Effects of Irradiation on Mandibular Scintigraphy

K. Aitasalo and P. Ruotsalainen

Departments of Otolaryngology and Radiotherapy, University Central Hospital of Turku, Turku, Finland

Technetium-99m methylene diphosphonate (Sn) scintigraphy with computer analysis was used to investigate alterations in the pathophysiology of the normal mandible and the pathologic mandible during and after irradiation. Slight but significant elevations of uptake levels were recorded as an early effect of irradiation. The elevations correlated with the duration of treatment and normalized over a follow-up period of 6 to 12 mo. Increased mandibular metabolism was found during irradiation and in osteomyelitis and osteoradionecrosis of the mandible. Scintigraphy with computer analysis proved a simple and valid method in the evaluation of early irradiation damage and pathophysiologic conditions of the mandible. The method can also be used to predict whether the irradiation damage will become irreversible.

J Nucl Med 26: 1263–1269, 1985

Head and neck irradiation is well known to induce dental and periodontal damage which frequently leads to inflammatory reactions in the involved tissues (*1–4*). Mandibular osteomyelitis or osteoradionecrosis is a serious complication of the radiotherapy of oral carcinoma (*4–9*).

The radiologic diagnosis of early mandibular irradiation is difficult (*10*). The main radiologic signs are incipient atrophy and diminished density of bone (*11–13*). On the other hand, in infectious processes of the mandible the clinical symptoms precede the radiologic changes. Thus, at least 30–60% of calcium salts are lost before the lesion is radiographically detectable (*10,11,14*).

Bone scintigraphy of sites of previous radiation therapy may provide earlier indications of postirradiation changes than other available methods (*15–18*). The use of scintigraphy in the examinations of the bone is based on the fact that alkaline earth elements such as technetium-99m- (^{99m}Tc) labeled tin-phosphorus complexes react with the components of bone (*19,20*). Bauer (1966) (*21*) suggested that this affinity is based on either ion exchange (adsorption to the crystal surface) or bone neogenesis (diffusion into the crystal inside the bone).

The present study used scintigraphy to find how the normal mandible reacts during and after radiation therapy. To our knowledge, there are no previous reports of scintigraphy used in the diagnosis of irradiation effects on the mandible. We used the quantitative methylene diphosphonate (MDP) (Sn) scintigraphic technique to study the possibilities of scintigraphy in the identification of this lesion.

MATERIALS AND METHODS

Two series of patients were examined. The series without bone involvement (primary series) consisted of 28 patients (15 men and 13 women with a mean age of 57 ± 14 yr) admitted in 1979–1980 for radiation therapy of the mandibular region and meeting the following criteria: They had tumors of the oral cavity, naso- or hypopharynx and were treated with radiotherapy directed at the mandibular region, but they had no evidence of spread or metastasis to the mandibular periosteum or bone marrow. This was verified by radiographic and scintigraphic methods.

Received Oct.31, 1984; revision accepted July 19, 1985.

For reprints contact: Kalle Aitasalo, MD, DDS, Dept. of Otolaryngology, University Central Hospital of Turku, SF-20520 Turku, Finland.

Comparisons were made between the primary series and secondary series of patients admitted with mandibular involvement. The latter series of 11 patients (seven men and four women with a mean age of 43 ± 20 yr) had osteomyelitis or osteoradionecrosis of the mandible. Diagnosis was based on histopathologic studies.

The initial mandibular scintigraphic examination (S_0) and orthopantomographic examinations for later evaluation were carried out before irradiation. In addition to scintigraphy, the following laboratory tests were simultaneously performed: hemoglobin (Hb), leukocytes (B-leuk), alkaline phosphatase (S-AFOS), calcium (Ca) and phosphorus (P).

The first follow-up examination (S_1) and laboratory tests were performed in the middle of the radiotherapy course, immediately before a treatment interval after a dose of 30–32 Gy. The second follow-up examination (S_2) and laboratory tests were performed at the end of the radiotherapy at a dose of 46–68 Gy. Since eight patients had not received the full-dose irradiation treatment, the S_2 examination was only carried out in 20 patients who had received full-dose treatment. The third follow-up examination (S_3) was performed at 6 to 12 mo after irradiation during the remodeling of bone after irradiation. Of the 20 patients who had received full-dose treatment, only 11 could be followed up after the last irradiation treatment.

TABLE 1
Primary Series: Accumulative Radiation Doses in Gray Units (Gy) at Different Scintigraphies of 28 Patients (mean ± s.d.)

Scintigraphy	No. of patients	Dose at time of scintigraphies	
		Right mandible	Left mandible
S_0*	28	None	None
S_1†	28	27.3 ± 4.6	27.0 ± 4.6
S_2‡	20	50.7 ± 9.	51.9 ± 9.6
S_3§	11	49.2 ± 10.7	50.1 ± 11.1

*S_0 = Baseline scintigraphy; before radiotherapy.
†S_1 = First follow-up scintigraphy; 30 ± 9 days after onset of radiotherapy.
‡S_2 = Second follow-up scintigraphy; 90 ± 37 days after onset of radiotherapy, 20 patients.
§S_3 = Third follow-up scintigraphy; 241 ± 94 days after last radiation dose, 11 patients.

Radiation treatment

The radiotherapy was given at the Department of Radiotherapy and the surgical therapy at the Department of Otolaryngology of our hospital.

The irradiation was given with cobalt equipment or with photons from a 6.6 MeV linear accelerator. Most patients were irradiated with equal doses to both right and left angles of the mandible. Three patients received irradiation to only one angle of the mandible. The split-course technique was used: The dose in the mandible was 30 Gy in 3 wk, then an interval of 2–3 wk followed, after which another 30 Gy in 3 wk were given. In 14 cases recovery from operation, partial resection of the tongue and/or neck dissection involving the soft-tissue areas of the tongue or the bottom of the mouth without injury to the mandibular periosteum postponed administration of the remaining radiotherapy by 3 wk. Table 1 shows the doses and duration of the radiotherapy.

Scintigraphic examination

Technetium-99m MDP by CIS with a physical half-life of 6 hr was used in the mandibular scintigraphies. It was administered intravenously; the usual dose was 10 mCi (370 MBq). Scintigraphy was performed 3 hr after the injection. Two hours before injection of the tracer; the patients were given a 30-ml oral dose of a 1% aqueous solution of potassium perchlorate to reduce uptake by the salivary glands, which might otherwise have interfered with the interpretation of the bone scans.

Gamma camera examinations were performed.* At each examination three pictures with 300,000 counts were taken in three projections, the anteroposterior (AP) and both right and left lateral projections. For the AP projection, the patient was placed in a sitting position with the orbitomeatal base line perpendicular to the detector and the tip of his nose in the center of the detector field. For the lateral projection, the sagittal plane of the patient was placed parallel to the front of the camera with the nasopharyngeal region in the center. All pictures were stored on the computer.

Calculation of mandibular uptakes

In each picture regions of interest (ROIs) of 4 × 4 pixels (1.5 × 1.5 cm^2) were selected from the areas of mandibular angles and one from the frontal area of the skull. The latter ROI was used as activity control to eliminate the variation of the uptake of normal bone. This variation is mainly due to variation of the injected dose of radioactivity. The activity control area in the skull was protected from irradiation during therapy.

Relative mandibular uptake

The relative uptake of the mandible was calculated by dividing the average net counts of mandible ROIs by the average net counts of the activity control ROIs.

Normalized mandibular uptake

To facilitate the comparison of mandibular uptakes in different scintigrams in the same patients and between different patients, the S_1, S_2, and S_3 uptakes were normalized using the relative uptake of the mandible in

TABLE 2
Primary Series: Mandibular Scintigraphy Before, During, and After Irradiation. Normalized Uptakes of Right and Left Angles of Mandible in Anterior-Posterior (AP) and Lateral (L) Projections (mean ± s.e.e.)

Scintigraphy	No. of patients	Projection of scintigraphy: AP-projection left	AP-projection right	L-projection left	L-projection right
S_0	28	1.000	1.032 ±0.024	1.022 ±0.048	0.980 ±0.046
S_1	28	1.184 ±0.031	1.190 ±0.045	1.169 ±0.053	1.140 ±0.059
S_2	20	1.253 ±0.051	1.292 ±0.077	1.240 ±0.083	1.246 ±0.078
S_3	11	1.001 ±0.051	1.085 ±0.086	0.905 ±0.070	0.909 ±0.088

Statistical significance (t-test) of differences at consecutive scintigraphies in each projection. $S_0 - S_1$ $p < 0.001$; $S_0 - S_2$ $p < 0.001$; $S_0 - S_3$ $p > 0.5$; $S_2 - S_3$ $p < 0.01$.

the S_0 examination as a basic unit. In the AP projection, where both mandibular angles can be seen, the relative uptake of the right mandible was used as a normalized unit. Thus, the normalized uptake of the mandible before irradiation (at the S_0 examination) was considered to be 1.000. An uptake exceeding 1.000 on S_1 or later examinations meant that the activity in that area of the mandible had increased and vice versa.

Statistical analysis

Statistical analysis of the results was carried out on a computer† using the BMDP-81 library (*28*). The methods were regression analysis, applied regression analysis, one- and two-way analysis of variance, t-test, Bonferron's t-test, and Mann-Whitney U-test.

RESULTS

Evaluation of scintigraphic uptakes in patients without bone involvement (normal mandibular bone)

The relative mandibular uptakes of the patients were calculated and showed a normal biological distribution. The relative uptakes on the right and the left side of the mandible showed a highly significant correlation between both sides of the mandible in both anteroposterior (AP) and lateral (L) projections before, during, and after radiotherapy ($p < 0.001$). A highly significant correlation was also seen between AP and L projections in all examinations (S_0, S_1, and S_2) ($p < 0.001$). Both projections showed equally well the mandibular response to radiation therapy. Subsequently, we used the AP projection, since the intensive uptakes of the secondary series distorted the uptakes of lateral projections.

Mandibular uptakes during and after radiotherapy

Table 2 shows the normalized uptakes in different phases of radiotherapy. The uptakes were significantly higher during and immediately after radiotherapy (46–68 Gy) than before it ($p < 0.001$). At S_2 there was no statistically significant difference between patients who had been irradiated and operated on and those who had only been irradiated ($p < 0.001$). During follow-up, relative uptakes seemed to return to the pre-irradiation level. Figure 1 shows the changes in the normalized uptakes of the right mandible in the AP projection of S_0–S_3 examinations. The depicted 0.95 confidence limits were calculated for these uptakes. Almost identical values with similar statistical significance were found for the left mandible.

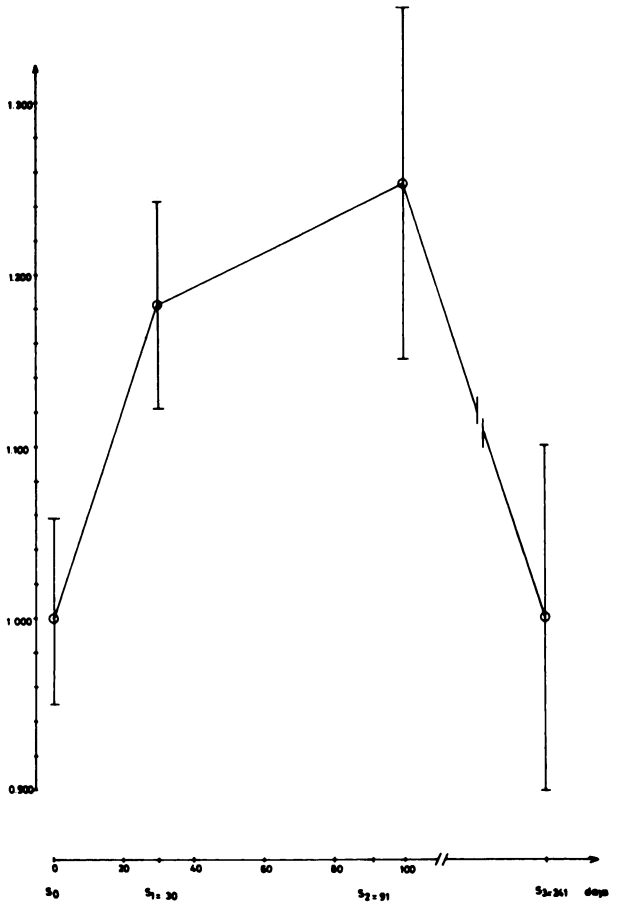

FIGURE 1
Standardized uptake of right anterior-posterior (AP) projection with 95% reliability limits (doses S_1 = 27 Gy and S_2 = 49 Gy)

TABLE 3
Primary Series: Regression Analysis of Uptakes in Three Scintigraphies, AP-Projection

Scintigraphy	Uptake of right angle of mandible	Uptake of left angle of mandible
S_1 25 patients	1.15 + 0.002 × dose	1.13 + 0.003 × dose
	1.10 + 0.003 × time	0.92 + 0.009 × time
S_2 20 patients	1.25 − 0.001 × dose	1.51 − 0.003 × dose
	0.87 + 0.004 × time	0.75 + 0.006 × time
S_3 11 patients	+0.01 − 0.006 × time	0.17 − 0.004 × time

Statistical analysis of the dose and time-uptake curve

The uptakes increased during irradiation therapy symmetrically on both sides of the mandible as functions of dose and time (Table 3). This agrees with changes in standardized uptakes shown in Table 2.

The increase of uptakes were most rapid between S_0 and S_1 and stabilized between S_1 and S_2 (the slope of dose = 0.001 on the right side and − 0.003 on the left side) (Table 3). During a mean follow-up period of 241 days mandibular uptakes returned to their original levels. The S_3 examination showed decreasing uptakes of both mandible angles (the time slope = −0.006 on the right side, −0.004 on the left side, Table 3). The standardized uptakes of S_0 and S_3 examinations were statistically similar ($p > 0.5$), whereas those of S_2 and S_3 were different ($p < 0.001$) (Table 2). The effect of radiotherapy on scintigraphic values was both time and dose dependent.

Biochemical blood changes

Biochemical blood changes were slight during the radiotherapy. The mean values, which had changed more than normal variation permits, returned to normal before the last (S_3) scintigraphic examination. The decrease in the leukocyte count was statistically significant ($p < 0.05$) at the beginning of the radiotherapy (S_1). The decrease of hemoglobin and alkaline phosphatase levels between S_0 and S_2 examinations was statistically significant ($p < 0.05$). The calcium levels of the serum and the phosphorus of the plasma remained unchanged during the study. All biochemically examined patients came from the primary series. The second series of patients with osteoradionecrosis in the chronic phase showed no statistically significant changes in biochemical blood tests.

Evaluation of scintigraphic uptakes in patients with bone involvement

Secondary (S_s) mandibular uptake

In the other group of patients with bone involvement, osteoradionecrosis or osteomyelitis, relative uptakes in scintigraphies of the involved side were higher than those of the noninvolved side, ($p < 0.05$ for osteoradionecrosis and $p < 0.001$ for osteomyelitis). The values for the involved side differed from the mean value of the nonirradiated mandibles of 28 patients of the primary series (Table 4), while the counts for the noninvolved side did not.

The standardized uptake in osteoradionecrosis was 1.6, when the right side was involved, and 1.4, when the left side was involved. These values were outside the calculated 95% reliability limits even in the primary series (Fig. 1). In acute osteomyelitis they were many times higher (standardized uptakes 3.5 on the right side and 3.5 on the left side). This finding shows how scintig-

TABLE 4
Secondary Series: Relative Mandibular Uptakes in Secondary Series, AP-Projection (mean ± s.e.e.)

	Scintigraphy	Right side	No of patients	Left side	No of patients
S_{SR}	Mandibular uptakes on the side of osteoradionecrosis	560 ± 8	3	581 ± 8	2
		1.63		1.36	
	Mandibular uptakes on the healthy side	344 ± 18	2	426 ± 23	3
S_{SM}	Mandibular uptakes on the side of acute osteomyelitis	1,682 ± 412	3	1,154 ± 264	3
		3.50		3.53	
	Mandibular uptakes on	480 ± 21	3	327 ± 20	3
S_0	Mandibular uptakes in the primary series before irradiation	435 ± 21	28	426 ± 21	28

Statistical significance of results was analyzed by one-way analysis of variance and Mann-Whitney U-test. $S_{SR} - S_0$ $0.01 < p < 0.05$ (SR = osteoradionecrosis); $S_{SM} - S_0$ $p < 0.001$ (SM = osteomyelitis).

raphy of the normal mandible changes during radiation therapy. Early increase in scintigraphic uptakes (exceeding the normal values shown in Fig. 1.) seems to predict that the patient will later develop severe pathologic changes. This is very important in view of decisions on special periodontal, dental, or oral prophylaxis.

DISCUSSION

Technetium-99m MDP (Sn) has specific affinity for normal bone structures. This affinity is increased or decreased at the sites of metabolic disturbances, which makes it possible to visualize bone lesions (*21,23,24*). We found an increase in the uptakes of scintigraphies performed before and after irradiation. After a period of 6 to 12 mo radiation therapy, the uptake values returned to pre-irradiation levels. However, some reports are in partial or even total disagreement with our findings, but this may depend on the fact that their scintigraphic examinations were only performed during and after irradiation therapy.

Method of examination

The difficulty of administering equal doses to different patients or even to the same patient at different times is eliminated by the use of relative uptakes. Further, comparative studies have been made easier by the introduction of the concept of normalized uptake. This concept does not exclude the main disturbing factor, i.e., uptake by other tissues than bone. However, it has been shown that the disturbing effect of other tissues on the distribution and clearance of injected ^{99}Tc complex in the bone is insignificant (*22,25*).

In this study, the disturbance of adjacent tissues was also eliminated by the use of the AP projection. Similarly, very little disturbance from the opposite side was evident in the L projection. However, in cases of asymmetrical uptake, e.g., in osteomyelitis, the more active side may have caused a marked increase in the counts of the less active healthy side in the L projection.

Computerized counting of the pixels is necessary for detection of small but still significant changes in uptakes, which are not detectable by the eye.

Early bone response to radiotherapy

Blood circulation, osteogenesis, osteolysis, and osteoid collagen as well as the total bone crystal surface have been suggested as important factors influencing the uptake of the bone-seeking technetium compound (*26–28*).

Reports have been published on the early depressive effect of local external radiation on bone marrow (*29–31*), bone cells (*14,33,34*), and the periosteum (*34,35*).

The depressive effect of irradiation on the uptake of skeletal radionuclides has been evaluated quantitatively in experimental animals (*36*) and human patients (*15,16*). Cox (*16*) considered that decreased phagocytic activity coupled with reduced blood flow is responsible for the reduction of skeletal uptake.

An increased effect of irradiation on the uptake of skeletal radionuclides has been shown by Fordham and Ramachandian (*17*), and King et al. (*37*). The latter produced histologic and autoradiographic evidence that there was an early hyperemic ("inflammatory") response to the vascular and cellular damage caused by irradiation. Irradiation caused remodeling (resorption, neovascularization, and formation) of cortical bone. This remodeling was more pronounced in rabbits irradiated with single doses than in those treated with fractionated doses. In the present study, the uptake of bones irradiated by a dose of 46.5 Gy over 3 wk increased up to 6 mo and normalized after that.

We agree with King et al. (*37*) that the reaction of bone after irradiation is either circulatory or metabolic. Initially, the circulatory hyperemic effect dominates; later the metabolic changes become more important. The fact that metabolism is increased in spite of decreased blood flow secondary to vascular damage may be explained by the increase of the reactive cell surface in remodeling. This concept is supported by an early enzymatic increase after irradiation (*38*). Sykes et al. (*39*) and Rubin and Casarett (*40*) using histologic methods considered cell and matrix injury secondary to the degeneration of the microvasculature of bone.

In our earlier study, the amount of blood flow correlated with the uptake of ^{99m}Tc-compound in the bone, and it was later dependent on both blood circulation and remodeling.

Scintigraphic findings in the normal mandible during and after radiation therapy

King et al. (*37*) found that scintigraphic uptakes are increased by irradiation. We found that this increase is significant and dose dependent up to 60 Gy. Six to 12 mo after irradiation, the intensity of the uptake returned to the pre-irradiational level.

The finding of decreased intensity by Bell et al. (*15*) and Cox (*16*) may be due to the timing of scintigraphy. Computer analysis combined with a relevant technique is needed to reveal the slight but significant change brought about by irradiation.

Scintigraphic uptakes in bone involvement

It is possible to demonstrate inflammatory bone diseases by scintigraphy days or even weeks before the appearance of skeletal roentgenographic evidence (*41–43*). Thrall et al. (*44*) showed that pathologic hyperemia and impaired blood circulation in osteomyelitis caused "extended patterns" on bone scintigraphy. A decrease in uptake may characterize late osteomyelitis (*45*). No doubt similar changes could have been shown

in the two cases of osteomyelitis in our secondary series, if the necessary investigations had been carried out.

The details of variable uptakes in patients with bone involvement probably depend on the same basic mechanisms of incorporation into pathologic changes as in normal bone structures. We found increased uptakes in chronic mandibular osteoradionecrosis ($p < 0.05$) and acute mandibular osteomyelitis ($p < 0.0001$). The major histopathologic findings in osteoradionecrosis of the mandible is the appearance of chronic inflammatory cells (*46*). Continuous resorption and substitution of bone appear as changes of scintigraphic intensity.

CONCLUSION

The study focused on scintigraphic uptakes of the normal mandible during and after radiation therapy. A comparison was made between uptakes in irradiated normal mandible and those in irradiated pathologic mandible (in osteomyelitis and osteoradionecrosis). The latter were consistently higher in intensity than uptakes during irradiation therapy. Technetium-99m MDP (Sn) scintigraphy proved to be a suitable method for studying the effects of irradiation on the mandible and for early diagnosis of mandibular osteomyelitis or osteoradionecrosis. Slight but significant elevations of uptake levels detectable only by computerized analysis of scintigrams can be recorded as an early effect of irradiation. Return to pretherapeutic levels occurs in about 8 mo. Scintigraphy can be used to predict whether mandibular osteoradionecrosis will develop in the irradiation area.

FOOTNOTES

* Searle Pho gamma V with digital PDP 11/34 computer, Siemens Medical Systems, Iselin, NJ.

† DEC-system 20 computer, Digital Equipment Corp., Maynard, MA.

REFERENCES

1. Silverman S, Chierici G: Radiation therapy of oral carcinoma: 1. Effects on oral tissues and management of the periodontium. *J Periodontal* 36:478–484, 1965
2. Robinson JE: Characteristics of irradiated soft and hard tissue. *J Prosthet Dent* 35:549–552, 1976
3. Beumer J III, Curtis T, Harrison RE: Radiation therapy of the oral cavity: Sequelae and management, Part 1. and Part 2. *Head Neck Surg* 1:301–312; 392–408, 1979
4. Murray CG, Daly TE, Zimmerman SO: The relationship between dental disease and radiation necrosis of the mandible. *Oral Surg* 49:99–104, 1980
5. Wildermuth O, Cantril ST: Radiation necrosis of mandible. *Radiology* 61:771–785, 1953
6. Parker RG: Tolerance of mature bone and cartilage in clinical radiation therapy. *Front Radiat Ther Onc* 6:312–331, 1972
7. Beumer J III, Silverman S Jr, Benak S Jr: Hard and soft tissue necrosis following radiation therapy for oral cancer. *J Prosthet Dent* 27:640–644, 1972
8. Murray CG, Herson J, Daly TE, et al: Radiation necrosis of the mandible: A 10 year study. Part II. Dental factors: Onset, duration and management of necrosis. *J Radiat Oncol Biol Phys* 6:549–553, 1980
9. Morrish Jr RB, Chan E, Silverman S Jr, et al: Osteoradionecrosis in patients irradiated for head and neck carcinoma. *Cancer* 47:1980–1983, 1981
10. Edeiken J, Hodes J: *Roentgen Diagnosis of Diseases of Bone*, Vol. 1., 2nd ed., Baltimore, Williams & Wilkins, 1973
11. Malska JW: Microdensitometric analysis of the influence of X-irradiation on mature bone in humans. *Acta Med Pol* 12:357–362, 1971
12. Sengupta S, Prathap K: Radiation necrosis of the humerus. *Acta Radiol (Ther)* 12:313–320, 1973
13. Howland WJ, Loeffler RK, Starchman DE, et al: Postradiation atrophic changes in bone and related complications. *Radiology* 117:677–681, 1975
14. Ergün H, Howland WJ: Postradiation atrophy of mature bone. *CRC Crit Rev Diagn Imaging* 12:225–243, 1980
15. Bell EG, McAfee JG, Constable WC: Local radiation damage to bone marrow demonstrated by radioisotopic imaging. *Radiology* 92:1083–1088, 1969
16. Cox PH: Abnormalities in skeletal uptake of ^{99m}Tc-polyphosphate complexes in areas of bone associated with times which have been subjected to radiation therapy. *Br J Radiol* 47:851–856, 1974
17. Fordham EW, Ramachandan PC: Radionuclide imaging of osseous trauma. *Semin Nucl Med* 4:411–429, 1974
18. Marty R, Denny JD, McKamey MR, et al: Bone trauma and related benign diseases: assessment by bone scanning. *Semin Nucl Med* 6:107–120, 1976
19. Neuman WF, Neuman MW: *The Chemical Dynamics of Bone Mineral*. Chicago, The University of Chicago Press, 1958
20. Supramanian G, McAfee JG, Blair RJ, et al: Technetium-99m labelled stannous imidophosphate, a new radiodiagnostic agent for bone scanning: Comparison with other 99mTc complexes. *J Nucl Med* 16:1137–1143, 1975
21. Bauer GCH: Isotopes of calcium and strontium for studies of bone metabolism in man. In *Radioactive Pharmaceuticals*, U.S. Atomic Energy Commission Oak Ridge, 1966
22. Dixon WJ: *BMDD Statistical Software 1981*, Berkeley: University of California Press, 1981
23. Jones AG, Francis MD, Davis MA: Bone scanning: radionuclidic reaction mechanisms. *Semin Nucl Med* 6:3–18, 1976
24. Davis MA, Jones AG: Comparison of ^{99m}Tc-labeled phosphate and phosphonate agents for skeletal imaging. *Semin Nucl Med* 6:19–31, 1976
25. Krishnamurthy GT, Huebotter RJ, Tubis M, et al: Pharmaco-kinetics of current skeletal-seeking radiopharmaceuticals. *Isotopes* 126:293–301, 1976
26. Tilden RL, Jackson J, Enneking WF, et al: ^{99m}Tc-polyphosphate: Histological localization in human femurs by autoradiography. *J Nucl Med* 14:576–578, 1973
27. Genant HK, Boutovich GJ, Singh M, et al: Bone seeking radionuclides. An in vivo study of factors affecting skeletal uptake. *Radiology* 113:373–382, 1974
28. Kaye M, Silverton S, Rosenthall L: Technetium-^{99m}Tc-pyrophosphate: Studies in vivo and in vitro. *J Nucl Med* 16:40–45, 1975

29. Kinsky RM, Andrews GH, Edwards Cl, et al: *Scanning of Bone Marrow in Hematopoietic Disorders. Proceedings of the Symposium in Medical Radioisotope Scanning*, International Atomic Agency, Athens, al II Vienna, JAEA, 1964, pp 207-225
30. Knospe WH, Blom J, Crosby WH: Regeneration of locally irradiated bone marrow. 1. Dose dependent, long-term changes in the rat, with particular emphasis upon vascular and stromal reaction. *Blood* 28:398-415, 1966
31. Nelp WB, Larson SM, Lewis RJ: Distribution of the erythron and RES in the bone marrow organ. *J Nucl Med* 8:430-436, 1967
32. Rubin P, Casarett GW: Mature cartilage and bone. In *Clinical Radiation Pathology*, Vol II. Philadelphia, WB Saunders Co, 1968, pp 557-608
33. Gungör T, Hedlund T, Hulth A, Johnell O: The effect of irradiation on osteoclasts with or without transplantation of hematopoietic cells. *Acta Orthop Scand* 53:333-337, 1982
34. Rissanen P, Rokkanen P, Paatsamo S: The effect of Co^{60} irradiation on bone in dogs. *Strahlentherapie* 137:162-169, 1969
35. Aitasalo K, Lehtinen R: The influence of a free periosteal transplant on bone healing in the irradiated rabbit tibia. *Scand J Plast Reconstr Surg*: in press, 1984
36. Finston RA, Woodard HQ, Laughlin JS: Effects of external irradiation on mineral metabolism in the bones of adult dogs. *Clin Orthop* 46:183-201, 1966
37. King MA, Casarett GW, Weber D: A study of irradiated bone: I. Histopathologic and physiologic changes. *J Nucl Med* 20:1142-1149, 1979
38. Aitasalo K: Effect of different irradiation doses on early enzymatic changes in healing mandibular periosteum and bone. A histochemical study on rats: in press, 1985
39. Sykes MP, Chu FCH, Savel H, et al: The effects of varying dosages of irradiation upon sternal marrow regeneration. *Radiology* 83:1084-1087, 1964
40. Rubin P, Casarett GW: A direction for clinical radiation pathology. In *Front Radiat Ther Onc*, Vol. 6, Walth JM, ed. Baltimore, University Park Press, 1972, pp 1-16
41. Handmarker H, Leonards R: The bone scan in inflammatory osseous disease. *Semin Nucl Med* 6:95-105, 1976
42. Feine U, zum Winkel K: *Nuklearmedizin-Szintigraphische Diagnostik*. Stuttgart, Georg Thieme Verlag, 1980, pp 435-481
43. Noyek AM, Kirsh JC, Wortzman G, et al: The clinical significance of radionuclide bone and gallium scanning in osteomyelitis of the head and neck. *Laryngoscope* (Suppl 34) 94: 1984
44. Thrall JH, Geslien GE, Corcoron RJ, et al: Abnormal radionuclide deposition patterns adjacent to focal skeletal lesions. *Radiology* 115:659, 1975
45. DeNardo GL, Volpe J: Detection of bone lesions with a strontium-85 scintiscan. *J Nucl Med* 7:219-236, 1966
46. Happonen R-P, Viander M, Pelliniemi L, et al: Actinomyces israelii in osteoradionecrosis of the jaws. *Oral Surg* 55:580-588, 1983