

Osteoradionecrosis: A New Concept of Its Pathophysiology

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The classic sequence in the pathogenesis of osteoradionecrosis of the jaws has been accepted as radiation, trauma, and infection. This paper challenges this sequence and offers a new one more accurately describing the biochemical and cellular pathology. The clinical data are based on 26 consecutive cases of osteoradionecrosis from which 12 en bloc resection specimens were cultured and stained for microorganisms. Review of the histories and treatments, as well as the microbial assays, indicates that microorganisms play only a contaminant role in osteoradionecrosis and that trauma is only one mechanism of tissue breakdown leading to the condition. The sequence suggested by this study is as follows: (1) radiation, (2) hypoxic-hypocellular-hypovascular tissue, (3) tissue breakdown, and (4) chronic non-healing wound.

Osteoradionecrosis is neither a new disease nor a disease limited to the jaws. Bone necrosis secondary to radiation damage was reported as early as 1926^{1,2} and has occurred in other anatomic sites, such as the pelvis, sternum, clavicle, and femoral head.^{3,4} Reports of osteoradionecrosis of the jaws became frequent in the 1950s as irradiation of oral malignancies became a well-established practice.⁵ Since then, numerous publications have dealt with the identification of nonhealing exposed bone associated with a variable incidence of pain, orocutaneous fistulas, pathologic fractures, etc.⁵⁻⁷ Most authors have attributed osteoradionecrosis to trauma of devitalized bone and microbiologic sepsis.^{8,9} In fact, the following quotation summarizes the prevailing concept of osteoradionecrosis in our profession: "These progressive changes result in a gradual devitalization of bone. The introduction of sepsis into the essentially avascular bone produces a virulent form of osteomyelitis with extensive tissue destruction."⁹

Another author has defined osteoradionecrosis as "an osteomyelitis secondary to irradiation."¹⁰ However, published reports, as well as the experi-

ence of most practitioners, have documented a wide spectrum of presentation, from a local nonhealing socket, to areas with several centimeters of exposed bone, to sometimes exposure of an entire mandible with both mucosal and cutaneous breakdown.⁶ Suppuration and many of the cardinal signs of inflammation are an uncommon finding in many cases. Neither "extensive tissue destruction" nor obvious "virulent osteomyelitis" are seen as a consistent part of the clinical picture.

In an excellent monograph on infectious diseases of the jaws published in 1970, Meyer⁸ defined the classic triad of osteoradionecrosis as radiation, trauma, and infection. He described the role of trauma to be a portal of entry for oral bacterial flora into the underlying bone. He stated that the most common sources of trauma were tooth removal and sharp bony ridges after inadequate alveolectomies. He also went on to state that "infection apparently makes relatively rapid progress in the irradiated bone, which has lost its resistance to bacteria" and that "soon radiation osteomyelitis sets in and spreads throughout the bone, which cannot wall off the infection." He did not, however, demonstrate through cultures or tissue sections such a spread of osteomyelitis and microorganisms throughout the bone; neither did he demonstrate septic destruction in such avascular tissue, which cannot mount an inflammatory response or wall off microorganisms. The common observation of persistent, chronically nonhealing irradiated bone that neither produces extensive suppuration nor consistently breaks down

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in a septic course suggests that microorganisms may not play such a pivotal role in the pathophysiology of osteoradionecrosis. Yet, the terms osteoradionecrosis and osteomyelitis are often used synonymously when referring to irradiated patients, and the term radio-osteomyelitis is still seen in many publications today.^{9,11}

The role of trauma as the absolute initiating factor in osteoradionecrosis has also been recently challenged. Daly and Drane¹² have reported a 39% incidence of osteoradionecrosis unassociated with any specific trauma. Bedwinek et al¹³ have also identified "spontaneous osteoradionecrosis" and related it to higher radiation doses. Clinical experience suggests that osteoradionecrosis is related to a basic tissue damage effect more than to subsequent trauma or invasion by microorganisms. To test this hypothesis, 26 consecutive cases of osteoradionecrosis of the mandible diagnosed in the Department of Oral and Maxillofacial Surgery at Wilford Hall USAF Medical Center were studied microbiologically.

Materials and Methods

The diagnostic criterion used for case selection was an area greater than 1 cm of exposed bone in a field of irradiation that had failed to show any evidence of healing for at least six months. The case histories were reviewed with respect to the type and dose of irradiation, as well as possible initiating factors in the development of osteoradionecrosis.

Twelve of the 26 cases required a continuity violating resection of the mandible at least 3 cm long during the course of treatment. These 12 specimens were subjected to microbial investigation. Portions of all specimens were cultured for aerobes, anaerobes, and fungi, the specimens being separated into exposed surface bone specimens and deep medullary bone specimens.

Fungal and aerobic culture specimens were transported in Aimes medium. Anaerobic culture specimens were transported in an anaerobic specimen collector with an atmosphere of 10% H₂, 10% CO₂, and 80% N₂ by volume. Aerobes were cultured on blood agar, chocolate agar under 10% CO₂, MacConkey's medium, and eugon broth separately at 35°C. Growth or no growth was determined at 72 and 120 hours. Anaerobes were cultured on cooked meat broth, CDC anaerobic blood agar, phenol-ethanol blood agar, BBE for *Bacteroides fragilis*, and CDC kanamycin-vancomycin blood agar separately at 35°C. Growth or no growth was determined at seven and ten days. Separate specimens were also cultured in thio glycolate for *Actinomyces* spe-

cies and read at ten and 15 days. Fungi were cultured on Sabouraud's medium, brain-heart infusion, and mycocol at 30°C. Growth or no growth was determined at three and five weeks.

The remaining block of each bone specimen was fixed in 10% formalin for four days and slowly decalcified en bloc in 5% formic acid. Sections of 8-micrometer thickness were stained with hematoxylin and eosin and the stain of Brown and Brenn¹⁴ to identify microorganisms. In addition, specimens from eight cases of osteomyelitis of long bones, three cases of osteomyelitis of the mandible, and one case of osteomyelitis of the maxilla were cultured and stained in an identical manner. Specimens from four cases of clinically infected bone grafts to the jaws and four cases of clinically infected bone grafts to long bones were similarly cultured and stained.

Results

INITIATING FACTORS

Nine of the 26 cases studied (35%) could not be correlated with an episode of trauma. In general, these cases of spontaneous osteoradionecrosis occurred in patients receiving much higher total radiation doses and were associated more often with implant and supervoltage radiation sources. Of the 17 cases related to trauma, 15 were associated with postirradiation tooth removal (88%), and one each was associated with a denture flange or sharp bony ridge (6% each).

TYPE AND DOSE OF IRRADIATION

Only four of the 26 patients studied had received orthovoltage (500 KV or less; 6000 to 7200 rads) from an external beam source. Sixteen had received supervoltage (1-10 MEV) Telecobalt (60 external beam; 6200 to 9100 rads). Six had received implant sources (radon, radium 226 or iridium 192; 8000-14,000 rads) combined with external beam sources. Of the 12 specimens in this study that required resection, six were from supervoltage sources and six from combined implant/external beam sources. Of the nine cases of spontaneous osteoradionecrosis, four were due to supervoltage and five were due to implants combined with external beam. It is interesting that both the average dose and the range of absorbed radiation increased by 15% to 20% with the use of supervoltage vs orthovoltage as well as a further 15% to 20% increase in total dose when implants were added.

Table 1. Microbial Analysis of Osteoradionecrosis

Source	Specimens	Surface Organisms	Deep Organisms	Surface Organisms	Deep Organisms
		Identified on Culture	Identified on Culture	Observed in Tissue Section	Observed in Tissue Section
		No. (%)	No. (%)	No. (%)	No. (%)
Osteoradionecrosis	12	8 (67)	0 (0)	9 (75)	0 (0)
Osteomyelitis of long bones	8	7 (87.5)	8 (100)	6 (75)	8 (100)
Osteomyelitis of mandible or maxilla	4	4 (100)	3 (75)	2 (50)	4 (100)
Infected bone grafts of the jaws	4	4 (100)	4 (100)	4 (100)	4 (100)
Infected bone grafts of long bones	4	4 (100)	4 (100)	4 (100)	4 (100)

MICROBIAL STUDY

These results are presented in Table 1. Although many different microorganisms were consistently identified in all cases of osteomyelitis and infected bone grafts, both superficial and deep (Figs. 1, 2, and 3), no organisms could be cultured or observed in the deep, so-called "infected bone" of osteoradionecrosis (Fig. 4). However, organisms were cultured or readily observed with either hematoxylin and eosin or the Brown and Brenn stain on the surface of 67% to 75% of the osteoradionecrosis specimens (Fig. 5). In no case were organisms identified by either culture techniques or tissue staining in any other area of osteoradionecrotic bone. The organisms were solely limited to the surface of bone exposed to the oral environment. (Fig. 5). In contrast organisms were found throughout both infected bone grafts and osteomyelitis of all bones studied when they were cultured or stained (see Figure 3).

The surface organisms identified by culture in eight specimens of osteoradionecrosis varied greatly (Table 2). A high incidence of streptococci, *Candida* species, and gram-negative organisms suggested saprophytic contaminants. The tissue sections failed to show any evidence of bony invasion. In contrast, osteomyelitis and infected bone grafts to long bones consisted primarily of one pathogen, usually a staphylococcal species. Osteomyelitis and infected bone grafts of the jaws showed a more varied group of organisms, including *Bacteroides* and *Eikenella* species as well as *Staphylococcus aureus*, which were not encountered on the surface of osteoradionecrotic bone.

Discussion

The results of this investigation indicate that microorganisms play a very minor role in the pathophysiology of osteoradionecrosis of the jaws. Rather, they appear to act more as surface contaminants than as infective agents. Similarly, the direct role of trauma is questioned here, just as it has been by others. There is no doubt that spontaneous osteoradionecrosis is a valid entity and is related to higher total irradiation doses and perhaps to implant sources. The enhanced tissue damage effect of implants is due to a radiation source closer to the target tissue as well as to a continuous cellular damage without recovery for the duration of its action. Although the classic sequence of radiation, trauma, and infection once seemed to explain osteoradionecrosis to the profession's satisfaction, a more accurate and basic explanation of the pathophysiology is now required.

When tumor tissue or normal tissue is struck by small particles (electrons or smaller particles) of high energy (500 KV to 25 MEV), RNA, DNA, and enzymes are usually not affected directly. Instead, the more numerous water molecules are converted into free radicals such as $H\cdot$, $OH\cdot$, or $H_2O + e^-$, which in turn react with DNA, RNA, or enzyme molecules to disrupt or disorganize their nucleotide or amino acid sequence.¹⁵ On the cellular level, this may be seen as chromosome breakage, cross-linking, or frank chromosomal disintegration. The cell may quickly die, may repair its DNA and enzymatic damage to survive with impaired function such as loss of normal replication or synthetic abil-

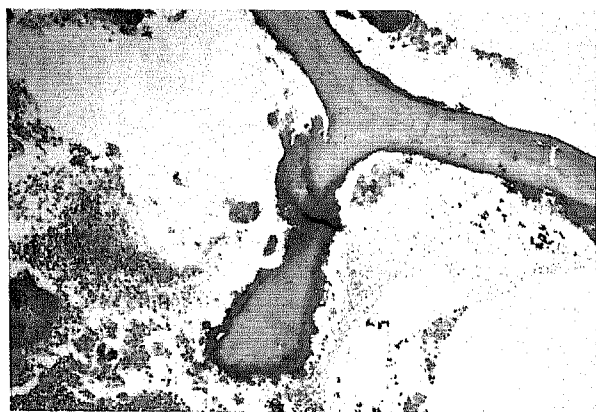
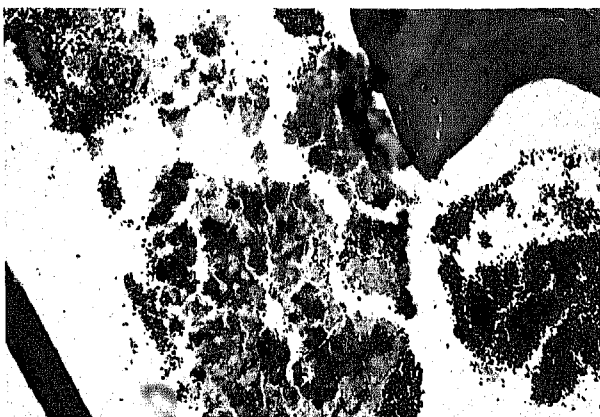
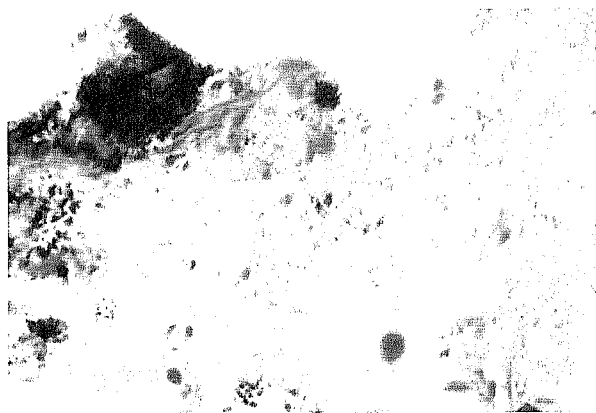


FIGURE 1. *Above*, Clusters and chains of gram-positive organisms from a case of osteomyelitis of the mandible. (Brown and Brenn stain, original magnification $\times 450$ under oil.)

FIGURE 2. *Center*, Cluster of gram-positive organisms from an infected bone graft to the mandible. (Brown and Brenn stain, original magnification $\times 450$ under oil.)

FIGURE 3. *Below*, Colonies of organisms on bony trabecular in medullary bone of mandibular osteomyelitis. (Hematoxylin and eosin, original magnification $\times 250$.)

ity, or may repair its DNA damage and then function normally. Indeed, after irradiation to the jaws, the cells of each tissue undergo a certain percentage of each type of radiation response.

The important tissues in the development of osteoradionecrosis are endothelium, bone, periosteum,

and fibrous connective tissue of the mucosa and skin. The radiation effects on the tissue level are endothelial death, hyalinization, and thrombosis of vessels. Periosteum becomes fibrotic. Bone osteoblasts and osteocytes become necrotic, with fi-

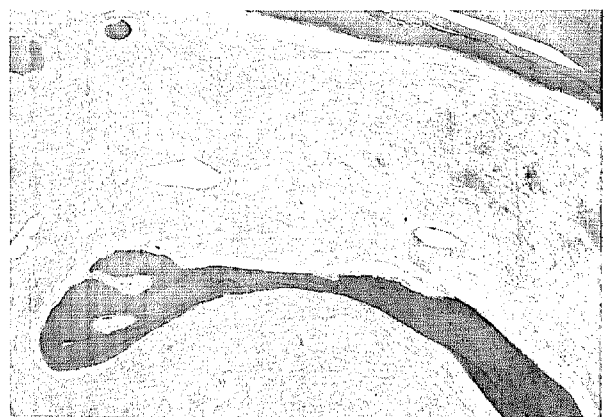
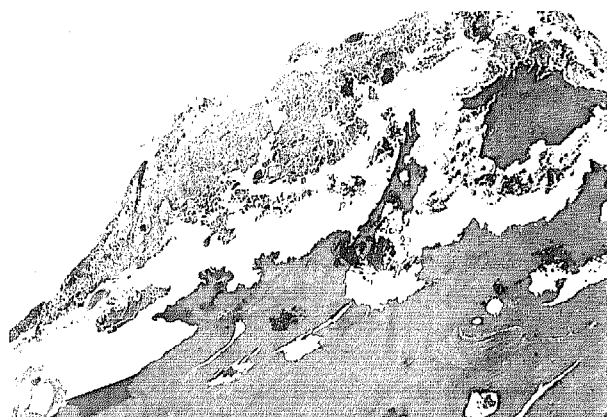


FIGURE 4. *Above*, Organism-free tissue typical of osteoradionecrosis specimens resected in this study. (Brown and Brenn stain, original magnification $\times 250$.)

FIGURE 5. *Center*, Colonies of organisms and debris on surface of osteoradionecrotic bone exposed to oral environment. (Hematoxylin and eosin, original magnification $\times 10$.)

FIGURE 6. *Below*, Representative specimen of mandibular osteoradionecrosis evidencing complete fibrosis of marrow space, loss of demonstrable fibroblasts, osteoblasts, osteocytes, and functioning vessels. No inflammation evident. (Hematoxylin and eosin, original magnification $\times 40$.)

Table 2. Surface and Deep Organism Identification in Osteoradionecrosis

Specimen No.	Surface Organisms Cultured	Surface Organisms Seen on Tissue Section	Deep Organisms Cultured	Deep Organisms Seen on Tissue Section
1	<i>Candida</i> sp. <i>Str. faecalis</i> <i>Str. sanguis</i>	+	None	None
2	<i>Candida</i> sp. <i>Enterobacter</i> sp.	+	None	None
3	<i>Str. viridans</i> <i>Staph. epidermidis</i> <i>Klebsiella pneumoniae</i>	+	None	None
4	<i>Haemophilus parainfluenzae</i> <i>Staph. albus</i> <i>Staph. epidermidis</i> <i>Proteus vulgaris</i>	+	None	None
5	None	+	None	None
6	<i>Candida</i> sp. <i>Staph. albus</i>	+	None	None
7	<i>Str. faecalis</i> <i>Klebsiella pneumoniae</i>	+	None	None
8	None	None	None	None
9	None	None	None	None
10	<i>Enterobacter</i> sp. <i>Str. sanguis</i> <i>Staph. epidermidis</i>	+	None	None
11	None	None	None	None
12	<i>Candida</i> sp. <i>Str. viridans</i> <i>Lactobacillus</i> sp. <i>Proteus mirabilis</i>	+	None	None

brosis of the marrow spaces. Mucosa and skin also become fibrotic, with markedly diminished cellularity and vascularity of the connective tissue. This histologic pattern was consistently seen in all 12 resection specimens (Fig. 6). The result on the organ level is a composite tissue, which is hypovascular and hypocellular, and has proved to be hypoxic compared with nonirradiated tissue by direct measurement.^{16,17} This result is referred to as the "three H" principle of irradiated tissue.

The relationship of such hypovascular, hypocellular, and hypoxic tissue to the development of osteoradionecrosis is best understood in terms of normal tissue homeostasis. Most structural tissues undergo a normal cellular life span, death, and replacement by new cells from a primitive cellular pool or from preexisting cells. Our bony skeleton undergoes resorption and remodeling with loss of osteocytes and new osteoid production by osteoblasts everyday. In a similar fashion, structural collagen undergoes a normal daily lysis with replacement by newly synthesized collagen. In the hypoxic, hypocellular, and hypovascular irradiated tissue, the ability to replace normal collagen loss or normal cellular loss is severely compromised or nonexistent. The result can be a breakdown unrelated to microorganisms but related more to the degree of original radiation damage and the rate of

normal or induced cellular death and collagen lysis. Indeed, the role of trauma in the initiation of osteoradionecrosis can now be seen as a single quantum of collagen lysis and induced cellular death. This creates a wound with an oxygen requirement and a demand for the basic elements of tissue repair that are beyond the capabilities of the local tissue to provide. The incidences of osteoradionecrosis unrelated to trauma in this study (35%) and in that of Daly and Drane¹² (39%) are consistent with a pathogenesis that does not necessarily include direct trauma as the etiologic agent. More likely, spontaneous osteoradionecrosis results when mucosal breakdown or even breakdown of skin is due to the tissue's inability to keep up with the cellular turnover and collagen synthesis. Once any wound is created, it would be unrealistic to expect effective healing, considering the greatly increased demands for oxygen, energy, and nutrition in a tissue that could not maintain itself at its former level of metabolic demand.

The overall conclusion is that osteoradionecrosis is a problem of wound healing rather than of infection. It is more similar to the diabetic ulcer of the extremities than to osteomyelitis. Indeed, the existence of radiation-induced aseptic necrosis in such sites as the femoral head, lumbar spine, and clavical without the introduction of oral bacterial flora is

well known and well documented.^{3,4} Furthermore, osteoradionecrosis is as much a disease process of the enveloping soft tissue as of the underlying bone. To add to the foundations of understanding first established by Meyer in 1970, it is suggested here that the following sequence summarizes the pathophysiology of osteoradionecrosis and that it applies to the composite of both soft and hard tissue:

1. Radiation
2. Formation of hypoxic-hypovascular-hypocellular tissue
3. Tissue breakdown (collagen lysis and cellular death exceeding synthesis and cellular replication)
4. Chronic nonhealing wounds (in which energy, oxygen, and structural precursor demand exceed supply)

The importance of this sequence is that it gives a more accurate view of the basic pathophysiology of osteoradionecrosis on the biochemical and cellular levels. Since treatment is based on intercepting or altering the pathologic process of a disease, more effective therapy for osteoradionecrosis, yielding better results than those currently obtained, may be possible with treatment modalities based on this concept.

Conclusions

1. Osteoradionecrosis is not a primary infection of irradiated bone. It is a complex metabolic and tissue homeostatic deficiency created by radiation-induced cellular injury.
2. Microorganisms play only a contaminant role in its pathophysiology.
3. Trauma may or may not be an initiating factor. When trauma is associated with osteoradionecrosis, it is usually caused by tooth removal (88%). The role of trauma is seen as part of a more comprehensive pathologic process involving cellular death and collagen lysis, which place greater energy, oxygen, and other metabolic demands on tissues unable to meet them.
4. The occurrence of spontaneous osteoradionecrosis is related to the use of implant sources and higher total radiation doses. The mechanism is seen as an inability of both soft and hard tissue to keep up with cellular turnover and collagen synthesis.
5. The use of supervoltage irradiation has neither eliminated nor reduced the frequency of osteoradionecrosis of the jaws, despite claims as to its bone-sparing effects; 80% of cases of external beam-related osteoradionecrosis were associated with supervoltage sources. Perhaps this finding is

related to the higher total radiation doses used when supervoltage sources were employed.

6. The classic sequence of radiation, trauma, and infection should be replaced by a sequence more indicative of the metabolic and cellular changes we now recognize as being basic to the pathophysiology of osteoradionecrosis. The classic sequence offered here is as follows: (a) radiation, (b) hypoxic-hypovascular-hypocellular tissue (the "three H" principle), (c) tissue breakdown (cellular death and collagen lysis exceed synthesis and cellular replication), and (d) nonhealing wound (a wound in which energy, oxygen, and metabolic demands exceed supply).

References

1. Phemister DB: Radium necrosis of bone. *Am J Roentgenol* 16:340, 1926
2. Ewing J: Radiation osteitis. *Acta Radiol* 6:339, 1926
3. Stampfli WP, Kerr GD: Fracture of the femoral neck following pelvic irradiation. *AJR* 57:1947
4. Hart GB, Mainous EG: The treatment of radiation necrosis with hyperbaric oxygen. *Cancer* 37:2580, 1976
5. McLenna W: Some aspects of the problems of radionecrosis of the jaws. *Proc R Soc Med* 48:1017, 1955
6. Rankow RM, Weissman B: Osteoradionecrosis of the mandible. *Ann Otol Rhinol Laryngol* 80:603, 1971
7. Mainous EG, Hart GB: Osteoradionecrosis of the mandible: Treatment with hyperbaric oxygen. *Arch Otolaryngol* 101:173, 1975
8. Meyer I: Infectious diseases of the jaws. *J Oral Surg* 28:17, 1970
9. Bump RL, Young JM, David JC, Heimbach RD: Hyperbaric oxygen: Treatment of osteoradionecrosis and osteomyelitis. *Med Serv Digest* 26:17, 1976
10. Titterton WP: Osteomyelitis and osteoradionecrosis of the jaws. *J Oral Med* 26:13, 1971
11. Obwegeser HL, Sailer HF: Experience with intraoral resection and immediate reconstruction of radio-osteomyelitis of the mandible. *J Maxillofac Surg* 6:257, 1978
12. Daly TE, Drane JB: Management of teeth related to the treatment of oral cancer. *National Cancer Conference Proceedings* 7. New York, American Cancer Society, 1973, p 147
13. Bedwinek JM, Shukowsky LJ, Fletcher GH, Daly TE: Osteoradionecrosis in patients treated with definitive radiotherapy for squamous cell carcinomas of the oral cavity and naso and oropharynx. *Radiology* 119:665, 1976
14. Lune LG (ed): *Manual of Histologic Staining Methods of the AFIP*, 3rd ed. New York, McGraw-Hill Book Co., 1968, p 223
15. Okada S: *Radiation Biochemistry*. New York, Academic Press, 1970, p 1
16. Stevens MR, Marx RE: Complete resolution of osteoradionecrosis with a new protocol combining hyperbaric oxygen and resection. *Scientific Abstracts Session*, 63rd Annual AAOMS Meeting, San Francisco, 1981
17. Sheffield PJ, Dunn JM: Continuous monitoring of tissue oxygen tension during hyperbaric oxygen therapy. Smith G (ed): *Proceedings of 6th International Congress of Hyperbaric Medicine*. Aberdeen University Press, 1979, p 125