HISTOPATHOLOGIC AND ROENTGENOLOGIC STUDIES
ON THE EFFECTS OF IRRADIATION ON
THE HUMAN MANDIBLES

BY

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ABSTRACT

The present study deals with the pathologic change of the mandible following radiation therapy for oral cancer, histopathologically and roentgenologically. The results are summarized as follows: 1) As the resorptive change of the cortex and the trabeculae, irregular and bizarre resorption and enlargement of the lacunae were observed. 2) The grade of injury of the osteocytes was described by the percentage of the number of the lacunae, which were empty and in which the nuclei of the osteocytes could not be seen. Consequently these results corresponded considerably well with the clinical aspects. 3) Osteophytes in the spongy and compact bone were observed, and also narrowing and plugging of the Haversian canal and the canal of Volkmann with mineral were seen as the sclerotic change. 4) Thickening of the tunica intima, obstruction, disarrangement of the elastic fibers and disruption of the vessels were observed in the inferior alveolar artery, the arterioles, and also occlusion, which gave various appearances, in the vessels within the Haversian canal and the canal of Volkmann was seen. 5) The following four groups, based upon the radiographic change, were classified as: Group I, irregular osteolytic change; Group II, marked osteosclerotic change; Group III, irregular mixture of osteolytic and osteosclerotic change; and Group IV, no remarkable change.

INTRODUCTION

Radiation therapy is the first choice of effective treatment for cancer of the oral region. Indications for this therapy are increasing more and more with the improvement of therapeutic results.

On the other hand, the problem of radiation injury to the normal oral tissues, especially the jaws, following radiation therapy is important clinically in regard to prevention and treatment, and also pathologically and roentgenologically in regard to its nature.

Many clinical cases of osteoradionecrosis of the jaws have been reported in the world, but few histopathologic and roentgenologic studies on clinical materials have been reported except for the descriptions by Kanthak (1941) 2, Niebel & Neeman (1957) 3, Meyer (1958) 4 and Rübe & Flöte (1960) 5.

Many authors, for example Leist (1926) 6, Baserga et al. (1961) 7, Meyer et al. (1963) 8, Bond et al. (1967) 9, Schüle & Betzold (1969) 10 and Rissanen et al. (1967) 11, reported on the experimental studies about radiation osteodysplasia, but no reports in which mandibular changes similar to the actual clinical case are described have been published except for the papers by Medak & Burnet (1954) 12, Goggiel (1960) 13 and
Chambers et al. (1958)\textsuperscript{14).}

In the present study the authors observed some changes in the radiation injury of the human mature mandibles histopathologically and roentgenologically, by comparing each other.

**MATERIAL**

The materials for this study were the mandibles obtained at surgical operations carried out in our clinic and at autopsy, only one case, during the period from November 1966 to February 1972. These consisted of 32 cases of the irradiated group and 14 of the control or non-irradiated group. The primary sites of the former group, all of which were carcinoma, were the lower gingiva in 11 cases, the tongue in nine cases, the floor of the mouth in six cases and the other sites in six cases. The latter group consisted of ten cases of oral malignant tumor treated surgically without radiation therapy and four cases with other mandibular lesions treated surgically. As to the sex and age distribution, 28 cases of the former were males, while four cases were females, all of them being more than 30 years of age. Eleven cases of the latter group were males and three cases were females, the majority of them being more than 30 years of age.

**METHOD**

We classified first the 32 cases of the irradiated group of the material into the following subgroups:

1) Late radiation bone damage subgroup (LRBD) of 23 cases which were diagnosed clinically as osteoradionecrosis.

2) Preoperatively irradiated bone subgroup (PIB) of nine cases which consist of four cases resected following prooperative radiation therapy, four cases resected after radical radiation therapy and one case dying in the midst of radiation therapy.

We divided the irradiated group into open 20 cases and non-open 12 cases according to whether the mandible had communication with the outside or not, and also differentiated histologically ten cases with tumor infiltration in the mandible and 22 cases without tumor infiltration.

1. Histopathologic observations

The resected mandibular bones were fixed in 10\% neutral formalin or phosphate buffer formalin and were crosscut into 5–10 mm thicknesses at one or two parts of the molar or premolar region of the mandible for decalcified stained sections, and the adjacent segments of 10 mm in thickness were sawed for undecalcified sections, by referring to roentgenograms taken by the method which is described in item 2.

1) Decalcified stained sections

The specimens were decalcified by Plank & Rychlo's method and embedded partly in celloidin and mostly in paraffin. The embedded specimens in celloidin were sectioned crossly in 15–20 \( \mu \) thicknesses, the specimens in paraffin sectioned 6–8 \( \mu \) in thickness and the rest of the specimens were sectioned longitudinally. These sections were stained with hematoxylin-eosin and by the Elastica-Van Gieson staining.

2) Microradiography of undecalcified ground sections

After the specimens were embedded in the B.P.S. (Kyoto Kagaku Co.), ground sections of 70–100 \( \mu \) in thickness were prepared by the Thin Sectioning Machine (Bromwill Co.) and whetstones. With the X-ray Diffraction Generator Type PW 1008 (Phillips Co.) microradiographs were taken on the Kodak Spectroscopic Plate 659–0 under the condition of tube voltage of 22.5 KVp, tube current of 16–17 mA, FFD of 27 cm and time of exposure of 15–17
minutes, developed by the D-19 developer, fixed by the F-5 fixer and enclosed by the HSR.

2. Roentgenologic observations

Roentgenograms of the resected mandibles were taken on the non-screen type film MR (Sakura) under the condition of tube voltage of 50 KVp, tube current of 100 mA, time of exposure of 0.8–1.2 seconds and FFD of 8 cm. These roentgenograms were observed in detail, by referring to all the clinical roentgenograms.

Results

1. Histopathologic observations

1) Periodontal tissues

Periodontal tissues could be observed in seven cases of LRBD and six cases of PIB.

In the periodontal membrane inflammatory round cell infiltration was observed sometimes without relation to marginal or radicular periodontitis and with relation to the cell infiltration in the bone marrow spaces of the mandibular body.

In the alveolar bone advanced and irregular resorption was seen, but the osteoclasts could not be seen except in one case (Fig. 1).

2) Periosteum

Periosteum was observed in four cases of LRBD and seven cases of PIB.

The osteoblasts and the fibrocytes in the periosteum seemed to be decreased in number and a hyaline degeneration of the collagenous fibers was observed.

3) Compact bone

In the cortical bone the pronounced findings were the resorptive changes. Moth-eaten, strange and irregular resorption was seen in almost all cases of the irradiated group (Fig. 2). This type of resorption was not seen in the control group at all, and the degree and extension of this resorption were varied. In the cases sustained intensive resorption, cortical bone of both the lingual and buccal side or either of one side was destroyed throughout and the remaining part became less than the resorbed part (Fig. 3). In the other case slight resorption was seen here and there independently and scatteringly. These resorption cavities seemed to form intricate and irregular tunnels in the serial sections.

Resorption cavities independently of these sizes were occupied generally by connective fibrous tissues, the density of which was varied.

In the cases with infection, inflammatory cell infiltration was observed in the resorption cavities, and also findings, in which the figure of cellular and fibrous components was lost, were seen, and these were considered as dissolution of the tissues.

The osteoclasts in the resorption cavities could not be seen except for one case of LRBD in which the resorption cavities were seen except for one case of LRBD in which the resorption cavities were not so irregular (Fig. 4).

This resorption was more intensive in LRBD than in PIB and in the open cases than in the non-open cases.

Resorption of ossein around the lacunae, that is to say, enlargement of the lacunae was seen intensively and widely in LRBD. These enlarged lacunae were often seen collectively and with some of the lacunae the neighboring enlarged lacunae were partly fused (Fig. 5). Also the findings that these confluent lacunae were adjoined to the irregular and strange resorption cavities were frequently seen (Fig. 6).

As the expression of death of the osteocytes, we calculated the percentage of the number of the lacunae which were empty and in which the nuclei of the osteocytes could not be seen on the decalcified stained
sections.
On H-E-stained sections cut crosswise we distinguished nearly three parts, the buccal, lingual and basal parts, and also for each part four histologic elements of the outer basic lamellae, the interstitial lamellae, the Haversian lamellae and the inner basic lamellae. We counted 100 osteocyte lacunae in every histologic element and calculated the average percentage of the number of the lacunae in which the nuclei of the osteocytes could not be seen, excluding the parts of new bone formation. The results are shown on Fig. 7 and summarized as follows:

Interstitial lamellae—Percentages in the control group were about 50 to 90% and in PIB and LRBD about 70 to 100% and there was no difference between the control and the irradiated group.

Outer basic lamellae—Percentages in the control group were about 20 to 50%, in PIB 5 to 95% and in LRBD about 60 to 100% and the percentages in LRBD were considerably high in contrast with the control group.

Inner basic lamellae—Percentages in the control group were 5 to 30% and in the irradiated group 15 to 100%, and the percentages of the large part of the irradiated group were considerably high in contrast with the control group.

Haversian lamellae—In the control group about 5 to 40%, in PIB 50 to 95% and in LRBD about 50 to 100%. The percentages in PIB were somewhat high and the percentages in LRBD considerably high in contrast with the control group.

In the Haversian canal, as a fairly advanced change we observed the amorphous

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Fig. 7. Lacunae which were empty and in which the nuclei of the osteocytes could not be seen (CG: control group)
inside of the canal and findings that even blood vessels could not be distinguished on the decalcified H-E-stained sections. These findings showed considerably loose, eosinophilic, or somewhat basophilic appearance in contrast with the Haversian lamellae, and also as dense as the Haversian lamellae, eosinophilic or some staining between eosinophilic and basophilic or basophilic like the resting line (Figs. 8, 9). Findings of narrowing of the Haversian canal were also observed like the above-mentioned findings of complete plugging.

In some instances many osteoblasts along the wall of the Haversian canal and new bone formation were observed along with the findings of narrowing of the Haversian canal.

On the other hand, findings of plugging of the Haversian canal with mineral of a density higher than that of the normal bone were observed more clearly on the microradiogram (Fig. 10).

It seemed that these findings of plugging of the Haversian canal were observed not scantly but concentratingly in some regions, and that these findings were observed more frequently in LRBD.

On the longitudinal decalcified H-E-stained sections we observed the same findings of narrowing and plugging as in the Haversian canal (Fig. 11). These findings of the canal of Volkmann were also observed more frequently in the cases in which these findings of the Haversian canal were observed more frequently.

Findings of bone addition outside of the cortex were observed in fairly many cases of the irradiated group. Mode of this bone addition was classified into three types as follows:

i) Lamellated bone addition with the resting line but without the Haversian system

ii) Compact bone with relatively the premature Haversian system

iii) Proliferation of the bone trabeculae

Additional bone was necrotic in some cases but in most cases a new vital bone was seen surrounding the existing necrotic cortical bone. Between the new bone and the existing cortical bone, only a clear resting line lay partially (Fig. 12). In some cases the bone trabeculae with many osteoblasts proliferated in the area of the cortical compact bone which was absorbed and had disappeared (Fig. 13).

It seemed that these findings were observed more frequently and more remarkably in the cases which had a longer period from irradiation to resection and also in the areas relatively far from the areas which had sustained severe injury.

4) Spongy bone

Various degrees of resorptive changes in the trabeculae were observed. Irregular and severe resorption was also seen in some cases. In one case we observed an interesting finding that the basophilic linear substance which was maybe regarded as the resting line was left remaining without being absorbed (Fig. 14). As a relatively characteristic resorptive change we also observed the finding that a large part of the trabecula was incompletely absorbed leaving only the peripheral part of the trabecula (Fig. 15).

Few osteoclasts were found at the sites of these resorptive changes as in the cortex.

These resorptive changes of the trabeculae were more intensive in LRBD and in the open cases.

We also calculated the average percentage of the number of the lacunae in which the nuclei of the osteocytes could not be seen (Fig. 7). The percentages in the control group were about 20%, in PIB 10 to 100%, and in LRBD about 40 to 100%.
The percentages in the irradiated group were relatively high in contrast with the control group.

Findings of relatively dense trabeculae were observed in some cases in LRBD including the non-open cases. The trabeculae became relatively thicker and also increased in number.

In the control group the bone marrow had generally a fat marrow but fibrosis in the bone marrow was seen in connection with the tumor and/or inflammation. In the irradiated group fibrosis in the bone marrow was observed with considerably high frequency and with various degrees of density from loose and fine to dense and thick (Fig. 16). These findings of the fibrosis were seen more densely in LRBD and also in the open cases.

We also observed various degrees of inflammatory cell infiltration in the irradiated group, especially in the open cases in LRBD (Fig. 17). These findings were localized in the region of the alveolar bone or extended to the lower part of the mandibular body and also localized in the inferior mandibular border or extended to the mandibular canal or localized in the mandibular canal only.

As the inflammatory round cells, we observed lymphocytes most frequently and also polymorphonuclear leukocytes and plasma cells. These inflammatory cells infiltrated sometimes relatively scattering and sometimes densely forming an abscess.

Also in many open cases in LRBD we observed findings of tissue dissolution where amorphous material with irregular staining occupied the bone marrow spaces and the mandibular canal, and also the cellular and fibrous components could not be distinguished (Fig. 18).

In especially severely affected cases we observed dissolution of the inferior alveolar artery, vein and nerve in the mandibular canal (Fig. 19).

5) Vessels

The inferior alveolar artery which belonged to the medium-sized artery and its arterioles were observed and recorded.

Thickening of the tunica intima was seen in many irradiated cases. As a more remarkable change we observed findings of intensive narrowing of the inferior alveolar artery (Fig. 20) and complete obstruction of the arteriole (Fig. 21).

In elastic fibers — composing the tunica elastica interna which belonged to the tunica intima — considerably remarkable disarrangements were seen in almost all irradiated cases. We also observed the findings that the tunica elastica interna swelled and lacked clearness in staining partially or almost completely in the cross sections of the arteries, and that the lamellae of the elastic fibers increased in several lamellae (Fig. 22) and also were in fragments. Moreover, findings of disruption of the elastic fibers were observed in relation to the disruption of the wall of the vessels.

We observed findings of disruption (Fig. 23) and dissolution of the vessels which showed irregular staining and seemed to be amorphous.

These findings were more frequently seen in LRBD and especially in the open cases and seemed to be relatively severe in the arterioles than in the inferior alveolar arteries.

In the veins and capillaries no remarkable changes were seen.

6) Nerve

In severely affected cases findings of dissolution of the inferior alveolar nerve were observed as stated above, but minimal changes were not distinct.

2. Roentgenologic observations
Twenty-seven cases in the irradiated group, except several cases from which resected materials were too small to interpret the roentgenograms and intensively influenced by tumor infiltration, were classified into the following four groups based upon the radiographic changes:

Group I—Irregular osteolytic change, two cases. Group II—Marked osteosclerotic change, six cases. Group III—Irregular mixture of osteolytic and osteosclerotic change, 17 cases. Group IV—No remarkable changes two cases.

Findings of each group were as follows:

Group I—Fairly diffuse, ill-defined and irregular osteolytic change with unclear trabecular pattern was seen in the molar region of the mandibular body. A typical case is shown in Fig. 24.

Group II—Osteosclerotic change with diffuse and unclear trabecular pattern was increased in low, middle or high grade in the region of the upper or whole part of the mandibular body. The outline of the mandibular canal disappeared because of the sclerotic change and in some cases findings of collection of white small spots of about 1 mm in diameter were seen. A typical case is shown in Fig. 26.

Group III—Findings of irregular mixture of osteolytic and osteosclerotic change were seen at a glance. In a normal case marked radiopacity of several millimeters in width is seen corresponding to the cortex of the mandibular base. As findings of resorptive change, this radiopacity disappeared partly in various degrees of extent, and also linear radiolucency in every direction, partial enlargement of the mandibular canal and enlargement of the mental foramen and the mandibular foramen were observed. As more remarkable findings, a small round or round-like osteolytic change showed a moth-eaten appearance or honeycomb appearance diffusely and scantly, or solitarily in not only the mandibular body but also in the mandibular rami.

On the other hand, osteosclerotic change increased in a greater or less degree as in Group II as stated above was seen around or at a short distance from the region with an osteolytic change. Typical cases were shown in Fig. 29 and 31.

Group IV—No remarkable changes were seen.

Also the relation among these four groups and classification of the material of this study were as follows:

Group I—All cases were PIB, non-infective.

Group II—One case was PIB, five cases were LRBD and two cases in LRBD were the open cases.

Group III—Two cases were PIB, 15 cases were LRBD and LRBD were all open cases.

Group IV—All cases were PIB and non-open cases.

It seemed that most cases belonged to Group III, the open cases belonged mostly to Group III and the non-open cases in LRBD belonged to Group II.

3. Comparative observations between roentgenologic and histopathologic findings

In every group classified by the radiographic changes, we picked up the histopathologic findings which were considered to be able to affect the changes in radio-lucency and radiopacity.

Group I—Resorption of the cortex and the trabeculae was remarkable, especially the findings that the upper part of the two-thirds of the cortex of one side was almost resorbed being characteristic. Findings of resorption were mostly strange and irregu-
lar (Fig. 25).

Group II—Trabeculae of the spongy bone were fairly dense in the whole section or lingual half of the section. Also the findings of bony plugging of the Haversian canal and the canal of Volkmann were observed (Fig. 27, 28).

Group III—Histologic findings were irregular and diverse corresponding with the roentgenologic findings. Marked and irregular resorptive changes of the trabeculae and the cortex were seen corresponding with the moth-eaten appearance on the radiograph.

On the other hand, proliferation of the dense trabeculae of the spongy bone, apposition of the new fine trabeculae in the outer and previously resorbed region of the cortex and addition of the compact bone with only the lamellated structure or with the Haversian lamellae surrounding the necrotic cortex were observed. Also the findings of bony plugging of the Haversian canal and the canal of Volkmann were seen (Fig. 30, 32).

Group IV—No remarkable changes were seen in the histopathologic findings.

**Discussion**

The authors looked up the irradiated mature human mandibles in order to elucidate the pathologic nature of radiation osteodysplasia after radiation therapy for malignant neoplasms in the oral region histopathologically and roentgenologically and to make clear the mechanism of the occurrence of this radiation injury.

The mandible is more frequently involved by irradiation than the maxilla in radiation therapy for the malignant neoplasms in the oral region, because the mandible is nearer to the tongue and the floor of the mouth, which are predilection sites of the tumor, and metastases to the submaxillary lymph-nodes develop frequently. Therefore radiation injury develops more frequently in the mandible.

We could not find any reports about radiation injury in the periodontal tissue in the clinical cases. In the present study we observed findings of advanced and irregular resorption and these findings were considered to be directly or indirectly related to irradiation.

In the literature on the clinical cases are described findings of decrease of osteoblasts and hyalinization in the periosteum. In this study we observed the same findings and decrease of fibrocytes in the periosteum. It was considered that the periosteum was fairly affected by radiation.

Findings corresponding to bizarre resorption which Rowland et al. (1959) observed first on the microradiograph of radium-burdened bone were seen frequently not only on the microradiograph but also in the decalcified stained sections. Jowsey (1963) stated that these findings of bizarre resorption were found sometimes in the bone disorders involving rapid resorption such as osteoporosis, Paget's disease and renal failure and that the areas of particularly active resorption appeared microradiographically as very irregular surfaces with numerous uneven projections into the wall of the cavity. But Jowsey did not mention by what kind of cells this resorption occurred or by what kind of tissue these resorption cavities were occupied.

On the other hand, in regard to the clinically irradiated bone some authors described resorptive changes in the trabeculae and the cortex, but they did not refer to the participation of the cell components, and other authors described that osteoclasts were seen scatteringly in the region of bone resorption in some cases.
but not in the other cases. Bonfiglio (1953)\(^{17}\) and Vaughan (1956)\(^{15}\) stated that osteoclasts played a minimal role in the resorption of the irradiated bone and this opinion is noteworthy in contrast with the result of the present study. In experimental studies Gowgiel (1960)\(^{13}\), on the monkey, observed resorption of the trabeculae and the cortex by the osteoclasts.

In general, findings of bone resorption by the osteoclasts are seen in ordinary osteomyelitis of the jaw.

In the present study osteoclasts were not seen in almost any of the cases. With regard to these findings we speculated on the following two possibilities:

a) Osteoclasts disappeared rapidly after these had appeared and absorbed the bone actively.

b) There were other types of bone resorption without participation of the osteoclasts.

When a fairly large osteocyte lacuna is seen on the microradiograph it is called an enlarged lacuna. In general, osteocyte lacuna is large in the newly formed bone\(^ {25}\) and the enlarged lacuna is seen in vitamin D-resistant rickets and osteomalacia because of imperfect calcification\(^ {26}\).

On the other hand, it is recently believed that osteolysis by the osteocytes is present in the matured bone\(^ {28-29}\). These findings had been called Onkose by von Recklinghausen\(^ {20}\) and some researchers\(^ {26}\) had observed the same findings. Zawisch-Ossenitz (1927)\(^ {21}\), Ruth (1954, 1961)\(^ {22}\) and Bélanger\(^ {27}\) observed changes around the osteocyte lacunae, which were called Inseln von basophiler Substanz, intermediate resorption area or basophilic island and basophilia, respectively. Recently Bélanger \textit{et al.} (1963\(^ {27}\), 1969\(^ {25}\)) called this phenomenon osteocytic osteolysis. Osteocytic osteolysis is considered to be an active two-step resorption by the osteocytes in that calcioysis or halisteresis—disappearance of bone mineral—occurs, followed by resorption of the bone matrix.

Johnson (1964)\(^ {30}\) observed the enlargement of osteocyte lacuna as one of the findings of aseptic bone necrosis and called it oncosis. And he described that this finding was related to Frost's halo volume, Litttle's foci of structureless degraded collagen and Bélanger's osteocytic osteolysis. Ruthschauser & Majno (1951)\(^ {31}\) have observed perilacunar resorption as the result of cellular activity. They called it "physiological necrosis" and described the phenomenon as occurring at the center of the trabeculae in the spongy bone and at the periphery of the Haversian system in the compact bone.

Reports of these researches were about the bones of the extremities and ribs but never about the jaws.

In the irradiated long bone Ewing\(^ {19}\) observed an enlargement of the osteocyte lacunae and canaliculi and Rowland \textit{et al.}\(^ {18}\) recognized the enlarged lacunae, but nobody described about the mandible.

From the result of the present study we speculated that a part of the osteocyte function was apparently reinforced and enlargement and confluence of the osteocyte lacunae appeared at a period of process in which the osteocytes were going to die by some lethal factors, and also it was considered that there might be relevancy between the enlarged lacunae and bizarre resorption.

As findings of irradiation changes of the osteocyte reported previously, decrease of staining\(^ {19,21}\), piknosis\(^ {8,18,32}\), degeneration of osteocyte\(^ {8,18,28}\), destruction\(^ {1,19}\), Hyperchromasie\(^ {19}\), necrosis\(^ {8,9,13,35}\), empty lacunae\(^ {8,9,10,28}\) and ghost space\(^ {4}\) are described.

Weinmann & Sicher (1955)\(^ {37}\) stated that
empty lacunae were seen frequently in normal interstitial lamellae of the cortex, and Frost (1960)\textsuperscript{28} described that there was a steadily increasing incidence of empty lacunae with increasing age in the undecalcified basic fuchsin stained sections of long bones and ribs. Weinmann & Sicher\textsuperscript{27} stated that necrosis of the bone was characterized microscopically by degeneration and final necrosis of the osteocytes, Pritchard (1956)\textsuperscript{26} described that osteocyte death was synonymous with bone necrosis and Frost\textsuperscript{40} recommended that bone necrosis ought to have been expressed as for example as 30\% death of the osteocytes or total death of the osteocytes.

According to the result of the present study, in the cases which seemed to be clinically affected severely, injury of the osteocytes were severe as well and also it was considered that the osteocytes sustained already considerable injury even if the symptoms did not develop yet.

In general, as bone sclerosis there are two modes of proliferation or addition of calcified tissue and hypermineralization\textsuperscript{41}. In ordinary osteomyelitis or periostitis findings of reactive new bone formation are frequently seen. About the new bone formation in the irradiated bone some authors were negative\textsuperscript{28} and fairly many authors affirmative. Meyer\textsuperscript{4} recognized findings of new bone formation with light staining quality in the irradiated human mandible and regarded these findings as the active changes of early irradiation stage. In experimental studies some authors observed proliferation of the osteoid tissue\textsuperscript{14,42}, new dense trabecular bone formation with an eburnated appearance\textsuperscript{13} and apposition of immature cancellous bone under the periostium or outside the necrotic bone\textsuperscript{49}. In the present study, the cases in which the active new bone formation was progressive at the time when mandibulectomy was performed were rather less, but the findings by which it was considered that new bone formation was active at a certain period after irradiation were seen in many cases.

Findings of a new bone formation are to be classified as follows:

a) Trabecular proliferation in the spongy bone
b) Trabecular proliferation outside of the cortex
c) Addition of the compact bone (with or without the Haversian system) outside of the cortex
d) Addition to the Haversian canal or the canal of Volkmann

Weinmann & Sicher\textsuperscript{27} described that when a sequestrum was formed and involucrum formation was seen surrounding the sequestrum in osteomyelitis, a layer of granulation tissue existed always between the sequestrum and the new bone. In the present study when a new bone formation was seen surrounding the necrotic bone, only partially resting line lay between the two layers and no granulation tissue was seen. It was thought that apposition of the lamellated bone occurred or that the newly formed fibrous trabecular bone was replaced with the compact bone by remodeling.

In general, it is considered that the osteoblasts are more sensitive to radiation than the ostoclasts\textsuperscript{4,5,13,20,28,43,44}. In the present study, the findings of osteophytes were not seen in the cases in which the doses of irradiation were relatively small or in the non-open cases in which, even if the doses of irradiation were considerably large, the duration from irradiation to resection was relatively short, but findings of remarkable osteophytes were seen in the open or non-open cases with infection in
which the duration from irradiation to resection was considerably long. From these findings it seems to be true that the osteoblasts in the irradiation field have a relatively high sensitivity to radiation but the osteoblasts which differentiate under a certain condition are able to take part in the active formation of a new bone even under circumstances which have received some influence of irradiation.

Rowland et al.\textsuperscript{181} described the findings of the plugged canals on the microradiograph of the irradiated long bones obtained clinically and Jee (1964)\textsuperscript{36} observed findings of plugged Haversian canal in the decalcified stained sections of the irradiated long bones of the dog. These findings were characterized by the intake of radioisotopes (the former : Ra\textsuperscript{226}, the latter : Pu\textsuperscript{239}). We could not find any description of these findings following external irradiation and interstitial irradiation.

On the other hand, regarding the non-irradiated bone, some authors\textsuperscript{25,41,45} observed findings of rare plugged canals on the microradiograph and described an increase in frequency with increasing age and also being related to arteriosclerosis\textsuperscript{11}. But Manson & Lucas\textsuperscript{46} and Ito\textsuperscript{47} did not describe findings of plugged canals on the microradiograph of the mandible and stated that changes with increasing age were not clearly observed in the mandible as compared with the femur and other long bones. In the present study we did not observe these findings in the non-irradiated group.

In general, the bone marrow of the normal mandible of the aged person is a fat marrow. In the literature changes in the bone marrow of the irradiated bone were almost similar in both the clinical and experimental studies. These were exchange by fibrous tissue\textsuperscript{4,5,8,23}, degeneration\textsuperscript{9,23}, inflammatory cell infiltration\textsuperscript{4,12,14,28} and abscess\textsuperscript{23}. In the present study such findings as mentioned above were observed and moreover findings of tissue dissolution were considered to be the same as the amorphous granular material described by Thoma & Goldman\textsuperscript{28}. And the findings of inflammatory cell infiltration around the inferior alveolar nerve seemed to be related to the development of pain in the patient.

Arteries which nourish the mandible are the inferior alveolar artery, the sublingual artery, the submental artery, the lower labial artery, the lingual artery and branches of the facial artery. But in the present study we observed mainly the inferior alveolar artery which belonged to the medium-sized artery and its arterioles.

In the literature regarding the irradiated mandible and long bones there are described proliferation of the endothelial cells\textsuperscript{1,5}, vacuolisation\textsuperscript{10}, degeneration\textsuperscript{11}, swelling\textsuperscript{1,19} and necrosis\textsuperscript{11} of the endothelial cells, thickening of the tunica intima\textsuperscript{13}, narrowing or occlusion because of fibrosis\textsuperscript{4,48,49}, formation of thrombi\textsuperscript{4,8,10,28,48,49} and obliterative endarteritis\textsuperscript{48,50}. One author\textsuperscript{1} described that these changes occurred relatively early after irradiation and called it the early inflammatory phase. In the present study we could not observe any clear findings of the formation of thrombi but observed findings of such severe thickening of the tunica intima as obliterative endarteritis and regarded these important findings as proof of disturbance of circulation. MacLenann (1955)\textsuperscript{43} observed findings of the destruction of the elastic fibers in the irradiated human mandible and Rubin & Casarett (1968)\textsuperscript{1} described findings of separation and fragmentation of the elastic fibers in the irradiated aorta and carotid artery which belonged to the artery of the elastic type.
In the present study we observed findings corresponding to the so-called elastosis and contrarily disruption or dissolution of the elastic fibers. The former was considered to be the findings of reactive changes and the latter to be findings of degenerative changes, and both findings were regarded as changes due to radiation damage. Findings of disruption and dissolution of the vessels seemed to be related to the secondary changes due to infection, but no description about these findings was seen in the literature.

Description of the findings of radiation damage to the vein was not seen in the literature. In the present study changes of the vein were not clear, and it was considered that the vein was not apt to sustain radiation damage.

Bond et al. observed fibrous thickening of the wall of the vessels or occlusion of the lumen of the vessels in the Haversian canal in the irradiated mandible of the monkey, and Jee described findings of the lack of the vessels in the Haversian canal in the irradiated long bone of the dog. In the present study we observed findings of occlusion of the vessels in the Haversian canal proving the disturbance of circulation.

With regard to the radiation sensitivity of the vessels, Gowgiel described that the arteriole was affected first, the medium-sized artery was sometimes affected and the capillary and the vein were not affected. We roughly speculated a line of radiation sensitivity as the arteriole ≥ the medium-sized artery ≥ the capillary or the precapillary ≥ the vein, from the result of the present study.

In the literature we could not find any description of the morphologic changes of the peripheral nerve by irradiation. Rubin & Casarett described that the nerve axon fibers were extremely resistant to the direct destructive action of radiation and that the degeneration or necrosis of nerve axon developed as a secondary change following the vascular damage. Findings obtained in this study were considered to be related to secondary infection and also to the loss of sensation in the patients.

Roentgenologic findings of the human irradiated bone described in the literature are summarized as follows:

1) Resorptive change only
2) Sclerotic change only
3) Mixture of resorptive and sclerotic change

It seemed that in the experimental study roentgenologic findings belonged to 1) mentioned above. In this study roentgenologic findings of a great number of the cases belonged to 3), and it was considered that the roentgenologic findings were based on the sclerotic change.

Histologic findings which were considered to have a great influence on the roentgenologic findings are summarized as follows:

1. Resorptive change — Findings of resorption of the cortex and the trabeculae which were featured by irregular and bizarre resorption.

2. Sclerotic change — Proliferation of the trabeculae in the spongy bone and outside of the cortex and addition of the compact bone outside of the cortex.

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EXPLANATION OF FIGURES

Fig. 1. Advanced resorption in the alveolar bone (H-E stain \times 50)

Fig. 2. Strange and irregular resorption in the cortical bone (Microradiograph \times 100)

Fig. 3. Intensive and irregular resorption in the cortical bone (H-E stain Original magnification, \times 80)

Fig. 4. Osteoclastic resorption cavity in the cortical bone (H-E stain \times 100)

Fig. 5. Enlarged and confluent lacunae (Microradiograph \times 150)

Fig. 6. Enlarged and confluent lacunae adjoined to the irregular and strange resorption cavities (H-E stain \times 200)

Fig. 8. Plugging of the Haversian canal showing basophilic and considerably loose appearance in contrast with the Haversian lamellae (H-E stain \times 300)

Fig. 9. Plugging of the Haversian canal showing considerable eosinophilic appearance (H-E stain \times 300)

Fig. 10. Plugging of the Haversian canal with mineral of a density higher than that of normal bone (Microradiograph \times 100)

Fig. 11. Plugging of the canal of Volkmann showing basophilic appearance (H-E stain \times 100)

Fig. 12. Additional compact bone interlaying resting line outside of the necrotic bone (upper part) (H-E stain \times 50)

Fig. 13. New bone trabeculae with many osteoblasts in the region of the absorbed cortical bone (H-E stain \times 120)

Fig. 14. Irregular and intensive resorption of the trabecula. Arrow shows basophilic linear substance (H-E stain \times 60)

Fig. 15. Relatively characteristic resorptive change of the trabecula (H-E stain Original magnification, \times 120)

Fig. 16. Intensive fibrosis in the bone marrow (H-E stain \times 60)

Fig. 17. Intensive inflammatory cell infiltration in the bone marrow (H-E stain \times 100)

Fig. 18. Necrosis and tissue dissolution in the bone marrow (H-E stain \times 40)

Fig. 19. Necrosis and tissue dissolution in the mandibular canal (H-E stain \times 30)

Fig. 20. Intensive narrowing, disarrangement and proliferation of the elastic fibers in the inferior alveolar artery (E-V stain Original magnification, \times 200)

Fig. 21. Complete obstruction and disarrangement of the elastic fibers in the arteriole (E-V stain \times 350)

Fig. 22. Proliferation of the elastic fibers in the inferior alveolar artery (E-V stain \times 100)

Fig. 23. Disruption of arteriole (E-V stain \times 200)

Fig. 24. Group I. Irregular osteolytic change in the upper part of the molar region

Fig. 25. Crosscut section in the region of the arrow of Fig. 24. Intensive resorption (H-E stain Original magnification, \times 5)

Fig. 26. Group II. Diffuse osteosclerosis in the region of the mandibular body

Fig. 27. Crosscut section in the region of the arrow of Fig. 26. Proliferation of the bone trabeculae in the region of the inner side of the lingual (L) cortical bone (H-E stain Original magnification, \times 5.5)

Fig. 28. Microradiograph in the same region as Fig. 27. Marked proliferation of the bone trabeculae in the spongy bone (Original magnification, \times 11)

Fig. 29. Group III. Pathologic fracture, moth-eaten or honeycomb appearance in the region of the molar and mandibular rami and also marked osteosclerosis in the premolar and anterior region

Fig. 30. Crosscut section in the region of the arrow of Fig. 29. Additional compact bone outside of the cortical bone on the lingual side (L), the lower part of the buccal side (B) and the region of the lower margin of the mandible. And also proliferation of the bone trabeculae in the space of the absorbed cortex in the lower part of the lingual side (H-E stain Original magnification, \times 5)

Fig. 31. Group III. Partial defect in the region of the lower margin of the mandible, linear radiolucency and also osteosclerosis

Fig. 32. Crosscut section in the region of the arrow of Fig. 31. Intensive destruction on the lingual side (L) and additional compact bone on the buccal side (B) (H-E stain Original magnification, \times 4.5)
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Fig. 8.

Fig. 9.

Fig. 10.

Fig. 11.

Fig. 12.

Fig. 13.