"Open Access" to Scientific Literature

There are always new ideas in the publishing world to try to bring information to a broader audience in an affordable way. Certainly the advent of the Internet has helped, because anyone with Internet access can now perform Medline searches on virtually any medical topic. These searches generally reveal pertinent references, and most of the references that come from peer-reviewed journals have abstracts that allow the reader a glimpse at the author's interpretation of the pertinent material from that article. In addition, readers can often purchase the individual article through the publisher.

The availability of information through these means is a definite improvement from the days when individuals were forced to maintain vast stockpiles of back issues of their favorite journals. Even if the journal was available, retrieval of specific articles was dependent upon the reader's access to and understanding of indexing systems such as Index Medicus. Readers today have the additional benefit of electronic subscriptions to printed journals. Combining the ability to search the expanses of medical and dental literature with the ability to access back issues of journals to which the reader subscribes results in a valuable set of informational tools.

One factor that remains to be considered is the cost of subscriptions. Medical libraries find themselves faced with increasing subscription costs, while budgets rarely keep pace. A solution that has been proposed to address the condition of rising costs and dwindling budgets is described as "open access" (OA). In an OA system the scientific literature is made available to any reader free of charge while the literature is maintained by the publisher. Although this sounds like a great idea on the surface, this business model has no obvious revenue stream to support the expenses of publication and literature maintenance.

This issue of revenue is addressed in most OA proposals by having the author pay for manuscript management through the peer review system. The figure that is mentioned most often is US $3,000 per manuscript, and the assumption is that this charge will be made for every submitted manuscript. Since most peer-reviewed journals reject more articles than they accept, an "author pays" system could result in major up-front costs to authors who may never see their material published. It is not difficult to imagine a reduction in the number of submitted manuscripts because of the cost, and with a reduction in submissions, the quality of publications could suffer. Should submissions decrease and revenues fall, the survival of the OA publishers could be threatened, and retrieval of previously published articles from an exclusively OA publisher might be impossible. In that situation, published material could be lost forever.

The assumption is that the OA approach maintains the current method of peer review. Unfortunately, this may not be the case for all OA articles, and distinguishing peer-reviewed articles from non–peer-reviewed articles might be impossible. If peer review were eliminated, the system would change from open access to open forum, and the reader would be unable to determine which authors spoke from a platform of investigation and which described opinion only. Rather than looking to the literature for answers, readers would find themselves mired in a vast Internet wasteland unable to differentiate between truth and fiction.

Would OA create a better environment for distribution of scientific knowledge? At this point the question may be moot as dental, oral, and maxillofacial journals have yet to embrace this system, but the discussion rages on. There are legislative actions in the United States and Europe that would mandate the free distribution of any governmentally funded research. Given the paucity of governmentally funded research in the implant field, such a mandate would have a limited impact on publications in this area.

Today *The International Journal of Oral & Maxillofacial Implants* (JOMI) provides its readers a printed version of the journal as well as electronic access to past issues through the Quintessence web page. Subscribers must register for access, but the process is relatively painless. This system, however, is not OA. Manuscripts are submitted to the journal without charge to the authors, and each manuscript goes through an editorial and peer review process. Most articles published in JOMI have been reviewed by 1 or 2 editors and 2 reviewers. At its best, peer review performed in this manner prevents publication of flawed research, but there can be situations where differences of opinion exist, and in those situations the readers often benefit from open debate of the described differences. The system is not flawless, but

the reader can rest assured with some level of comfort that the material published in this journal has been scrutinized by many eyes and minds.

For the field of oral and maxillofacial implants, the need to maintain current knowledge is obvious. The value to readers of journals like JOMI is established by providing a product, the journal, that presents solid peer-reviewed material at a reasonable cost. When this information comes from a publisher that is likely to survive in the volatile economic landscape of scientific publishing, the reader may take comfort in the knowledge that material will be retrievable for years to come.

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COMMENTARY ON:

Bone Regeneration in Standardized Bone Defects with Autografts or Bone Substitutes in Combination with Platelet Concentrate: A Histologic and Histomorphometric Study in the Mandibles of Minipigs

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As an educator and Director of Research in an oral and maxillofacial surgery program with considerable experience in growth factor research, I read the article "Bone regeneration in standardized bone defects with auto grafts or bone substitutes in combination with platelet concentrate: A histologic and histomorphometric study in the mandibles of minipigs" by S.S. Jensen et al (Int J Oral Maxillofac Implants 2005;20:703–712) with concern for the journal reader as well as concern for the credibility of growth factors. It is apparent that the authors made several fundamental oversights or errors in their study that determined their results rather than a real test of the potential for growth factors to enhance healing.

Their first glaring error is their selection of a research model. The minipig has a different blood viscosity and therefore a different centrifugation requirement than that of humans. The authors state that they used the platelet concentration collection system (PCCS; 3i Implant Innovations, Palm Beach Gardens, FL) to develop their platelet concentrate (PC). This system is an excellent device for concentrating platelets from human blood. However, it is only capable of separating platelets and then concentrating them based on the whole blood viscosity and red blood cell density of human blood. I know this because I was a consultant in developing this device and have used it extensively myself. It therefore is not surprising that the authors stated in their results "no correlation was found between platelet count in whole blood and platelet count in PC." The authors did not need to conduct an animal study to discover this; they only needed to read the specifications of the PCCS device and understand the difference between minipig blood and human blood. Their second error was confusing a "standard bone defect" with a "critical size defect." A critical-size defect is mandatory in bone graft and/or growth factor research. A critical-size defect is essentially one that does not regenerate bone on its own by native growth factors and spontaneous bone regeneration. In fact, the authors' surgical defects of only 5 mm × 9 mm in an animal with considerable self-healing potential would be expected to heal this defect without any graft material or growth factor additions. The authors also failed to use a standard "sham surgery control" for comparison, making their results even more dubious.

However, the most serious oversight is not clotting the platelet concentrate. The authors used only calcium chloride to activate the anticoagulated platelet concentrate. This by itself does not initiate normal clotting and does not initiate the release of the growth factors from the platelets in any vertebrate. The alpha granules in platelets contain incomplete protein growth factors. They are only stimulated to migrate to the platelet cell membrane surface and fuse to it by the cell membrane chemical and conforma-

tional change initiated by the coagulation cascade. At the cell membrane these protein growth factors are completed to a bioactive state by the addition of carbohydrate side chains and histones.[1] Any platelet concentrate that is not specifically activated by either concentrated human or bovine thrombin or several available alternatives will not release their growth factors or release incomplete bio-inactive growth factors.[2] This is why the authors noted "no correlation between the platelet count of the PC and the concentration of PDGF-ab and TGFb" when several authors, including the Center for Blood Research in Boston, Massachusetts, have found a linear correlation.[3]

I am personally sorry to be critical of well-intended authors. However, I am equally outraged to see a study actually published that did not meet minimum research methodology standards. It seems that the authors took the easy road here by merely drilling a group of holes in the jaws of minipigs and stuffing various grafting materials into them including a platelet concentrate without setting up an appropriate research design and without understanding the basic biology of platelets. My personal concern is that growth factors availability to clinicians has finally become a reality and has the ability to benefit a vast number of our patients. Currently recombinant human bone morphogenetic protein (rhBMP-2; Infuse Medtronic Sofamor Danek, Memphis, TN), recombinant human platelet-derived growth factor bb (rhPDGFbb GEM 21 Biomimetic Pharmaceuticals, Franklin, TN), platelet-rich plasma (7 growth factors, PDGF aa, PDGF bb, PDGFab, TGFb1, TDGFb2, VEGF, and EGF, as well as 3 cell adhesion molecules, fibronectin, fibrin, and vitronectin; Harvest Technologies, Plymouth, MA, and 3i Implant Innovations) and recombinant human parathyroid hormone (rhPTH-Forteo; Eli Lilly, Indianapolis, IN) are available. It is concerning and worrisome to see naïve and improperly conducted studies undermine their credibility, confuse journal readers, and limit the benefit they can provide. It is the charge to all researchers to understand the technology behind the devices that they test and the mechanism of the biologic process to be studied as well as to develop a study design with appropriate controls. It then becomes the charge to journal readers that they read the methods and material section as carefully as they read the results and conclusions. If this is the era of "evidence-based medicine" we must be sure the evidence is correct.

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AUTHORS' RESPONSE

The increased use of platelet concentrates over the last decade has caused significant debate in the oral and maxillofacial literature. We are in the era of evidence-based medicine, as Prof Marx states, and we therefore welcome the possibility to discuss the 4 controversies raised by Prof Marx:

1. The suitability of platelet collection system for the planned animal model
2. The fact that the chosen bone defect morphology has to be relevant for the phenomenon's to be studied
3. The inclusion of a negative control defect (sham surgery defect) to validate the results
4. The proper way to activate the platelet concentrate

All 4 issues are essential within this field of research and were of course individually thoroughly discussed during the planning phase of the present study:

Re *(1),* the minipig was chosen for the present study because of its close similarity to humans with respect to bone metabolism and clotting parameters.[1] To make sure that we were actually able to produce platelet concentrate from minipig blood, whole blood from two pilot minipigs was centrifuged according to the platelet concentration collection system (PCCS; 3i Implant Innovations, Palm Beach Gardens, FL) protocol, whereby a platelet concentrate was obtained that fulfilled the criteria for platelet-rich plasma put up by Prof Marx himself.[2,3] In addition, a morphological analysis of the platelets was conducted in association with the hematological laboratory (University Hospital, Inselspital, Bern, Switzerland) to make sure that they were morphologically comparable to human platelets. Later studies in minipigs have also confirmed that platelets can be separated and concentrated by both blood banks and the PCCS method,[4,5] and that the biological activity of these harvested platelets can be preserved.[5] Last but not least, it has to be mentioned that the study was conducted in close collaboration with the 3i company, the producer of the PCCS, which never indicated a concern about the suitability of the chosen model.

Re *(2),* Prof Marx claims that "standard bone defect" is confused with "critical size defect" (CSD). It should be perfectly clear from the text (p. 710, l. 4) that the prepared defects deliberately were intended to be *non*-CSDs. We have to disagree that "a critical size defect is mandatory in bone graft and/or growth factor research." It most certainly depends on the aim of the study. The aim of the present study was not to evaluate *if* healing could take place by adding platelet concentrate, but *how* healing took place by adding platelet concentrate. If platelet concentrate in the present study would have had a consistent accelerating effect on the proliferation of new vessels and of osteogenic cells, the bone healing in these defects would have been expected to be faster than in the defects where no platelet concentrate was added. An ingrowing vessel and an osteoblast starting to form bone are both probably completely unaware whether they are situated in a CSD or a non-CSD.

Re *(3),* inclusion of a negative control defect or a "sham surgery control" is mandatory in the evaluation of augmentation of a CSD. We know from previous studies using the same defect location that these defects ultimately will heal without any grafting material.[6] But again, the purpose of the study was to conduct a comparative investigation of a potential positive impact of autologous growth factors on early bone healing events. Inclusion of an additional negative control defect would have only increased the amount of experimental animals needed, without contributing anything to answering the raised questions of interest.

Re *(4),* in all defects, the grafting material was mixed with autologous whole blood. By adding calcium chloride to the mixture of platelet concentrate/grafting material and placing it in a fresh osseous wound, all the factors that are necessary for degranulation of the α-granules and activation of the growth factors in the platelets are present: calcium, thrombin, collagen, and other subendothelial factors. Exactly the same factors are present at bone fracture sites, where they are known to play important roles in bone fracture repair.[7] In addition, in vitro studies have shown a stimulatory effect on human osteoblasts of platelet concentrate activated with calcium chloride only.[8,9] Therefore, several authors have found it unnecessary to add (bovine) thrombin for the activation of PRP.[10–12]

Today, a vast body of literature exists dealing with the addition of platelet concentrates in bone regeneration procedures. The promising results published by Prof Marx caused significant investments in blood centrifuges by thousands of colleagues around the world. Although nobody is questioning the potential of growth factors to enhance bone healing,[13] today it would be lenient handling of very divergent scientific data to claim that the use of platelet concentrate in reconstructive osseous surgery is based on sound scientific evidence. Divergent results from clinical and experimental studies should only encourage additional research into the mechanisms of action, with the ultimate goal of identifying a way to obtain predictable results with platelet concentrate, and not only in the hands of Prof Marx. Our study does not reduce the "credibility of growth factors" and does not intend to disqualify platelet concentrate for future use in bone regeneration procedures. We do, however, have serious concerns about an uncritical use of a therapeutical concept where neither the content of the active substance nor the treatment outcome can be predicted with the current knowledge.

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