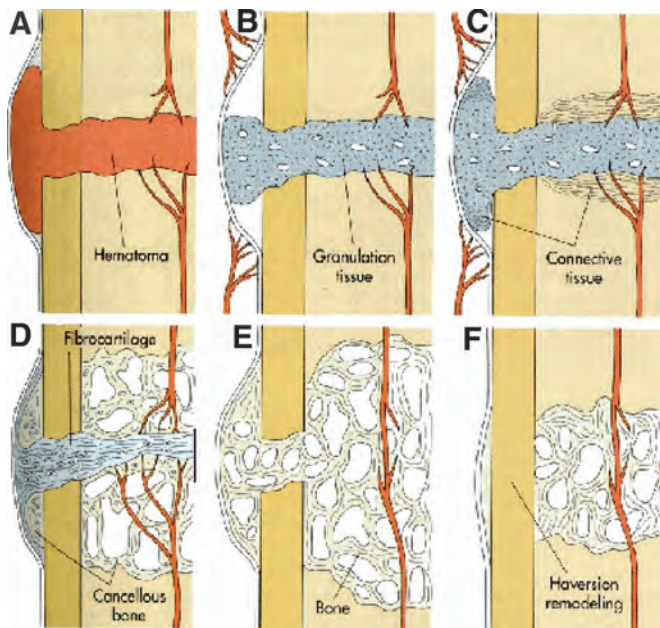
FIGURE 7.1. The phases of bone healing and bone fusion.

FIGURE 7.2. Overcompression can result in fracture (or failure of the graft). Conversely, the shielding of the graft site (stress shielding) can result in failure of fusion (pseudarthrosis), as depicted.

autograft (e.g., when sufficient autograft is unavailable). Of note, allograft performs particularly poorly in osteoporotic bone.

New and more recent applications include the use with autologous stem cells such as found in bone marrow aspirate (BMA). This type of application, whereby a structural component (in this case autograft) is combined with a cellular component, is termed a "composite." Such a composite combines the benefits of the osteogenesis and osteoinduction components of bone fusion with the osteoconduction capacity provided by the structure of the allograft bone matrix.

The Three Components of Bone Healing

With consideration of the aforementioned, it is important to recall the three components of bone healing and bone fusion: osteogenesis, osteoinduction, and osteoconduction. Osteogenesis enhances bone formation or forms bone through cellular (e.g., osteoblastic) activity. It depends on the presence of osteoprogenitor stem cells. Osteoinduction forms or enhances the formation of bone by recruiting and differentiating bone-forming cells through factors that induce undifferentiated tissue to differentiate into bone. Osteoconduction involves the bony apposition of growing bone to the three-dimensional surface of a suitable scaffold that guides growth in three dimensions. Each of these three components plays a vital role in the bone healing and bone fusion process. The incorporation of as many of these components as possible will increase the chance of surgical success.

Allograft provides an osteoconductive scaffold and nothing more. This must be carefully considered in the decision-making process regarding technique selection and clinical outcome optimization.
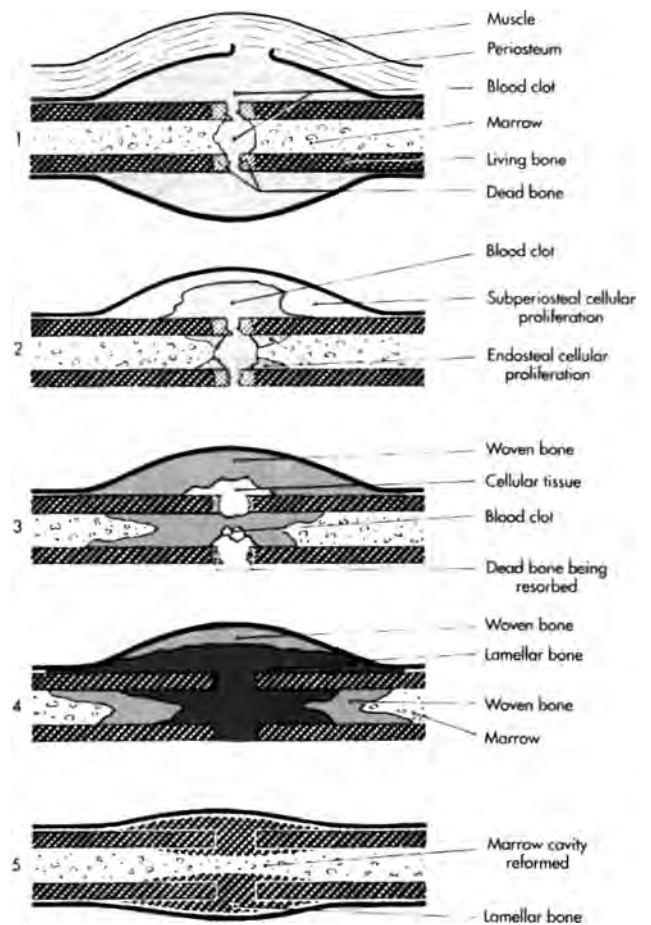

FIGURE 7.3. Cloward recommended that 80% of the end plate be covered by intervening interbody bone graft as illustrated. Such is uncommonly achieved today.

Demineralized Bone Matrix

Demineralized bone matrix (DBM) is derived by removing the mineral component of bone through acid digestion. The DBMs used clinically are combined with a carrier such as glycerol or collagen to facilitate surgical delivery. DBMs, therefore, are theoretically composed of osteoinduction agents. The actual amount of such agents is often disappointingly low.

Xenograft

Bone harvested from animals such as kiel bone, Bio Oss (Geistlich Pharma AG, Wolhusen, Switzerland), and Oswestry bone have been used as a graft alternative in the past. The processing required to reduce immunogenicity unfortunately also removes osteoinductive matrix proteins. Success with this option has been marginal at best.

Interbody Spacers

Interbody spacers and strut grafts perform two functions: 1) induction of bone growth to achieve ultimate bony stability; and 2) the provision of immediate stability and construct integrity. The latter is accomplished by a cortical bone effect, whether through a rigid implant or the use of cortical bone itself (*Fig. 7.4*).

Synthetic Bone Substitutes

Synthetic bone substitutes are osteoconductive. They are not osteoinductive nor are they osteogenic. Such substitutes include hydroxyapatite, calcium sulfate, tricalcium phosphate, and beta-tricalcium phosphate. Each provides a three-dimensional osteoconductive structure, is resorbable, and is also biologically active in the sense that each adapts to the clinical situation by permitting or facilitating remodeling. Each provides, to one degree or another, open and interconnected porosity, a pore structure that wicks blood and other cells, a surface that supports cell attachment and activity, and a chemistry and structure that guide bone regeneration in three-dimensional space; moreover, they are structurally sound in their formed state

and exhibit resorption patterns that are characteristic of the substitute (*Fig. 7.5*). A consideration of such technology warrants careful scrutiny to establish whether the desired structural integrity can be ultimately achieved. Clinical correlates and confirmation of efficacy are somewhat lacking. Clinical success depends significantly on the characteristics of resorption and remodeling associated with the bone substitute used and, of equal importance, on the timing of such. The surgeon who entertains the use of synthetic bone substitutes should be well informed regarding both the quantitative remodeling attributes and the timing.

Bioactive Strategies: Autologous Growth Factors and Stem Cells

Bioactive strategies (Table 1) involve the use of bioactive compounds (osteoinduction) and osteoprogenitor stem cells (osteogenesis). Collectively, they are categorized as either autologous growth factors or stem cells.

Bone Morphogenetic Proteins

Although DBMs are bioactive, they are weak in this regard. Bone morphogenetic proteins (BMPs), on the other hand, are essentially the substances that define the nature of bioactivity as it pertains to bone healing. First accomplished by Marshall Urist, BMPs were initially retrieved from bone.[20] The retrieval rate, however, was unsatisfactory. Therefore, the genetic engineering of BMPs has successfully resulted in the acquisition of adequate and biologically active BMPs to the extent that they can be useful clinically.

Recombinant human proteins such as recombinant human BMP-2 and recombinant human BMP-7 have found clinical application. They provide a potentially significant advantage, but caution must be exercised to avoid possible complications. The lack of long-term experience with BMPs obligates them to a continued and obligatory scrutiny. In addition, they each enhance a limited number of many components of the overall

FIGURE 7.4. The use of a rigid implant, whether a spacer or a cantilever fixation device, in conjunction with autograft or an osteoconductive bone substitute (*A–B*), provides the acute healing phase structural integrity that is necessary for both the maintenance of spinal integrity and for the optimization of the healing process. The resilience and strength of such cortical bone or implant derived acute support are defined from the biomechanical perspective as defined by a load-deformation (stress–strain) analysis by the dotted and hashed shaded areas, respectively (*C*).
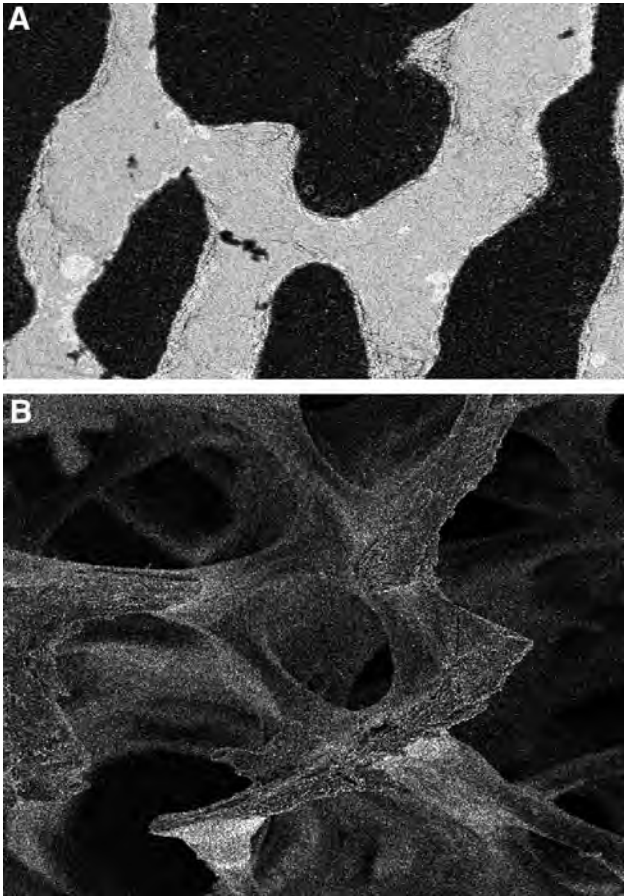
FIGURE 7.5. The infrastructure of ceramic synthetic bone substitutes (*A*) should replicate that of normal bone (*B*).

fusion acquisition pathway. This pathway most likely involves greater than 40 growth factors. Using a single agent may not be sufficient for an effective bony fusion to occur; hence, delivery of a "cocktail" of different proteins may be required or, alternatively, delivery of "upstream" agents that are able to upregulate the expression of the required osteogenic proteins.

Cytokines and Related Agents

Cytokines and other inductive agents (e.g., from the transforming growth factor-beta superfamily, human growth hormone, homologous pituitary homogenate, fibroblast growth fac-

TABLE 7.1. Table of bioactive strategies

1. Bone morphogenetic proteins
2. Recombinant human proteins
3. Cytokines and related agents
4. Bone marrow aspirate and blood spin-down technologies
5. Composite technologies
6. Gene therapy approaches

tor, B-EGF, insulin-like growth factor, Sonic hedgehog, and others) are likely part of the overall scheme of bone fusion. They will see varying extents of use in the future as we approach the use of orchestrated cocktail employment or harnessing of upstream agents.

Bone Marrow Aspirate and Blood Spin-down Technologies

Blood spin-down technologies have been used to extract platelet-derived growth factor and other "humors." Autologous BMA is the technology that, perhaps, at present best combines the simplest and most effective method of deriving both the osteogenic and osteoinductive components of bone fusion. Selective stem cell acquisition has been spearheaded by multiple corporate endeavors. These include osteoblasts, mesenchymal stem cells (Osiris Therapeutics, Baltimore, MD), pluripotent stem cells (Geron, Menlo Park, CA), and others. The source of these is both allogeneic and autogenous.

Composite Technologies

Composites, which are composed of an osteoconductive component such as allograft bone or a ceramic and BMA, theoretically apply the ideal cost-effective solution for bone fusion. This "composite" strategy provides an osteoconductive component in the form of the allograft or ceramic and the osteogenetic and osteoinductive component by virtue of the cells and "humors" provided by the BMA. The ceramic or allograft provides the resorbable osteoconductive scaffold that retains open interconnected porosity. The BMA provides the osteogenic cells and agents (e.g., BMPs). Collectively, they provide the scaffold, the signals, and the cells.

Gene Therapy Approaches

Gene therapy approaches involve the use of both a vector and a transgene or transgene products. Vectors include viral vectors (retrovirus, adenovirus, adenoassociated virus, and so on), nonviral vectors (plasmid, liposomal, peptide, and so on), and others such as polymeric vectors. Transgenes or transgene products include the genes for Homologous Pituitary Homogenate, fibroblast growth factor, latent infection membrane protein-1, and so on. Each strategy is specifically directed at a target.

It is emphasized that cost is a factor with all strategies used with BMPs being both the most effective and the most expensive technology available. With value (value = quality/cost) in mind, expensive technologies such as BMPs should be used selectively and sparingly.

Today's and Tomorrow's Alternatives to Autograft

Today's alternatives to autograft include allograft, synthetic alternatives, autogenous marrow, and blood spin-down products, all with or without carriers. Tomorrow's solutions might include single recombinant growth factors, "cocktails"

of factors that are used in a precisely and meticulously "orchestrated" manner, and gene therapy techniques. There is much to look forward to in this arena. Again, we are to be forewarned that cost may be a limiting factor and in fact a "deal-breaker."

Physiology Enhancement and Augmentation Strategies

Electrophysiological Strategies

Yasuda observed, in the 1950s while studying bone fracture, that compression applied to bone resulted in an electronegative charge, whereas tension produced an electropositive charge.[2] This, from an electrophysiological perspective, legitimized Wolff's observations made more than a half century before. Wolff's law,[21] as the distillation of his observations has been coined, is slightly paraphrased as follows: "Every change in the form and function of a bone, or of function alone, is followed by specific definitive change in its internal architecture and equally definitive secondary changes in its external configuration, in accordance with mathematical laws. . . . Structure is nothing else than the physical expression of function . . . under pathologic conditions the structure and form of the parts change according to the abnormal conditions of force transmission."

Hence, it has been known for over a century that bone will remodel through deposition of new bone in regions where it is compressed and be absorbed in regions where it is placed under tension. Evidence of this process is evidenced by the columnar arrangement of trabeculi in medullary bone (*Fig. 7.6*). This arrangement is not always vertical in nature. The loading pattern is affected by both gravity and by muscle action on the vertebrae. The loading pattern roughly follows the contour (axis) of the spine. Such loading patterns, termed "follower loads," have been replicated in the laboratory setting by Patwardhan et al.[15] It has subsequently been observed that a fractured bone becomes electronegative with a maximum electronegativity observed at the fracture site. Of further and very significant note, it has been shown
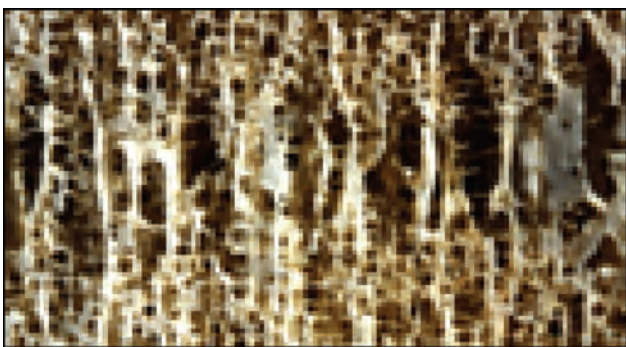

FIGURE 7.6. The columnar arrangement of trabeculi are arranged along the lines of loading (as suggested by Wolff), as depicted. Such lines of loading are not truly vertical, but usually along the contour and axis of the spine.

that osteoblasts are activated by a negative charge. These and more observations have spurned the notion that electrical stimulation could alter, and in fact improve, bone healing.[1,2,7,10,12]

Electrical currents as small as (and optimally in the range of) 5 to 20 microamperes have been shown to stimulate bone growth around the negative electrode (cathode).[2] Two different techniques have been used to stimulate bone growth through electrophysiological means: 1) direct current stimulation (DC stimulation); and 2) pulsed electromagnetic field (PEMF) applications.[2,7,12]

Direct Current Stimulation

Either through the positioning of an electrode (cathode) at the fracture site percutaneously or through an open surgical technique, bone stimulation can ensue as a result. The anode is placed at a distant site, usually under the skin or situated at or on the battery pack in the case of internally implanted devices.[2,6,12] The indications for DC stimulation are broad. Surgical cases in which bony fusion is the desired result theoretically are potential indications for DC stimulation.

Pulsed Electromagnetic Fields

PEMF uses opposing pairs of coils placed on either side of a fracture or a surgical site. This technique is external and does not require surgery. In its purest form, a 110-volt power source is required. This confines the patient for a significant portion of the day. PEMF is indicated for complicated cases, usually involving failure of fusion or delayed unions, infection, osteoporosis, and so on.[2]

Both DC and PEMF techniques use strategies that were initially defined by Wolff and his electrophysiological counterpart 5 decades removed. These techniques are both used to stimulate the bone healing process by creating a bone fusion-enhancing negative charge at the fracture or bone fusion healing site. Applying loads to bone (compression), as defined by Wolff, creates the negative charge that initiates osteoblastic activity, which in turn simulates the healing process. The electrophysiological bone fusion strategies outlined here simply bypass the compression (another "trick" on mother nature) component of the natural bone healing and augmentation process. Their application to the spine surgery arena has been accomplished with limited but somewhat positive results.

Physical/Mechanical Strategies

Dynamic spine stabilization is a term that has been used in a variety of ways. For the purposes of this article, it is defined as "spine stabilization through controlled permissive spine deformation." Such a strategy took roots years ago in orthopedic techniques with such clinical strategies as dynamic hip arthroplasty (*Fig. 7.7*). Bone fragment compression is allowed and, in fact, encouraged by the telescoping nature of the device. What is additionally unique is the fact that the surgeon dictates the trajectory and path along which
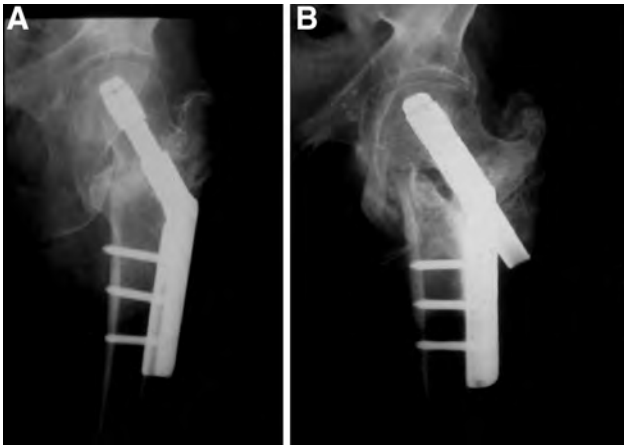
FIGURE 7.7. An immediate postoperative (*A*) and a long-term postoperative healed fusion (*B*) in a case of femoral neck fracture in a patient with osteoporotic bone who was treated with a dynamic hip arthroplasty. The implant allowed the bone (femoral neck) to subside along the trajectory defined by the surgeon through the implant. Note the telescoping of the implant (compare *B* with *A*) after fusion. This telescoping facilitated physiological subsidence, in which the bone (femoral neck and the fracture site) was able to "see" the bone healing-enhancing compression forces associated with the optimization of fusion, as suggested by Wolff.[21]

FIGURE 7.8. The fracture of the implant depicted here permitted further subsidence and the facilitated the transmission of bone healing-enhancing forces. A solid fusion ensued. This is uncommon in cases of implant fracture.

the bony subsidence take place, thus the derivation of the word "controlled" in the phrase "controlled permissive spine deformation." The "permissive" component derived from the fact that deformation (usually in the form of subsidence) is not controlled but is allowed to transpire. The only constraint is the trajectory along which the subsidence transpires. This is "controlled," or dictated, by the surgeon. Thus, the surgeon dictates the trajectory along which the spine will subside with such strategies.[18,19]

Such phenomenon have been observed clinically, albeit rarely, by accident. Occasionally, an implant will fracture and thus allow subsequent subsidence to occur that otherwise would not have occurred. This, in turn, may stimulate fusion (*Fig. 7.8*). The bone fusion-enhancing factors of bone compression and the resulting negative charge created around the bone healing site (that stimulate osteoblastic activity and bone healing[21]) are enhanced. It is in the aforementioned vein that dynamic spine stabilization techniques have been used (*Fig. 7.9*).

Biosensing Strategies

Biosensing strategies have been pursued in the research arena,[4,5,13,16,17] but have found limited application in the clinical arena to date. Such strategies can inform the treating physician of biomechanical parameters that could be altered for the patient's benefit. Intradiscal pressure, pressure at the bone graft–end plate interfaces, implant–bone contact pressure, and implant strain are but a few of the parameters that
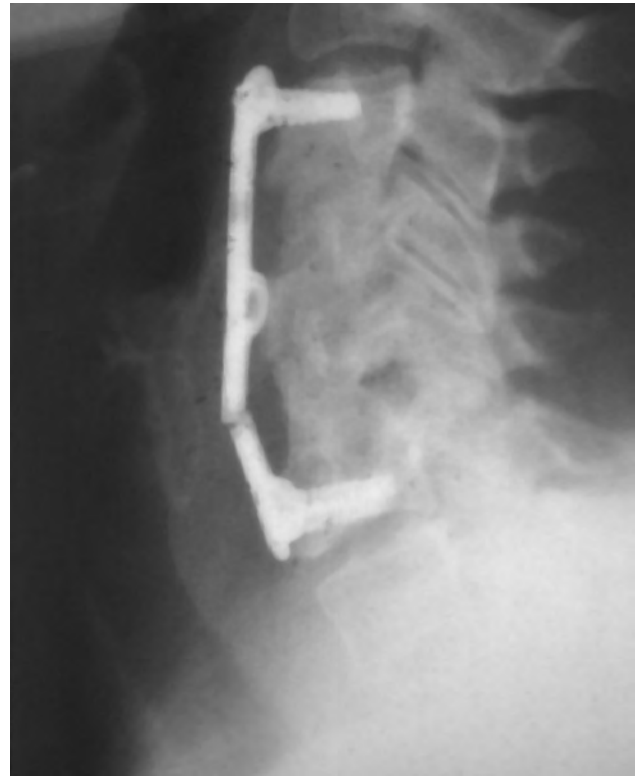
can be assessed with such strategies. They can be used to modify pain by surgically intervening in the case of aberrant intradiscal pressure patterns associated with mechanical back pain. Bone graft–bed interface pressures, implant–bone interface pressures, and implant strain are all indicative of fusion status after surgery. Such may be monitored so that early or more precise intervention may be used in the case of a suboptimal postoperative course.[13] Each of these strategies involves the assessment of bone loading parameters as initially defined by Wolff.[21] The modification of such parameters may lead to improved surgical fusion results through the optimization of the bone healing-enhancing forces (*Fig. 7.10*).

DiAngelo et al.[11] have observed that the load at the bone–bone interface of an anterior cervical fusion varies considerably with flexion and extension of the neck, even with the placement of a "rigid implant." This loading and unloading of the spine is characteristic of the early timeframe after a fusion procedure. As the fusion matures, this loading pattern changes. Pressure within a cage, or at bone–bone or bone–implant interfaces, would initially vary with loading. As fusion transpires and matures, this variation would diminish and stabilize at some point. Similarly, implant strain would diminish as the maturing, healing bone takes over the "responsibility" of load bearing.
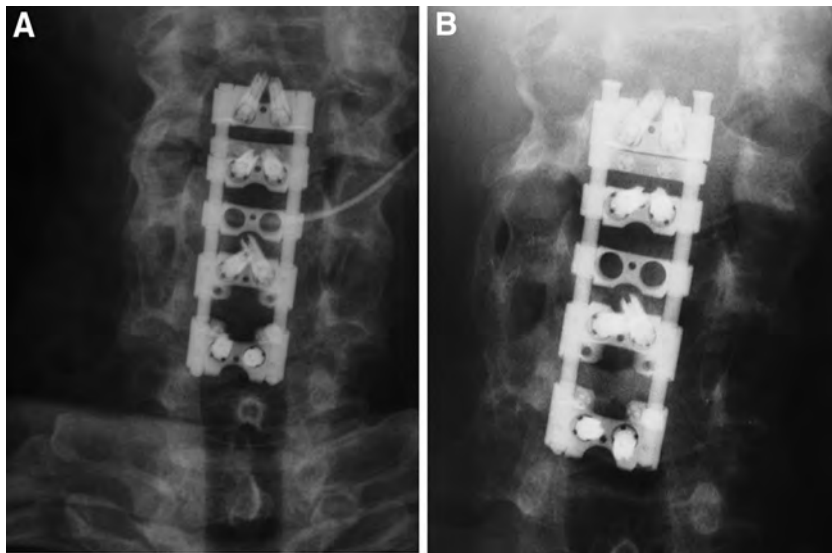
FIGURE 7.9. A dynamic cervical spine fusion implant that subsided further after surgery. Note the initial (*A*) and subsequent (*B*) positions of the telescoping platform in this axially dynamic implant.

Variance from the norm would suggest the development of a pathological situation such as pseudoarthrosis.

The Complexity of Bone Loading

We have much to learn regarding bone physiology and bone healing. The next frontier for research and clinical application in this arena may indeed involve the assessment and optimization of bone loading rates. In vivo loading rates vary significantly in the clinical environment, from 0.001 MPa/sec with slow walking to 0.03 MPa/sec for slow running. As a reference, high-impact trauma associated with fast running occurs in the range of 0.1 MPa/sec. Cortical bone is viscoelastic. Therefore, its behavior is sensitive to not only loads, but also to the rate at which the load is delivered to bone. The shape of the stress/strain curve, indeed, changes with the alteration of loading rate (*Fig. 7.11*).[14] Note that at higher strain rates, bone becomes more brittle, i.e., the slope of the stress/strain curve steepens. This is reflective of an increased stiffness associated with more rapid loading rates.

Although excessive loading rates can result in fracture, physiological loading rates (the lower three curves in *Fig. 7.11*) show an increased ability to absorb energy (area under the curve) as loading rate is increased. This is because the ultimate strain achieved is much greater. At very high loading rates, this relationship is altered, because the curve is shortened along the horizontal axis (the ultimate strain achieved is much less) and the area under the curve (strength) is obligatorily diminished. At very high rates of loading, such as those associated with fracture, the slope of the strain curve rises and falls rapidly. The increased slope is reflective of brittleness with an associated tendency to fracture.

Optimizing Bone Loading and Bone-loading Rates

It is interesting to note that the loading rates associated with activities of daily living are in the range of 0.01 to 0.1 MPa/sec. As pointed out by McElhaney, "this range suggests that bone has adapted to absorb energy from the impact that arises from relatively strenuous activities such as running." The aforementioned loading rates and related factors have wide and significant (but as of yet relatively unexplored) implications regarding strength, bone remodeling, and healing. Implants may be optimized or altered to optimize loads as well as loading rates. In fact, smart implants may be able to do this in real time. Biosensors will most certainly play a role in this arena, because they provide the much-needed insight into such complex, and yet clinically relevant, parameters.

Finally, biosensing technology can be used to optimize the rehabilitation process after trauma or surgery or even optimize the bone environment/milieu in cases of nontraumatic and non-surgically related pathology such as osteoporosis. Excessive or insufficient bone loading and/or loading rates can be normalized if these parameters are known.

SUMMARY AND CONCLUSIONS

The acquisition of bony fusion is a complex task. Attention paid to the details presented here may improve fusion rates and patient outcomes. We have much to learn. We should focus on the details of the present and on the possibilities of the future to guide our surgical decision-making process.

Indeed, "traumatized bone, whether disrupted via an overt act of trauma or via surgical intervention, heals best when bone healing enhancing parameters are optimized." Our problem to date is that we do not precisely know when, and
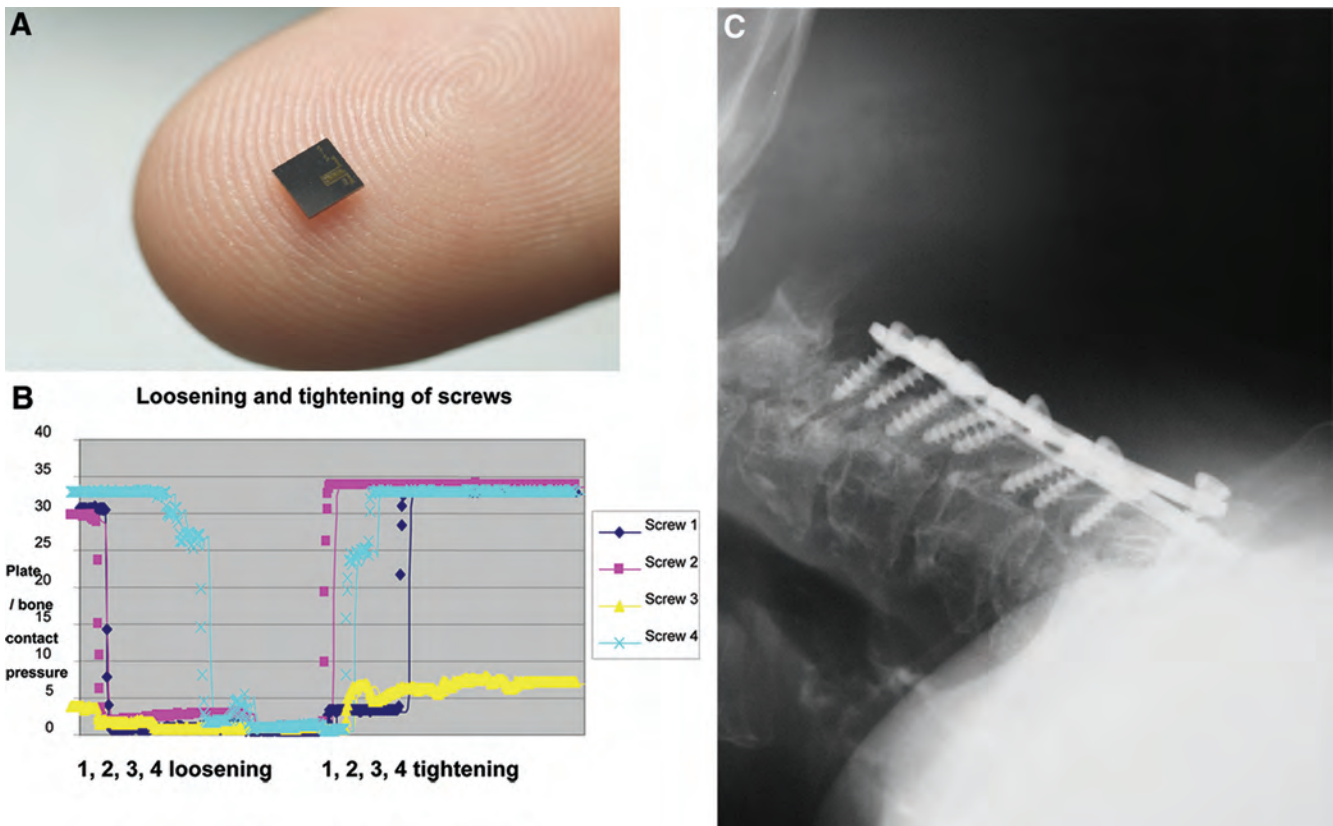
FIGURE 7.10. The observation of bone graft–fusion bed interface pressures (contact pressure) can provide information regarding the progression of fusion or lack thereof. Contact pressure (the pressure between a plate and underlying bone) under a plate using a batteryless telemetric sensor as depicted in A, (courtesy of OrthoMEMS, LLC) can be used to detect bone–implant contact pressure. This pressure remains high and constant as long as the implant is secure. When security is diminished through screw loosening, the contract pressure falls off precipitously as depicted in B. The superimposed radiograph depicts a postoperative spine in which failure occurred through liftoff (*C*). Retightening the screws can re-establish a high contact pressure as depicted on the right side of the graph in B.
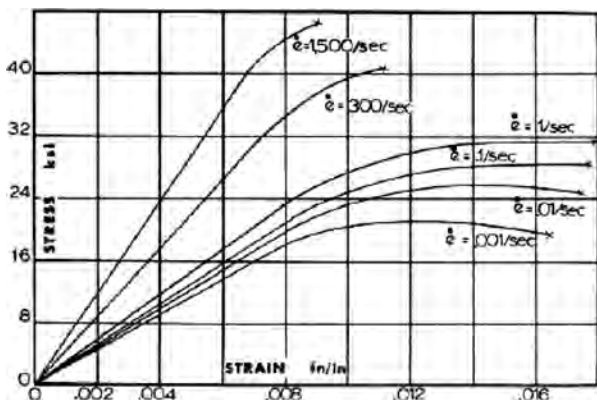

FIGURE 7.11. Strain rate dependence of cortical bone material behavior. Both modulus of elasticity and strength increase for increased strain rates (Used with permission from McElhaney JH. **J Appl Physiol** 21:1231–1236, 1966.).

under what loading conditions, such an optimization process occurs. It is certain that pressure and load affect this process, as suggested by Wolff.[21] This has been portrayed here. The measurement of these parameters in vivo in humans should provide insight into the process of bone healing and ultimately lead to our ability to positively affect the healing of bone and, hence, patient outcomes.

Disclosure

This similarly applies to the publication of information that may be perceived as positive regarding OrthoMEMS products use. Institutional and individual conflicts of interest in research and reporting are disclosed to and reviewed and managed by the clinic's Conflict of Interest Committee and are subject to approval by the Clinic's Institutional Review Board. The clinic has retained independent monitors to review the protocols, subject enrollment, follow-up, and data reporting and analysis of information reported in this publication.

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