Foreign Body Osseointegration

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The door between medicine and dentistry is a closed door. Please, open the door now.

In parallel with the discovery of osseointegration in 1962,[1] the medical profession discovered that peptic ulcers were caused by excess stomach acid and were best treated by antacids, and in severe cases, surgical removal of the stomach. Though bacteria were frequently observed and reported in the literature, the medical profession was absolutely certain bacteria could never survive in the highly acidic environment of the stomach, so bacterial findings were ignored. By 1982, the same year that Donath[2] first observed osseointegration histologically, Marshall and Warren[3] identified *Helicobacter pylori* as the causative agent for peptic ulcer. However, the medical community dismissed, even ridiculed, this conclusion. Donath[4] experienced a similar rejection in 1982 when he surmised that osseointegration was a foreign body reaction. By 1992, *Helicobacter pylori* causation was finally accepted by the medical profession and antibiotic therapy quickly replaced surgery. Interestingly, in 1992, Donath[4] published his seminal results on what he called *foreign body osseointegration*, but the dental profession instead dismissed his histologic findings out of hand, and in fact, remain skeptical to this day. While Marshall and Warren were receiving the Nobel Prize in Medicine in 2005, dental scientists were still busy describing osseointegration as a nearly magical melding of an "inert," nearly autologous object into bone that, when transgressed into the oral cavity, was subject to infection similar to that of the roots of teeth. Today, the dental profession appears absolutely certain of this paradigm of inertness.

Donath studied World War II shrapnel in bone—including one case where it had been lodged in the frontal bone for 45 years—and observed direct bone-to-metal contact. He realized that these lead fragments had been walled off from the body by bone. Much like fibrous encapsulation separates foreign bodies in soft tissue, he concluded that the direct bone-to-metal contact of osseointegration is a host foreign body reaction as expressed by bone.

Today we know much more about immunology, the diverse cell types involved, and why there are different immunologic constituencies around teeth and oral implants. However, the dental profession's response to this difference has been deafening in its silence. When Ericsson et al[5] first observed a greater number of neutrophils around oral implants than around teeth, the response of the dental profession was one of disappointment that the device was somehow inferior to a tooth. Though the mind always seeks to make comparisons, and the implant itself was promoted as a "dental" implant to assign it the same position of importance as a tooth, in reality, implants have never been teeth, and they cannot truly approximate viable dental tissue.

Modern immunology has come to understand osseointegration as an innate host protection mechanism. For example, without walling off lead shrapnel in the frontal bone, an effort by the body to extrude or sequestrate could have extended injury into the brain. So, self-protective osseointegration helps ensure host survival. Furthermore, this mechanism is highly conserved phylogenetically, as it is found in all mammals.

Today, this walling-off mechanism has become known as osteoimmunomodulation, which is continuously active, leading to a constant low-grade inflammation. The governing cell of this process is the proreparative M2 macrophage, which, when combined into a multicellular form, becomes the foreign body giant cell commonly evident upon surfaces of osseointegrated oral implants.

There is much evidence for this. In orthopedics, researchers have used in situ and extractive assay methods to demonstrate immune markers present in assessments of what has been previously only identified as aseptic loosening of hip replacements. PCR, next-generation sequencing methods, and transcriptomics are used to evaluate similar markers, as shown recently by Trindade,[6] who found that commercially pure titanium activated the host immune system. In fact, recent studies of human macrophages indicate that direct interactions between a titanium particle and cell surface are sufficient to activate osteoclastogenic signaling pathways.

Among the numerous different cell types operat-

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ing within the immune system, the osteoblast and the osteoclast are, in fact, counted among immune system functionaries. It is the immune system that decides whether bone formation or bone resorption will dominate in the presence of a foreign element. The immune reaction also protects against pathogen invasion, possibly through cellular action, but further scientific study is required to elucidate the precise manner of this defense.

Two types of immunity are at play in oral implantology, each with a unique cell-line response being activated. Type I inflammation is antigen-driven to fight off oral bacteria, and Type 2 inflammation is the foreign body reaction, which, in bone, is osteoimmunomodulation—in other words, foreign body osseointegration.

The activated immune system protects the host tissue from the device. This suggests that bone-implant modulation will include both anabolic and catabolic events. This will sometimes result in aseptic marginal bone loss of an oral implant. This catabolic equilibration within the milieu of foreign body equilibrium is not a disease process. This also implies, however, that should osteoimmunomodulation become compromised or break down, bacterial invasion will overcome the weakened immune system and secondary infection will occur, leading to additional bone loss and eventual exfoliation of the implant. (For orthopedic devices that may include both metallic and polyethylene debris, an immune system breakdown leads to complete loosening of the orthopedic replacement aseptically without secondary bacterial infection.)

Risk factors for oral implants have been recently published,[7] and there are many more factors than just smoking and history of periodontitis. Several factors are related to operator error, suggesting a lack of surgical or prosthetic expertise. For example, when an implant is placed improperly—for example, not deep enough, thereby leaving the rough surface exposed to the mouth—complication is assured. It is therefore important to state that properly trained and executed implant placement and restoration is required to assure osseointegration stability over time. This is exemplified by long-term differences observed in bone loss or implant loss from different operators within the same clinic.

What causes the host immune system to surrender is a fascinating subject that demands much more investigation, as various factors may combine to provoke immune compromise, not the least of which is genetic predisposition.

Bone loss around oral implants, like that found in orthopedic implants, is often aseptic—a result of perturbation within the foreign body equilibrium. Therefore, bone loss of previously existing osseointegration is a foreign body reaction and is the primary cause of bone loss in well-placed titanium oral implants.

This change in thinking also leads to a new interpretation of early treatment radiographic findings: it is important to distinguish between decreased density of bone from actual loss of osseointegration contact. This difference is impossible to delineate on standard radiographs.

This is important because reduced bone density is reversible since osseointegration is still intact. An example of this can be observed in early postsurgery radiographs, and it is commonly interpreted as having reduced bone levels. But these findings are changes in bone mass only and are caused by postsurgical inflammation. After 1 year, peri-implant bone is sometimes reported as having grown ("bone gain"), when in actuality there is simply an increase in bone density. This concept is further evidenced by the negative correlation between an increasing cumulative marginal bone loss and a decreasing risk of implant failures over time, indicating that peri-implant marginal bone loss does not necessarily represent a condition of disease.

In the field of biomaterials, an endosseous implant is osteoimmunomodulatory and not bioinert. This understanding has led to the development of a new field in medicine and dentistry, termed *osteoimmunology*. This discipline has led to improved understanding for why there is sustained inflammation around oral and orthopedic implant devices, and that though such inflammation might be modulated, it cannot be avoided for the entire lifetime of the implant. This ever-present, baseline inflammation should therefore not be thought of as a disease process, but a host tolerance and adaptation process.

The osteoimmunology discipline also helps to address inflammation-susceptible patients who can have a correlation between periodontitis with increased risk for cardiovascular disease and early mortality.

Another interesting nonlinear risk pattern is found for partially edentulous patients in which younger and older patients present with a lower risk of failure than middle-aged patients. This result suggests that a higher proportion of inflammation-susceptible patients are present in middle age, which correlates with orthopedic observations of patients provided with hip and knee implants.

The thinking that bone loss around a foreign body (eg, an implant) is entirely of bacterial origin is a Kochian conclusion that presumes that there can be no other way to induce loss of hard tissue structure than by a pathogen. But how, then, does bone maintain itself? This is a different question, and it has little to do with bacteria.

If you look diligently, you will discover evidence for what you are looking for, which is to say, you will find your confirmational bias. If, by chance, you observe

what you are not looking for, you then stumble upon a potential discovery. This occurred when struggling to determine the best material to place onto the sinus floor for developing bone. One day, a novel idea arose that bone graft substitutes, even autogenous bone graft material, interfere with bone formation, and they needed to be replaced in order to work properly.

The thought was, "Why not proceed without graft material at all and see what happens?" So, a lateral window was made, the sinus membrane was elevated, three implants were placed to hold up the membrane, and polytetrafluoroethylene was placed over the antrostomy site. A 4-month wait to see if bone formed confirmed that, of course, it did. Once this graftless procedure demonstrated bone growth, thinking changed from a search to find the perfect grafting material to trying to take advantage of this "perfect" regenerative environment. This change in thinking helped lead to the much less invasive procedures performed today.

Likewise, placement of implants into bone has focused on the biomaterial as if the material is what matters most. Hence, we have forgotten what we once knew: that matter is foreign to bone, and it is the bone's response—the clash of self vs not-self—that is transpiring. Once this fact is truly grasped, there is a profound change in thinking that may lead to new discoveries in osseointegration science and advances we still have not imagined.

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