The controversy concerning placement of dental implants into bone that has been irradiated has a long history. Much work has been done experimentally and clinically to elucidate the mechanism of radiation injury to bone. Understanding the principles believed to result in radiation injury is important, but the clinician, even armed with the most relevant and up to date knowledge, must weigh hyperbaric oxygen therapy (HBO) versus alternatives. When the alternative is nothing, the decision becomes more difficult. There is considerable evidence that radiation injury damages the vasculature, the cells, enhances susceptibility to infection, and creates a wound healing problem. First, any discussion of this problem must separate implant healing in previously radiated bone from radiation of bone containing implants and bone graft healing after transplantation. This article limits itself to questions related to placement of dental implants into previously irradiated bone. Major questions exist regarding several critical issues. The amount of radiation is critical with more than 5,000 cGy, which is often cited as a level for concern. The location of implant placement is critical because common understanding is that the mandible is more susceptible to injury than the maxilla and the symphysis area most resistant. Even this dictum deserves discussion given more recent information. Was the bone to receive implants in the field of radiation? Of great interest and importance, based on existing clinical studies, is the question of whether or not radiation injury is progressive or if it reaches a stable end point, thus enabling placement at a safe time. Thus, the time from radiation therapy to implant placement is critical to success. Time has 2 dimensions regarding clinical judgment. The first, should implants be placed close to the time of completion of radiation therapy for best results, or should one wait a year to place implants? The biologic basis for each has some support. In the former, evidence exists in soft and hard tissue that the acute changes of radiation injury are less detrimental than the chronic changes. The argument for delayed placement is based on the evidence that after a critical length of time, the bone and soft tissue changes following radiation therapy stabilize.

**Practical Science and Clinical Evidence**

The clinician can judge the presumed degree of radiation injury often by observation of clinical signs such as loss of facial hair in males or xerostomia. This, combined with the total dose of radiation and examination of the portals used, is often sufficient to permit good clinical judgment to choose implant placement without adjunctive treatment. The clinician should also consider the added time and expense of HBO and the complications and contraindications to HBO therapy. Importantly, there have been only rare reported cases of osteoradionecrosis (ORN) of the mandible after implant placement. In the context of overall incidence of ORN, which is reported as 3% to 22% in clinical studies, this low number is telling because it means that either great clinical judgment exists in placement, the problem is exaggerated, or reporting of long term failures is inadequate. For completeness, the contraindications to HBO treatment include: optic neuritis, pulmonary disease because of risk of tension pneumothorax, claustrophobia, and seizure disorders. Complications include eustachian tube dysfunction, seizures, decompression sickness, and tympanic membrane rupture. None of these represent an absolute contraindication if the case for HBO treatment is strong. This article will present the evidence, which is weak at best. A recent systematic review on this subject points out the problems in that no randomized clinical trials exist and even hand searching failed to disclose the article by Granström.
et al. In a comprehensive review of the problem in 2000, Granström stated that there is "... no general agreement that osseointegrated implants should fail to a higher degree due to radiation." Esposito et al concluded in another meta analysis that radiation itself is not a contraindication to implant installation. 

The clinician presented with the dilemma of placement of dental implants into a radiated patient should understand the current state of knowledge regarding bone formation and the potential injury that radiation can cause. Historically, injury was thought to involve both the vasculature and the cells present in the bone. The classic work of Marx and Johnson showed that ORN was not an infection but a wound-healing problem. The question today is, does that dictum hold for the radiation response and complications in hard and soft tissue? The difference between radiation response and complications in hard and soft tissue is a subject worth returning to. This may be because of the same mechanisms found in hypoxia of soft tissues. The mechanism of response in bone is not fully understood. HIF-1 has been detected in bone, but mounting evidence suggests that there is crosstalk between osteoblasts and blood vessels and that bone morphogenetic protein (BMP) may serve as an intermediary in bone rather than HIF-1. Wurzler et al studied rat calvarial defects and showed that BMP-2 could negate the damaging effects of radiation on healing. Lorente et al studied radiation injury in rats using a critical size defect. Results suggested that the radiation of the bone source of BMP rather than the mandibular defect was more important to healing, and also suggested that wounding closer to the time of completion of the radiation treatment was beneficial. This was the first instance that the time of surgery was considered; it is still an important thought today for the clinician. Should one wait a year to place implants or should implants be placed closer to the time of radiation?

Putting science into practice isn’t easy and that is the case with our dilemma. Much of the experimental work used single radiation doses rather than the fractionated methods used clinically. Can the rabbit, dog, or rat be compared with the human response? We need to examine the clinical literature for further evidence that HBO is not needed for treatment of most radiated patients requiring dental implant placement.

In 1997, the Journal of Oral and Maxillofacial Surgery highlighted a similar controversy. Keller and Larsen took opposing views. Keller examined 14 studies of implants in radiated tissue without HBO, which had remarkable success. He highlighted the paucity of reports of problems with such cases, especially in the radiated mandible, and focused attention on the success noted in the symphyseal area. Larsen based his use of an HBO protocol on animal studies and clinical use in ORN. The protocol was based on 28 mandibular implants placed in 5 patients. Granström and Larsen took opposing views. Keller examined 14 studies of implants in radiated tissue without HBO, which had remarkable success. He highlighted the paucity of reports of problems with such cases, especially in the radiated mandible, and focused attention on the success noted in the symphyseal area. Larsen based his use of an HBO protocol on animal studies and clinical use in ORN. The protocol was based on 28 mandibular implants placed in 5 patients. Granström et al reported on a 15-year follow-up of implants and included a case-controlled study for 1 group of these. The case-controlled group supported the use of HBO for implant placement, but some concerns should be noted. Implants reported on included 47 orbital, 16 temporal, 9 nasal, 8 maxillary, and 3 mandibular implants. Changes in radiation methods and implant surgical techniques were not accounted for, although the authors raised the question of whether a reduced time interval between radiation treatment and implant surgery improved outcome.

Present and Future Considerations

Granström’s 2000 review highlights some important findings that offer opportunity for further discussion. Analyses of multicenter data for mandibular, grafted mandibular, maxillary, orbital, and temporal bone implants are compared. A major finding was increased failure after 5 years, which is markedly diminished by the administration of HBO. Thus, recommendation for HBO with implant placement seems straightforward and acceptable regarding long-term survival. However, careful examination of the data suggests that factors such as soft tissue complications versus bony complications, cutaneous versus mucosa
locations of implants, and certainly the dose of radiation received deserve consideration. Ekert et al\textsuperscript{19} noted that the most significant problem for irradiated implant patients was related to soft tissue. August et al\textsuperscript{20} made similar observations. Interestingly, they reported on fixed mandibular implants, which was the successor to the staple denture. In this situation, both cutaneous and mucosal tissues are violated and the symphyses was radiated in many of their patients. Thus, both the questions of site sparing of the symphysis and the issue of skin versus mucosa may be examined. Unfortunately, most of the patients received microvascular grafts and thus comparison is impossible. Can the soft tissue reaction to irradiation at cutaneous sites like the orbit and temporal bone be compared to the tissue reaction of mucosal sites? A number of studies suggest that HBO makes implant survival more predictable, especially in the cutaneous sites and maxilla. But the question remains: is HBO necessary? It is somewhat paradoxical that the maxilla, usually promoted as more vascular than the mandible and therefore less prone to ORN, should be more susceptible to radiation injury affecting implant survival. Might these results be based on other factors like the quality of the bone itself, the width and height of the ridge, and so on?

The work of Marx and Johnson\textsuperscript{5} was transforming, but in the light of current biological knowledge even this should be re-examined. If HIF-1, BMP, and VEGF are important to the early healing response needed for osseointegration in hypoxic conditions, what role do they play in implant failure after several years? Animal studies showed that neoangiogenesis of the overlying soft tissue is reflected in a similar, although lesser, development in the underlying bone.\textsuperscript{21} In fact, improvement in the soft tissue and periosteal response, both by qualitative histology and quantitative angiogenesis assessment, were better than in the mandibular cancellous marrow space. Noteworthy in this rabbit study was administration of a radiation dose, which was equivalent to 60 Gy fractioned into 30 doses of 2 Gy, 5 days per week, thus mimicking clinical conditions. The actual experimental observation with HBO administration began 6 months after irradiation. In 1994, Granström et al\textsuperscript{22} commented on the potential beneficial effect of implant placement closer to the time of radiation completion; they also noted differences in the skin versus the mucosal response. All of these implants were in cutaneous sites. Unfortunately, the 1 study of transmucosal staple implants with radiation therapy that exists\textsuperscript{20} does not permit comparison of cutaneous and mucosal responses in 1 system. More recently, Abu-Serriah et al\textsuperscript{25} reported on the problems of extraoral endosseous craniofacial implants and radiotherapy.

It is also worthwhile to consider bone injury after radiation treatment. Opposing hypotheses can be offered. First, surgery early after radiation completion avoids the chronic changes that impede healing and second, delayed implant placement offers a bone environment stable for healing. No answer to this dilemma exists, but data that offer promise do exist. Wurzler et al\textsuperscript{15} studied healing calvaria defects in rats. It is important for any clinician to understand the difference between nonhealing, so-called critical size defects, and healing defects. Critical size defects do not heal on their own and thus the effects of healing accelerants are well studied in this model. Healing defects, like the ones studied by Wurzler et al,\textsuperscript{15} show the negative effects of radiation primarily. This study suggested that radiation-induced impairment of calvaria repair can be overcome by recombinant BMP-2. This in itself is interesting in terms of potential “smart” implants that might obviate the need for any consideration of HBO therapy, but the study also showed that the BMP effect and natural defect healing was greater when wounding was performed 7 days postirradiation versus 2 days postirradiation. The authors raised the possibility of enhanced cell recruitment at the later time. So timing of the procedure again appears to be important.

Last but not least, the apparent burst in new knowledge regarding oxygen sensing in tissues, which might lead to a marker useful for clinical appraisal of bone status before surgery, may lead to better radiation treatment of tumors. There is increasing evidence that radiation activates HIF-1 to regulate vascular radiosensitivity in tumors.\textsuperscript{24} We cannot separate the disease from the complication. So it is possible that tumors respond to radiation by secreting cytokines capable of inhibiting apoptosis or cell death in endothelial cells, thus decreasing treatment response by minimizing vascular damage. Inhibiting postradiation HIF-1 activation may enhance tumor radiosensitivity as a result of enhanced vascular destruction. Further work must differentiate tumor response from bone response.

In summary, there is only scant evidence that HBO treatment is necessary for the majority of patients receiving intraoral dental implants. Evidence supports enhanced long-term survival in all sites, but the clinician must weigh the availability, complications, and added cost in the decision-making process. The lack of randomized controlled trials in this important area leaves us with a need to rely on existing data and information to guide clinical judgment. Clinical appraisal with radiation dose less than 50 cGy, presence of facial hair, and lack of xerostomia remain critical issues. Despite data that shows enhanced transmucosal oxygen saturation with HBO, the longevity of the effect remains a question.\textsuperscript{25} Bone biology research
and development of new methods for the determination of bone quality and healing capacity will be the long-term solution to the problem at hand. Until then, HBO remains a questionable adjunctive treatment for most postirradiation patients in need of dental implants.

References