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EFFECTS OF ROENTGEN IRRADIATION OF THE JAWS ON SOCKET HEALING IN YOUNG RATS

by

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Extraction of teeth in areas of the jaws which have previously been exposed to ionizing irradiation may give rise to serious complications. Extensive destruction of the jaws, especially the mandible, with osteomyelitis and sequestration may result.

Various terms have been applied to this condition: osteoradionecrosis, radio-osteonecrosis, irradiation-osteonecrosis, radiation osteitis, and radiation necrosis. For reasons, which are to be discussed later, the term radio-osteomyelitis will be used in this paper.

In humans, the clinical manifestations of radio-osteomyelitis of the jaws have been described in numerous reports, of which only a few have included histopathologic findings (*Bernier* 1948, *Bianchi* 1943, *Mac Lennan* 1953, *Meyer* 1958). The data thus obtained are valuable in providing information about certain tissue changes, but systematic knowledge regarding the pathogenesis of this lesion and the effects of various therapeutic measures cannot be expected from investigations of this nature.

Animal experiments aimed at a clarification of these problems are few and have employed a diversity of techniques. *Gowgiel*

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(1960) exposed the jaws of young monkeys to roentgen irradiation in fractionated doses ranging from 4,500 r to 11,000 r. A few of the animals had a first molar extracted 2 to 18 months after the irradiation. Normal socket healing was observed in the 4,500 r and 5,500 r groups where the extractions were done four months after the irradiation, and in the 7,500 r group, where one extraction was done 19 months after the irradiation. In the 8,500 r group, where one extraction was done two months after the irradiation, sequestration and osteomyelitis of the socket area with necrosis of the gingiva developed within 20 days after the extraction. The dominant histologic picture was that of an infectious process. Vascular changes involving the arterioles and resembling arteriolosclerosis were seen as early as one and a half weeks after the irradiation. These vascular changes were considered as primary radiation effects, but not as the initiating factors in radio-osteomyelitis. The latter status was ascribed to the direct radiation damage to the osteocytes. No detailed histologic study of the socket healing was performed.

Chambers, Ng, Ogden, Coggs, & Crane (1958) irradiated the mandibles of adult dogs with fractionated doses of roentgen rays ranging from 3,000 r to 8,000 r. One group was irradiated with all of the teeth present while another had the right posterior teeth removed 7 to 28 days prior to the irradiation. A "surgical" procedure was used whereby a mucoperiosteal flap was retracted, the buccal cortical plate removed, and the teeth sectioned to facilitate atraumatic extraction. The extractions were followed by an extensive alveolectomy and the mucosal margins were trimmed and sutured. Penicillin was administered intramuscularly. Ulcerations of the alveolar soft tissue with concomitant osteomyelitis were dominant in the dentulous areas, whereas it was a rare finding where the teeth had been removed. It appeared that an ulcerative gingivitis gave rise to the portal of entry through which the inflammation spread to the bone. No osteomyelitis developed in the edentulous areas when the mucosa remained intact. Bone formation was noted even in areas that had been exposed to 8,000 r, both in connection with osteomyelitis and in the healing socket under an intact mucosa.

Stein, Brady, & Raventos (1957), using 100 days old rats, extracted the three upper right molars and implanted radon seeds

immediately lateral to the sockets at the time of extraction and at various intervals after, ranging from 4 to 20 days. The animals were killed 8 to 28 days after the extraction, the socket area having received doses of 1,200 r to 6,800 r. Severe changes were noted when the irradiation was started at the time of extraction or four days later. There were no osteoblasts present, which resulted in the absence of new bone, and only few osteoclasts were present. There was a decreased number of fibroblasts, and soft tissue necrosis and degeneration at the surface of the socket. The severity of these changes diminished as the interval between extraction and onset of radiation became longer. Neither bone necrosis nor osteomyelitis were described, and vascular changes were not evident within the experimental period.

Zerosi (1940) investigated the histopathology of radiation damage to the jaws of young dogs. After irradiation from external and internal sources respectively, bone resorption, bone necrosis, fibrous transformation of the marrow, hemorrhage, and peri- and endarteritis were noted. No teeth were extracted. Only one of the reports *(Stein et al.* 1957), offers a detailed histologic study of the socket healing process as observed during various postoperative periods, and, as mentioned above, radio-osteomyelitis was not produced.

It is well known that irradiation treatment of malignant tumors in the oral region causes a protracted, if not permanent, decrease in the resistance to local infection. Many reports relate the fatal effects of ordinarily trivial infections such as pulpitis, periodontitis, tooth extraction sequelae, and ulceration of the gum in previously irradiated jaw areas. This has led to the advocating of certain prophylactic measures aimed at avoiding post-irradiation infections. Most authors agree that irradiation treatment should be preceded by a thorough dental treatment whereby all hopelessly involved teeth are extracted and those remaining brought in the best possible condition. Further, it is generally recommended that all teeth, or at least all diseased teeth, in the field of irradiation should be removed before the onset of treatment (*Cook* 1952, *Cutler* 1951, *Daland* 1941, *Del Regato* 1939, *Heidsieck* 1957, *Lawrence* 1946, *Lympius* 1960, *Oelssner* 1960, *Thoma & Goldman* 1960, *Topazian* 1959). However, more conservative views have also been propounded (*Kaplan* 1955), and contrary views

were expressed by *Quick* (1950), who claimed that there was less danger of osteomyelitis when the necessary extractions were carried out in a clean mouth some time after the irradiation, and by *Wildermuth & Cantrill* (1953), who observed that irradiation before reconstruction of the alveolar ridge after prophylactic extraction resulted in permanently delayed remodeling of the jaw and a persistent threat to the integrity of the overlying mucosa. They further stated that teeth can be extracted if they become diseased after irradiation, provided meticulous care is observed and antibiotics given.

In the literature available to the author no reference to experimental work comparing the effects of pre- and postirradiation extractions has been found.

The objectives of the present work were the following:

1) To develop experimental procedures which would produce radio-osteomyelitis in laboratory animals, and allow the animals to live long enough to secure a study of the entire healing process following tooth extraction.
2) To examine histologically the healing process when the extractions were done prior to as well as after the irradiation.
3) To describe elementary histologic tissue changes, and thereby attempt a clarification of the pathogenesis of radio-osteomyelitis.

MATERIAL AND METHODS

The rat was chosen as experimental animal because of the rapid healing process after extraction, and because standards for the normal healing are well established in this animal (*Frandsen & Becks* 1962, *Huebsch, Coleman, Frandsen, & Becks* 1952).

Pilot study

In order to test the roentgen dose-survival time relation under the presupposed experimental conditions, the following pilot study was carried out.

Thirty male rats were divided into three groups, each comprising seven experimental and three control animals. When

approximately 56 days old, the rats of each group received single doses of 1,000 r, 2,000 r, and 3,000 r roentgen irradiation respectively, administered to the heads, the rest of the animals being shielded by lead.

In group I (1,000 r), the rats had the lower left first molar extracted 10 days after the irradiation, and they were then killed after various post-operative periods. It appeared that the treatment caused only slight interference with socket healing and weight increase. The irradiated rats of groups II and III (2,000 r and 3,000 r) all became moribund or died within 9 ± 1 days, making impossible the extractions and the study of post-operative healing.

Thus it was evident that the conditions chosen were unsuited for an experiment aimed at producing severe alterations in the socket healing, and to study these changes over a post-operative period of at least 40 days. Consequently, another experiment, primarily involving a change in the shielding of the animals, was carried out as described below.

Present study

Fifty-eight male rats of a Wistar strain were caged individually in wire bottom cages, fed a standard stock diet (Leo Pharmaceutical Co.), and allowed tap water *ad libitum*. They were weighed twice a week, and, at the beginning of the experiment, divided into 3 groups according to roentgen dose and time relation of irradiation to extraction.

Group I (20 rats) was irradiated when the rats were 52 days old and had a molar extracted when they were 60 days old. Group II (21 rats) had a molar extracted when 55 days old, and irradiated when 60 days old. Group III (17 rats) was irradiated when 55 days old, and had a molar extracted when 63 days old. Groups I and II received 1,725 r, and group III 2,400 r to the jaws in one treatment.

Within each group the animals were killed after various post-extraction periods ranging from 2 to 63 days. Each of these subgroups had one or two unirradiated rats serving as controls. (Table 1).

Table 1

Distribution of animals.

		Post-extraction interval								No. of rats	No.of irradiated rats with radio-osteomyelitis*)
		2 d	5 d	7 d	12 d	26 d	40 d	54 d	63 d		
Group I	exper.	2	2		3	3	4			14	6 (2)
1,725 r — extr.	contr.	1	1		1	1	2			6	
Group II	exper.			2	2	2	3	2	2	13	1 (1)
extr. — 1,725 r	contr.			1	1	1	2	1	2	8	
Group III	exper.	2	2		2	2	2			10	5 (2)
2,400 r — extr.	contr.	1	2		2	1	1			7	
Total no. of rats:										58	

*) The numbers in parentheses after the number indicating rats with radio-osteomyelitis represent animals killed shortly after the extraction and showing histologic evidence of beginning radio-osteomyelitis.

The anesthesia used for irradiation and extraction was accomplished by intraperitoneal injection of a 1 per cent solution of Sodium Nembutal® (0.6—0.8 ml per 100 g body weight). The lower left first molar was extracted using the technique previously described (*Huebsch et al.* 1952). At the time of irradiation, the control animals were anesthetized as well in order to secure identical conditions.

The physical factors of irradiation were: 200 KV, 20 Ma, filters: 0.5 mm Cu+conic Al-filter (1—7×0.32 mm), F.S.D. 41 cm, dose rate 46—48 r per minute. The amount of radiation administered was measured in air at the site of the rat head.

For irradiation purposes the anesthetized rats were mounted in a circular arrangement on a board and held in position by pins through the paws. On top of the board was placed a plexiglass table allowing just enough space for the rats between board and plexiglass. The latter supported the shielding which consisted of a circular plate of lead, 2 mm thick, in which an 8 mm broad circular band was cut out. (Text-figure 1). By careful mounting

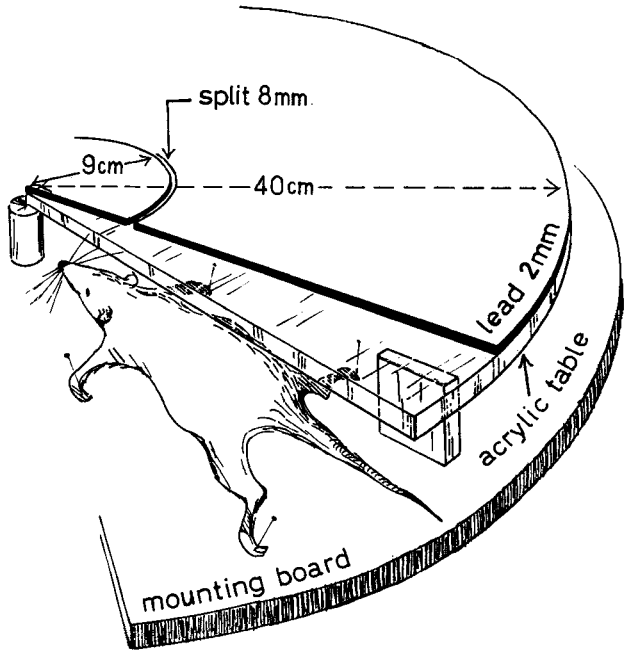

Fig. 1.

Mounting and shielding of rats.

of the rats it was arranged, that the molar region was situated immediately under this opening in the lead. The tissues thus irradiated include all upper and lower molars, the apical third of the lower incisors, possibly the germinative cells of the upper incisor, part of the facial airways, the eyes, and the very anterior part of the brain. Neither the hypophysis nor the major salivary glands were in the direct beam.

The animals were killed by decapitation after ether inhalation. The heads were skinned and fixed in 10 per cent neutral formalin. Before decalcification in 5 per cent nitric acid, the heads were cut sagittally in the midline and each half roentgenographed. The left lower jaws were embedded in paraffin and celloidin, sectioned mesio-distally, and stained with hematoxylin-eosin and van Gieson's connective tissue stain. The healing was studied on serial sections of the distal socket of the first molar.

RESULTS

Gross observations

The irradiated animals of all three groups exhibited similar gross pathologic changes. Those of Group III showed a tendency towards more severe alterations.

About one week after the irradiation the following pathologic conditions were noted: epilation, erythema, and exudation of the irradiated skin area, exudation from the nose, and rusty deposits around the nostrils and on the vibrissae. Intraorally, hyperemia, fibrinous exudate, and in some instances, ulcerations of the floor of the mouth were noted. At the extraction site of some of the animals, necrotic lesions with sequestration were seen, occasionally with sublingual abscesses and oro-cutaneous fistulae.

In the animals of the later post-extraction periods accentuated curvature of the upper incisors was noted, and occasionally, fracture of a lower incisor.

Composite weight curves made by averaging the individual curves of experimental and control rats within each group are illustrated in text-figure 2. It is noted that the experimental procedures had no effect on the weight increase of the rats of Group II. In Group I there was a slight plateauing of the curve for a few days following irradiation and extraction. In Group III, the larger roentgen dose caused a distinct weight loss in the days after irradiation and extraction. However, weight gain was resumed about 10 days after the irradiation.

Histologic observations

Histologic examination of the material revealed a rather frequent complication of the healing process by food impaction and bone and root fragments. This was the case in irradiated animals as well as controls. In order to arrive at a correct interpretation of the changes due to radiation damage, it was therefore necessary to analyze, in the control rats, first the undisturbed healing process, and then the various modifications of this process caused by the presence of food particles and bone and root fragments.

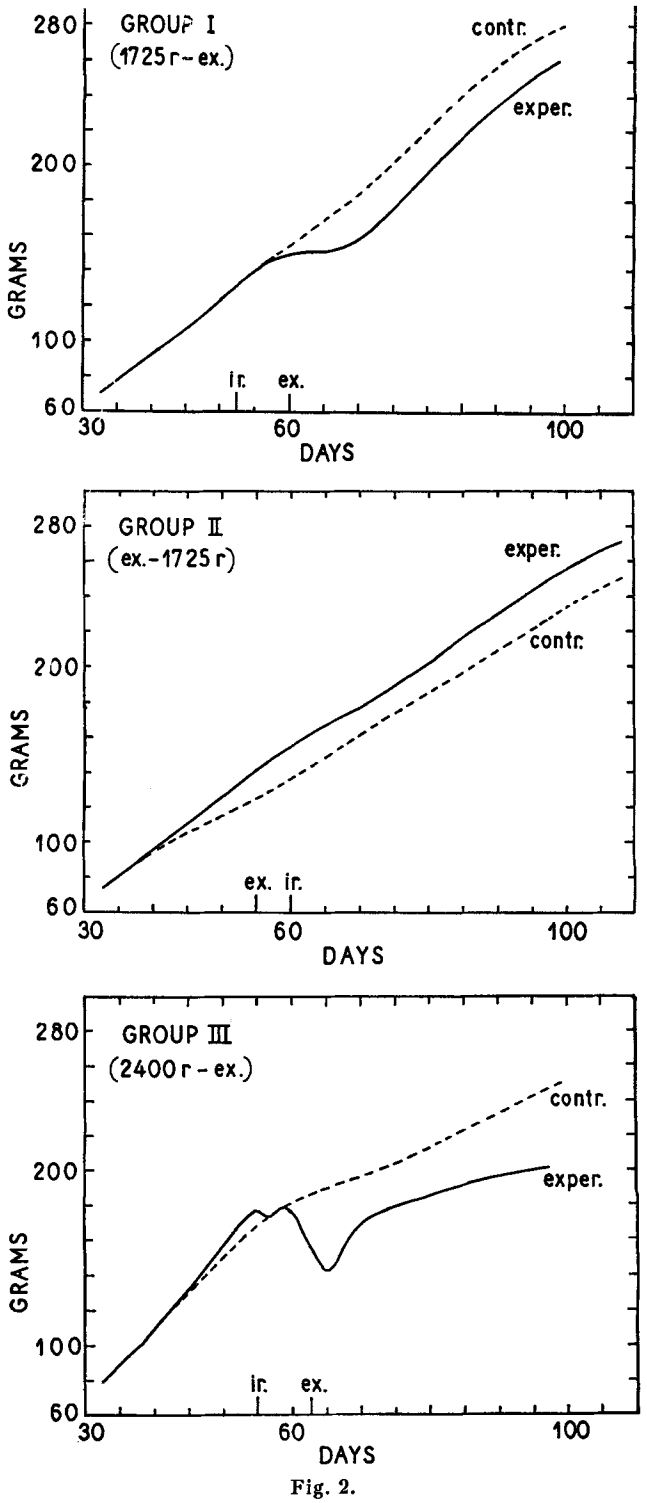

Fig. 2.

Composite weight curves.

Healing in control rats

Standards for the undisturbed socket healing in normal rats of the same age as in the present study have been established previously (*Frandsen & Becks* 1962, and *Huebsch et al.* 1952). They may be summarized as follows: Organization of the blood clot begins about 24 hours after the extraction indicated by ingrowth of capillaries and young fibrous tissue. After three to four days the socket is filled with a young cellular fibrous tissue, and bone formation is initiated in the fundus of the alveolus four to five days after the extraction. After two weeks young woven bone fills the entire socket. Resorption and replacement of the young bone by lamellar bone takes place in the following three weeks, and approximately six weeks after the extraction the bony healing is completed. Epithelial healing begins after two to three days and is completed five to eight days after the extraction. Examples of disturbed healing in control rats are illustrated in Plate 1. Fig. A is from a rat killed seven days after the extraction. Normally, epithelial healing would be completed and the formation of young woven bone well advanced at this time, but the presence of sequestra, caused by the extraction trauma, has evoked an inflammatory reaction and prevented epithelial and fibrous healing of the superficial parts of the socket. Deeper, the clot has been organized, and new bone is being formed. In Fig. B, 12 days after the extraction, a small sequestrum, partly encapsulated by epithelium, has prevented the bony healing of the upper part of the socket whereas new bone has been formed in the fundus. Fig. C illustrates the effect of food impaction 26 days after the extraction. A plant fiber has been pushed into the socket, causing inflammation and bone resorption. No new bone is seen. The effect of retention of a root is shown in Fig. D, 40 days after the extraction. The upper part of the root and a small sequestrum have been encapsulated by epithelium, and the lower part extends partly into the socket where it has prevented bone formation.

Healing in irradiated rats

In Plate 2 are illustrated examples of healing from Group I which received 1,725 r to the jaws, and then, eight days later, had the extractions performed. The socket, demonstrated in Fig. A,

is from a rat killed two days after the extraction. The socket is filled with a blood clot and remnants of the periodontal membrane are still distinguishable. After five days, Fig. B, the blood clot has been organized by young fibrous tissue. Pronounced resorption of the adjacent alveolar bone is noted, numerous osteoclasts are present, and only little bone is left. The marrow tissue is undergoing a change from hematopoietic to fibrous tissue.

In Fig. C, 26 days after the extraction, sequestra are noted at the surface of the socket area, where the healing of the epithelium is disturbed. The sequestra are surrounded by inflammatory cells, and deeper in the socket new bone has been formed. In another rat, also killed 26 days after the extraction, more severe changes are seen (Fig. D). The entire socket area is practically devoid of bone to the extent at which the continuity of the mandible, at least in the plane of sectioning, has been lost. Apart from an area next to the second molar epithelial healing is completed. A small sequestrum and a pronounced inflammatory reaction are seen in the underlying fibrous tissue. New bone is being formed in a small area at the base of the mandible.

Extensive destruction of the mandibles of two rats, also from Group I, is illustrated in Plate 3. In Fig. A, 12 days after the extraction, the entire alveolar process and the base of the mandible of the first molar region have been destroyed. The area is occupied by necrotic bone and root fragments as well as other debris. The overall picture is one of vast and progressive tissue destruction with no attempts at repair. A similar, but even more severe condition is shown in Fig. B, 40 days after the extraction. Here, the destruction has spread even further, involving major portions of the periodontium of the second molar and the subcutaneous muscle tissue of the chin. Remnants of the base of the mandible are seen as sequestra surrounded by pus. Figs. A and B are considered as illustrations of manifest radio-osteomyelitis.

Summarizing, it may be stated that the rats of Group I exhibited various influences of the irradiation on the healing ranging from retardation of bony healing to complete destruction of the socket area and adjacent tissues. Of 14 irradiated rats in this group, six developed manifest radio-osteomyelitis and two of the animals killed at early post-extraction intervals showed the initial changes of this lesion, namely absence or severe inhibition of the

early reparative processes: organization of the clot, epithelial proliferation, and bone formation. These changes were associated with early and excessive bone resorption.

The rats of Group II were irradiated with 1,725 r five days after the extraction. Representative animals of this group are illustrated in Plate 4. Fig. A shows the condition seven days after the extraction, two days after the irradiation. Food particles and a small sequestrum are seen at the surface of the socket where there is no attempt at epithelial healing. The socket is filled with granulation tissue with an inflammatory reaction towards the surface. Bone formation is negligible whereas bone destruction dominates. Twelve days after the extraction (Fig. B), epithelial healing has occurred, and the socket is partly filled with new bone. Fig. C shows a root left in the socket 40 days after the extraction. The root canal establishes a communication with the oral cavity, and a focus of inflammation is noted at the apex where some bone has been resorbed. In another specimen (Fig. D), 64 days after the extraction, complete healing has taken place. Lamellated bone has replaced the young woven bone, and some hematopoietic marrow has been established.

In this group of 13 irradiated rats, only one developed manifest radio-osteomyelitis and one showed the initial changes. The other animals exhibited strikingly less interference with the healing process than those of Group I.

The rats of Group III were irradiated with 2,400 r and had the molar extracted eight days later (Plate 5). In Fig. A, two days after the extraction, only the superficial part of the blood clot has been organized. Further down, fibroblast and endothelial cell proliferation is negligible. Twelve days after the extraction (Fig. B), epithelial healing is not completed, and pus cells in connection with a small sequestrum are seen at the surface. The fibrous tissue filling the socket is poor in cells, and no bone formation has taken place. In another rat from the same period (Fig. C), a root has been left in the socket. Portions of the alveolar wall are seen as sequestra next to the root covered by pus cells. No epithelium can be seen and extensive bone resorption has taken place. Forty days after the extraction (Fig. D), practically all bone in the socket area has been resorbed or expelled as sequestra. The presence of sequestra and of foreign bodies at the surface of

the socket has prevented epithelial healing. A part of a sequestrum surrounded by pus cells is seen in the fibrous tissue.

In this group, five out of 10 irradiated animals exhibited frank radio-osteomyelitis, and two the initial changes. In some of the cases with radio-osteomyelitis, the process had a tendency towards an even more progressive course than those of Group I (e.g. Fig. A, Plate 6). In this rat severe damage is evident as early as five days after the extraction. A part of the distal root has been left in the socket and a hematoma is covering the extraction site. No epithelial proliferation or ingrowth of fibrous tissue into the clot is taking place. Extensive bone resorption is seen, and the tissues anterior to the socket area are heavily inflamed. A peculiar finding from another animal of this group is illustrated in Fig. B, 40 days after the extraction. Loss of the vertical dimension of the alveolar process is evident, but healing has taken place after the extraction. The sockets can no longer be distinguished, and epithelial closure has occurred, although somewhat disturbed by a sequestrum. Despite this healing tendency, the periodontal tissues of the second and third molars have suffered severe damage. Almost all the alveolar bone has been destroyed to the extent that the third molar has been practically exfoliated. Bacterial plaques are seen on the roots, and the picture resembles that of a progressive periodontitis.[1]

Histopathology of radio-osteomyelitis

Regarding the pathogenesis of radio-osteomyelitis following tooth extraction, it is fully realized that critical changes may occur at a level which evades analysis by the ordinary histomorphologic means used. Nevertheless, it is felt that valid information may be obtained by a study of the elementary morphologic tissue reactions of the irradiated rats.

Bone changes may be evident very early. Fig. A in Plate 7 illustrates a part of the clot and the socket wall of a rat from Group I, killed two days after the extraction or 10 days after the irradiation. It is noted how the bony socket wall is being resorbed

[1] The periodontal changes in this material will be described in a subsequent report in Acta odont. scand.

by osteoclastic activity in the marrow cavities. A higher magnification (Fig. B) of the enclosed area shows that the osteocytes have either disappeared from their lacunae, or exhibit pyknotic or hyperchromatic nuclei. Similar changes in the fibrocytes of the periodontal membrane may be seen. This means that portions of the alveolar bone and the periodontal membrane are necrotic, a change which can be ascribed to radiation effects, inasmuch as it is not seen in the control rats. An exceptional finding of persistence of necrotic bone is illustrated in Fig. C from the anterior wall of a socket, 26 days after the extraction, 34 days after the irradiation. Bony and epithelial healing has taken place, and conditions are apparently normal. However, a closer inspection of a lamellar system of the former alveolar bone reveals necrotic bone (Fig. D). This bone has escaped resorption, and new bone has been deposited on it.

The behavior of bone forming and bone destroying cells is illustrated in Plate 8. It is a common finding that the bone of the socket area of the irradiated animals is rapidly resorbed. That this process also may involve adjacent areas is seen from Fig. A, where the osseous periodontium of the second molar is being resorbed by numerous osteoclasts. Simultaneously, the collagen fibres of the periodontal membrane have disappeared, and the previous hematopoietic marrow is being replaced by fibrous tissue. More conspicuous is the behavior of the osteoblasts. Fig. b is from the bottom of the socket, 26 days after the extraction, of a rat that developed radio-osteomyelitis. Practically all the bone of the socket area has been resorbed including the base of the mandible. Despite this, the tissue has retained its capability of forming bone which is demonstrated by a small area of new bone, surrounded by active osteoblasts. Another example of bone destruction and formation in areas closely related to each other is seen in Fig. C. This rat had manifest radio-osteomyelitis 12 days after the extraction with extensive destruction of the mandible. It is noted how the necrosis has penetrated under the second molar and onto the incisor. Immediately posterior to the incisor, osteoblasts are highly active forming considerable amounts of new bone.

The granulation tissue which grows into the clot of the irradiated animals differs from that of the controls. Fig. A in

Plate 9 shows the fundus of the socket in an irradiated rat five days after the extraction. In the control animals of the corresponding period, bone formation is taking place in a highly cellular fibrous tissue. In the rat illustrated, no bone formation is seen, and the fibrous tissue is poor in cells with the majority showing pyknosis and hyperchromatism of the nuclei. In Fig. B, 12 days after the extraction, still no bone formation has taken place, and the degenerative changes of the granulation tissue are even more pronounced. In Figs. C and D are illustrated the response of the fibrous tissue to a sequestrum situated immediately mesial to the second molar. In the irradiated animal (Fig. C) there is no cellular reaction whatsoever, whereas in the control (Fig. D) the normal inflammatory reaction is observed.

Vascular changes were observed in some of the irradiated rats. The most consistent finding was that of proliferation of endothelial cells, and this was seen as early as 13 days after the irradiation (Plate 10). Corresponding arterioles from an area anterior to the socket of an irradiated rat and its control are seen in Figs. A and B. It is noted how the intima of the vessel of the irradiated rat consists of densely packed endothelial cells with large round nuclei in contrast to the relatively few, flattened endothelial cells of the control. In this set of rats there is also a striking difference in the thickness of the muscular layer, but this was not a sufficiently constant finding to warrant any emphasis.

DISCUSSION

As in most biologic studies the present material did not show complete uniformity. The socket of one irradiated rat would heal whereas the socket of another, treated under identical conditions, would not. One irradiated rat exhibited complete lack of inflammatory reaction, another did not. However, certain definite trends became apparent and they form the basis for the present discussion.

The rather frequent finding of root and bone fragments and food impaction in the sockets of the irradiated rats necessitated an evaluation of the influence of these local disturbances on socket healing in control rats (Plate 1). Obviously, if food particles were impacted and retained in the socket immediately

after the extraction, socket healing was retarded (Fig. C). An inflammatory reaction and bone resorption in the adjacent areas of the jaw were associated with this disturbance.

With regard to root fragments, the control rats showed two reactions. If the fragments were small or situated deeply in the sockets in a way which permitted epithelial healing, fibrous and osseous healing would occur around them. If the fragments protruded out of the sockets, immediate epithelial healing was prevented, but the epithelium would proliferate along the root surface in what may be interpreted as an attempt to clear the root from the wound (Fig. D). In the various post-operative periods, this was illustrated by different degrees of encapsulation of the root fragments by epithelium. If the root canal established a communication with the oral cavity, an inflammatory focus at the apex could be seen.

Bone fragments will always be eliminated from the socket area, either through resorption or by expulsion, depending on the distance of the fragment from the surface and the vitality of the surrounding tissues. The findings regarding root and bone fragments in the healing socket of the rat were in accordance with those of *Glickman, Pruzansky, & Ostrach* (1947).

From the illustrations of disturbed healing in control rats it is apparent that the presence of food impaction and bone and root fragments may impede, partly or entirely, the healing after extraction. But even though the effect on healing may be severe, the surrounding tissues are capable of walling off the injury and thereby limiting the damage to the socket area.

In the irradiated animals, both disturbed and undisturbed healing were impaired. When food impaction and root fragments were found, the adverse effect on healing would frequently be far more severe than in the controls. A progressive and destructive process might spread out in the mandible from the socket area. When sequestra were present in the irradiated rats, it was difficult to ascertain whether they were produced at the extraction or by undermining resorption of radiation damaged bone. At any rate, extensive sequestration was a typical finding in cases of frank radio-osteomyelitis (Plate 3), and was suggestive of sequestrum formation beyond that which may take place due to the extraction.

In the last column of Table 1 is indicated the number of rats with radio-osteomyelitis. It is evident that irradiation eight days prior to the extraction (Groups I and III), caused considerably more cases of radio-osteomyelitis than irradiation five days after the extraction. Likewise, the illustrations from this latter group (Plate 3), show far less interference with the healing process. This points to the importance of the early phases of socket healing. If formation and fibrous organization of the clot and epithelial proliferation take place in healthy tissues and unimpaired by local disturbances, there is little likelihood of subsequent irradiation causing severe damage. Contrary, if these early phases of healing take place in tissues previously damaged by radiation, deficiencies in clot organization and epithelial proliferation may lead to a persistent surface defect and thereby facilitate the development of radio-osteomyelitis.

The clinical impression that post-irradiation extraction is a hazardous procedure has led to the generally accepted advocation of pre-irradiation extraction. That *Wildermuth & Cantril* (1953) arrived at the opposite conclusion, may be explained by analysing their patient material. In their pre-irradiation extraction group which developed radio-osteomyelitis, the patients were irradiated 5 to 14 days after the extractions. Considering that socket healing in man is a much slower process than in the rat, this means that irradiation took place when clot organization and epithelial proliferation were in process and thereby prevented or impaired surface closure. Another conclusion which may be drawn from their material is that tooth extraction prior to irradiation necessitates delay of irradiation for at least two weeks. (*Ellinger* 1957 a.)

The progressive mandibular destruction of the irradiated rats of the present study was characterised by a surface defect associated with extensive sequestration and an inflammatory reaction (Plate 3). The latter would in certain cases deviate from normal inflammatory reactions histologically, but the gross observation would in most instances show a purulent exudate in connection with the sequestra. The equivalent clinical condition is most frequently referred to under the term radio-osteonecrosis or other names which all emphasize the necrosis. However, the same terms are used to designate entirely different conditions in which irradiation treatment has caused bone necrosis, but where

the necrotic bone remains aseptic under an intact surface covering. This situation has been verified histologically from human biopsies or autopsies of irradiated pelvic bones, where the bone necrosis is ascribed to a direct radiation effect (*Bickel, Childs, & Porretta* 1961, *Stephenson & Cohen* 1956, *Truelsen* 1942), or to an effect, exclusively or in part, on the blood vessels (*Dalby, Jacox, & Miller* 1936, *Ewing* 1926 a., *Kok* 1953, *Mac Dougall, Gibson, & Williams* 1950, *Okrainetz & Biller* 1939). The inadequacy of this terminology could be overcome if the term radio-osteonecrosis were restricted to cases in which the necrotic bone remains aseptic, and the term radio-osteomyelitis were used in cases of surface discontinuity, inflammation, and sequestration. That there may be certain deficiencies in the inflammatory response is acknowledged by the use of the prefix radio-. A similar proposal was made first by *Jacobsson* (1948), and since by *Mac Lennan* (1955), *Roussel, Schoumacher, Pernot, & Poiret* (1958), *Seldin, Seldin, Rakower, & Selman* (1955), *Thoma & Goldman* (1960), and *Vaughan* (1956). *Medak & Burnett* (1954) also felt the need for a distinction between aseptic and infected radiation damaged bone and used the term radio-osteitis. Unfortunately, this term closely resembles the radiation osteitis of *Ewing* (1926 a, 1926 b), which is not an infectious process. For the latter condition the term radiation dysplasia has been suggested (*Vaughan* 1956).

The analysis of the elementary tissue changes (Plates 8—10) gives certain clues to the pathogenesis of radio-osteomyelitis. The condition of the tissues comprising the wall of the socket is of major interest in determining the course of the healing. It is from the remnants of the periodontal membrane, the subepithelial fibrous tissue, and the marrow cavities of the alveolar bone that the granulation tissue, which is to organize the clot, arises. If the proliferative powers of these tissues are impaired, a defective organization may result. Of equal importance is the closure of the surface defect by epithelial proliferation across the organized clot.

The cellulicidal action and the suppression of cell division are some of the basic effects of ionizing radiation. These mechanisms exert a profound influence on the early phases of socket healing in irradiated jaws, and they are considered instrumental in the development of radio-osteomyelitis. The socket wall illustrated in

Plate 7, Figs. A and B shows necrotic changes of bone and periodontal membrane. It is reasonable to assume, that conditions for capillary sprouting and fibroblast proliferation in this area are unfavorable. The resulting granulation tissue is illustrated in Plate 9, Figs. A and B, where the paucity of cells and capillaries is evident. This is in accordance with the observations made by *Grillo & Potsaid* (1961) and by *Schmid* (1959), who studied wound healing in irradiated tissues.

Resorption of the alveolar bone tends to begin earlier and to be considerably more extensive in the irradiated rats than in the controls. This is to be expected where the bone is necrotic, but it was also observed that areas of bone with apparently normal osteocytes would be involved in this excessive resorption process. This may be explained by assuming that the irradiation has caused resorption provoking bone changes which evade detection by the histologic technique used. Anyway, it is obvious that this extensive resorption will severely delay or completely prevent bony healing. In case of sequestration of the irradiation damaged bone, a surface defect and varying degrees of infection will always be present, and healing is prevented.

Even though the entire molar region was irradiated, the socket wall was the most frequent site for fibrous tissue and bone necrosis and sequestration. The most plausible explanation is that the extraction trauma here is superimposed on the decreased vitality and resistance of the area. The mechanism involved may be one or a combination of the following: The mechanical forces exerted on the socket wall, the infection made possible by the surface defect, or the influence of foreign body impaction into the socket.

The fact that bone resorption dominates in irradiated areas has fostered the supposition that osteoclasts are more radioresistant than osteoblasts (*Ellinger* 1957 b, *Gates* 1943). However, bone formation does take place in irradiated areas, even in close proximity to rampant bone resorption (Plate 8, Figs. B and C). Similar findings were made by *Gowgiel* (1960) and by *Ng, Chambers, Ogden, Coggs, & Crane* (1959), who observed bone formation in heavily irradiated jaw areas of experimental animals. Even though loss of osteoblasts may be an immediate effect of irradiation (*Levy & Rugh* 1952), it deserves consideration that osteo-

blasts only exist as a transitory state between undifferentiated mesenchymal cells and osteocytes (*Pritchard* 1956), and that substantial amounts of bone matrix are formed within a few days (*Carneiro & Leblond* 1959). Further it is maintained that osteoclasts have a life span of approximately 48 hours (*Hancox* 1956). Therefore, it is not likely that the osteoblasts and osteoclasts which may be observed after a few days in irradiated tissue were present as such at the time of irradiation. Consequently it appears more appropriate to speak of the presence or absence of these cells in terms of tissue changes favoring the differentiation of one or the other. It then may be stated that conditions which favor the differentiation of osteoclasts prevail in irradiated tissue, but if conditions which favor the differentiation of osteoblasts should exist, these cells will come into action as well.

Radiation damage to the epithelium is another factor responsible for the interference with healing. Destruction of the epithelium or suppression of its proliferation or capacity for migration leave the socket area unprotected toward the oral cavity and infection may result (Plate 3 and Plate 5, Figs. B, C, and D).

The characteristic feature of radio-osteomyelitis of the jaw is the progressive destruction of the tissues with little or no tendency toward demarcation and repair. Apparently, the normal defence mechanisms have been upset. This may in part be explained by the suppression of fibroblast proliferation (*Maximow* 1923, *Pohle & Ritchie* 1933, *Stein et al.* 1957) and of the differentiation of connective tissue cells into inflammatory cells (*Ellinger* 1957 c). (Plate 9, Figs. C and D).

Vascular changes, especially obliterating endarteritis, have been made responsible for the bone necrosis observed in irradiated areas (*Dahl* 1936, *Ewing* 1926 a, 1926 b, *Kok* 1953, *Mac Dougall et al.* 1950, *Mac Lennan* 1953, *Zwerg & Hetzar* 1936). Others have not observed any vascular changes in connection with bone necrosis, or maintain that vascular and bone changes both are primary radiation effects (*Bickel et al.* 1961, *Gowgiel* 1960, *Stephenson & Cohen* 1956, *Truelsen* 1942). In the present study, inflammation and necrosis made the interpretation of the vascular changes difficult, but there is little doubt that the irradiation did produce vascular changes, mainly a pronounced proliferation of endothelial cells (Plate 10). They were mani-

fested morphologically two weeks after the irradiation, but they were not considered sufficiently severe or constant to be a major factor in producing the bone changes. Furthermore, bone changes were evident as early as 10 days after the irradiation, and finally, the bony healing seen occasionally in irradiated areas indicated a sufficient blood supply.

Conclusions

The pathogenesis of radio-osteomyelitis as it appears from the present study may be interpreted as follows:

1) The irradiation causes necrotic or necrobiotic changes in the hard and soft tissues bordering the socket. These changes are accentuated by the extraction trauma.
2) Organization of the clot and epithelial healing are impaired, due to the tissue damage and the suppression of cell proliferation.
3) Conditions which favor bone resorption dominate over those favoring bone formation.
4) The tissue destruction which starts in the socket area spreads in the jaw relatively unopposed by the ordinary defence mechanisms: demarcation and repair.
5) Vascular changes, consisting of endothelial cell proliferation are noticed, but they are not considered a major factor in the production of the bony changes.
6) If irradiation is postponed until the socket has been sealed off by organization of the clot and epithelial healing, the chances of developing radio-osteomyelitis are greatly reduced.

SUMMARY

The molar regions of 37 rats, 52 to 60 days old, were exposed to roentgen rays in single doses of 1,725 r and 2,400 r. The lower left first molars were extracted either eight days before the irradiation or five days after. Twenty-one unirradiated rats with extractions performed at corresponding ages served as controls.

The gross pathologic changes were epilation, erythema, and exudation of the irradiated skin area, and oral changes varying from minor lesions of the floor of the mouth to frank radio-osteomyelitis of the jaw with occasional oro-cutaneous fistulae.

The frequency of radio-osteomyelitis was five to six times greater in the rats irradiated before the extraction than in those irradiated after the extraction.

Microscopically, bone and periodontal membrane necrosis in the socket wall could be demonstrated shortly after the extraction. The granulation tissue organizing the clot showed a low cellularity, and likewise, epithelial proliferation was impaired. Bone resorption was prominent, but areas with bone formation were seen. The cellular inflammatory response to surface defects and sequestra was absent in some rats whereas other irradiated rats formed numerous pus cells. Vascular changes consisting of vivid proliferation of endothelial cells with large nuclei were seen, but they were not constant.

When radio-osteomyelitis was present, it was characterized by a penetrating destruction of the mandible spreading far beyond the socket area and causing extensive sequestration. Apparently, the irradiated tissues had no or little capacity of limiting or repairing the damage.

The pathogenesis of radio-osteomyelitis is discussed.

RÉSUMÉ

L'EFFET DES RAYONS X SUR LA CICATRISATION D'ALVÉOLES DE JEUNES RATS IRRADIÉS LOCALEMENT SUR LES MACHOÎRES

Les régions molaires de 37 rats, âgés de 52 à 60 jours furent exposées aux rayons X à doses uniques de 1,725 r et 2,400 r. Les premières molaires gauches inférieures furent extraites soit huit jours avant soit cinq jours après l'irradiation. Comme contrôle ont servi vingt et un rats non irradiés dont on a extrait les dents correspondantes aux mêmes âges.

Les altérations pathologiques macroscopiques furent épilation, érythème et exsudation de la zone irradiée de la peau et des altérations de la bouche, variant depuis de petites ulcérations du plancher de la bouche jusqu'à de nettes radio-ostéomyélites avec des fistules orocutanées.

La radio-ostéomyélite fut cinq à six fois plus fréquente chez les rats irradiés avant l'extraction que chez les rats irradiés après l'extraction.

Peu après l'extraction on put voir au microscope de la nécrose du ligament alvéolo-dentaire et des parois osseuses de l'alvéole. Le tissu de granulation organisant le caillot montra peu de cellules et la prolifération épithéliale était aussi endommagée. La résorption osseuse était prononcée mais de la formation osseuse était aussi présente. Chez quelques rats irradiés l'inflammation cellulaire répondant aux défauts de la surface et aux séquestres était absente tandis que chez d'autres de nombreuses cellules d'inflammation se montrèrent.

Des altérations vasculaires consistant en une prolifération de cellules endothéliales à gros noyaux se présentaint, mais n'étaient pas constantes.

La radio-ostéomyélite se présentant était caractérisée par une destruction pénétrante du maxillaire inférieur s'étendant nettement en dehors de la région de l'alvéole et causant une séquestration extensive. Apparemment, les tissus irradiés possedaient peu ou pas de capacité de limiter ou réparer le dégât.

Discussion sur la pathogénèse de la radio-ostéomyélite.

ÜBER DIE EINWIRKUNG VON RÖNTGENBESTRAHLUNG DER KIEFER AUF DIE HEILUNG DER ALVEOLEN VON JUNGEN RATTEN

Die Molarregionen von 37 Ratten, die zwischen 52 und 60 Tagen alt waren, wurden einer Röntgenbestrahlung in Einzeldosen von 1,725 r und 2,400 r ausgesetzt.

Der erste linke Unterkiefermolar wurde entweder acht Tage vor der Bestrahlung entfernt oder fünf Tage hinterher. Als Kontrollobjekte dienten 21 unbestrahlte Ratten, an denen man die entsprechenden Zahnentfernungen zum gleichen Zeitpunkt vornahm wie bei denjenigen, die bestrahlt worden waren.

Die makroskopischen Veränderungen bestanden in Epilation, Erythembildung und Exsudation entsprechend dem bestrahlten Hautgebiet. An Veränderungen in der Mundhöhle fanden sich an Intensität wechselnde Beschädigungen, bestehend aus kleinern Schäden am Mundboden bis zu einer manifesten Röntgenosteomyelitis, die dann und wann oro-kutane Fisteln aufwies.

An mikroskopischen Veränderungen fanden sich folgende: Kurze Zeit nach der Zahnentfernung liess sich eine Nekrose des

Knochens der Alveolenwand und der Wurzelhaut feststellen. Das Granulationsgewebe, das in den Blutkegel hineinwuchs, war zellenarm und die Epithelzellenproliferation gehemmt. Knochenresorption war vorherrschend, doch konnte man hier und dort Knochenneubildung beobachten. Die zellulare Entzündungsreaktion blieb an den oberflächlichen Defekten und in den zu Sequestrierung neigenden Gebieten bei einigen der bestrahlten Ratten aus, während andere die Bildung zahlreicher Eiterzellen vermochten. Veränderungen an den Gefässen wurden in Form einer lebhaften Endothelzellenproliferation beobachtet, doch war dieser Befund nicht immer festzustellen.

Bei den Ratten, die eine Röntgenosteomyelitis bekamen, war der Zustand durch eine progressive Zerstörung des Unterkiefers mit daraus sich ergebender ausgesprochener Sequestrierung charakterisiert. Das bestrahlte Gewebe hatte offenbar nicht die Fähigkeit, die Gewebsschädigung abzugrenzen oder eine Wiederherstellung vorzunehmen.

Die Pathogenese der Röntgenosteomyelitis wird erörtert.

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PLATES

Plate 1.

Disturbed socket healing in control rats. Hematoxylin-eosin stain. Original magnification X 26.

A. Seven days after the extraction. Sequestra have prevented organization of the superficial part of the clot and epithelial healing.

B. Twelve days after the extraction. A small sequestrum partly encapsulated by epithelium has prevented bony healing of the superficial part of the socket.

C. Twenty-six days after the extraction. Impaction of foreign body has prevented healing and caused bone resorption.

D. Forty days after the extraction. A root left in the socket has prevented healing and caused bone resorption.

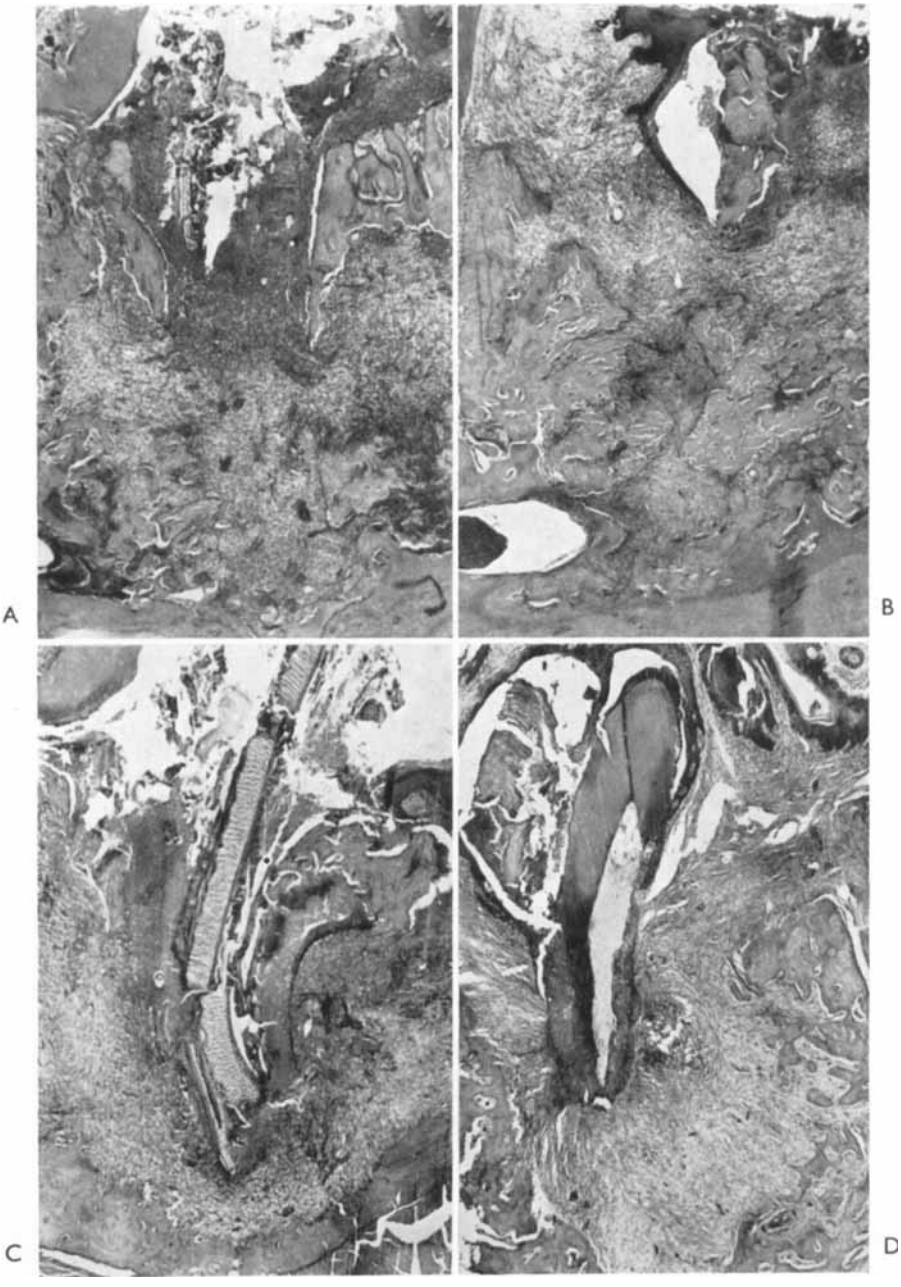
A
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Plate 2.

Socket healing in irradiated rats from Group I. Hematoxylin-eosin stain. Original magnification X 26.

A. Two days after the extraction. Blood clot and remnants of periodontal membrane in the socket.

B. Five days after the extraction. Organization of blood clot and pronounced bone resorption.

C. Twenty-six days after the extraction. Sequestra surrounded by epithelium, and bony healing in the deeper part of the socket.

D. Twenty-six days after the extraction. Inflammatory reaction around sequestra. Small area of bone formation at base of mandible.

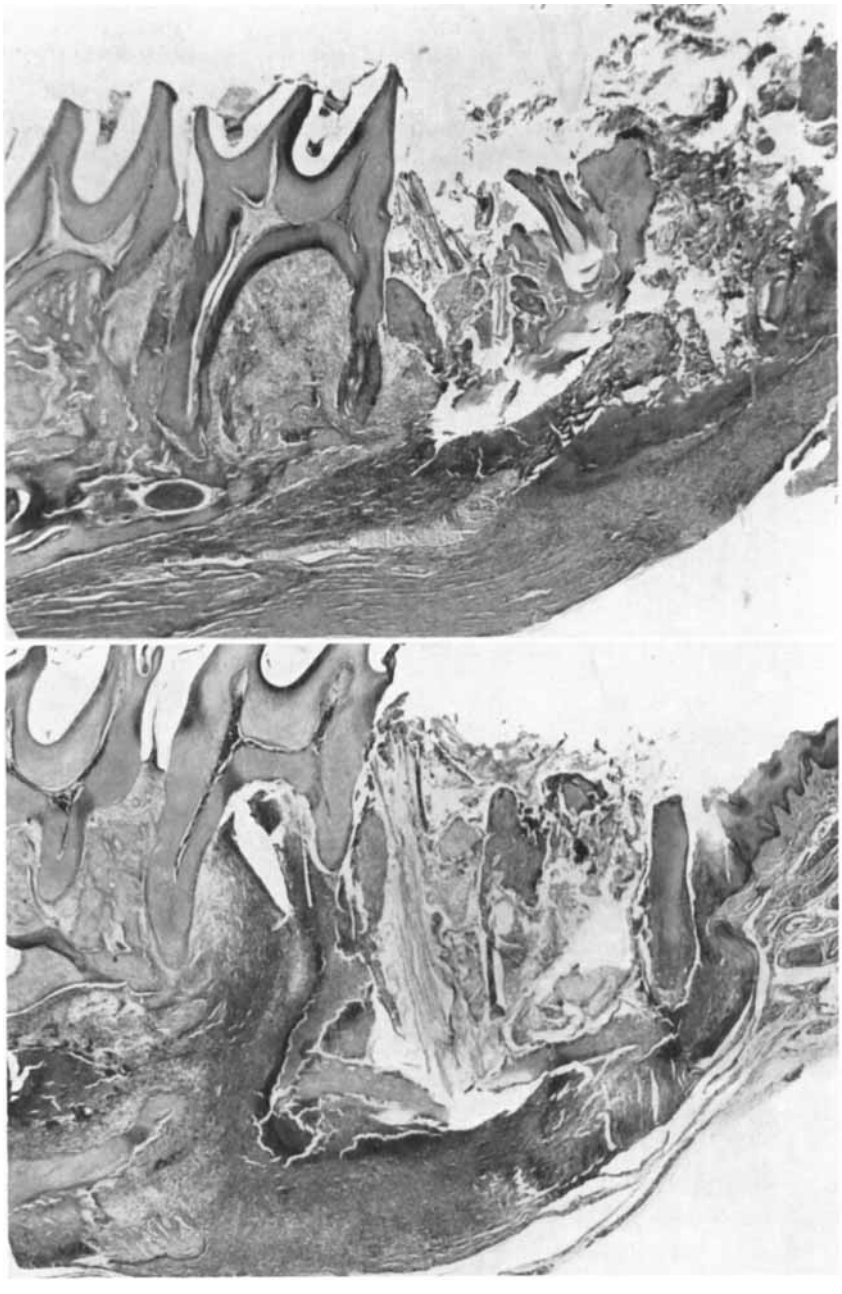
A
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Plate 3.

Mandibular radio-osteomyelitis in rats from Group I. Extensive destruction and sequestration extending from the first molar region. Hematoxylin-eosin stain. Original magnification X 11.

A. Twelve days after the extraction.

B. Forty days after the extraction.

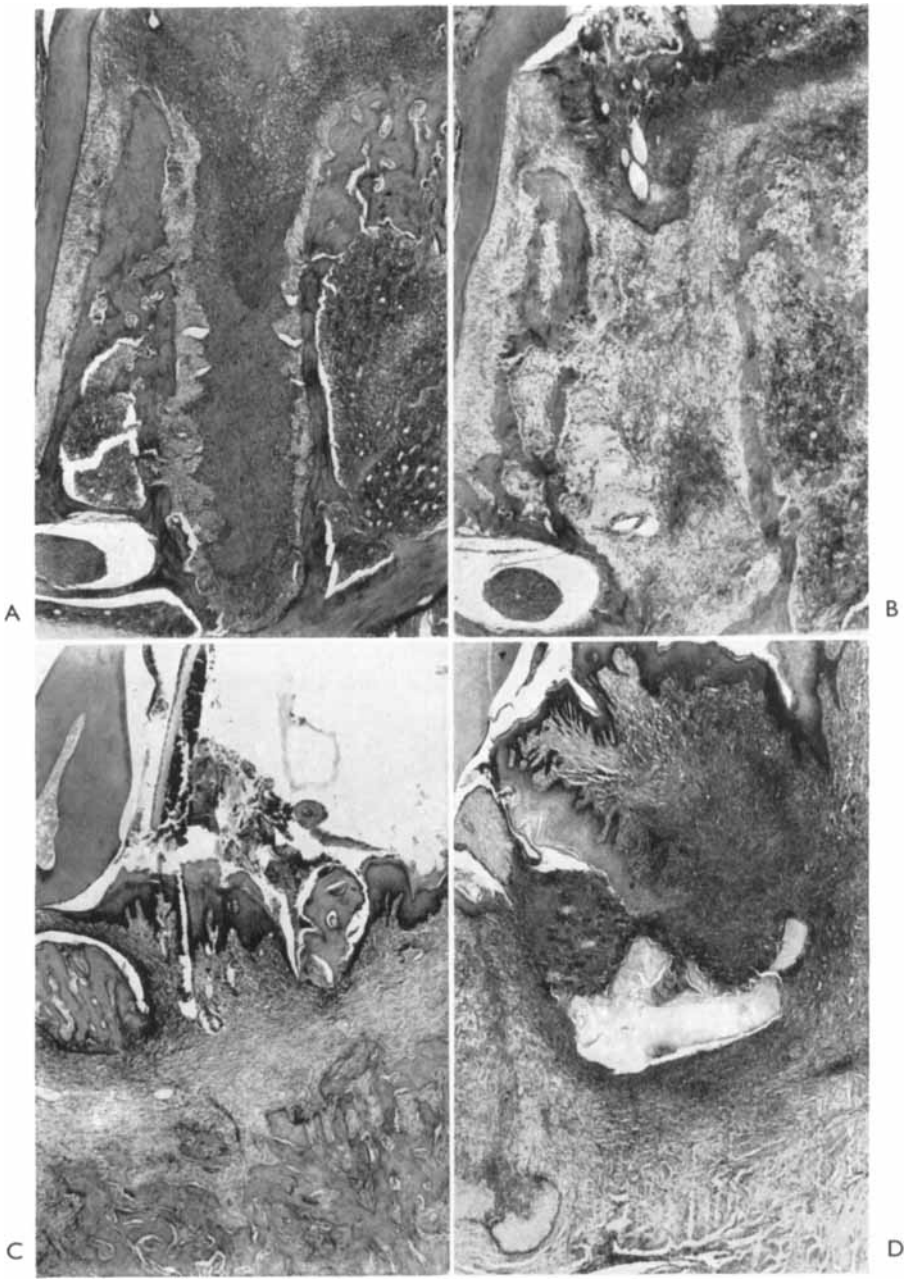
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Plate 4.

Socket healing in irradiated rats from Group II. Hematoxylin-eosin stain. Original magnification X 26.

A. Seven days after the extraction. Debris at the surface of the socket. Resorption of alveolar bone, and negligible new bone formation.

B. Twelve days after the extraction. Epithelial healing, socket partly filled with new bone.

C. Forty days after the extraction. Root left in the socket. Inflammatory reaction at apex associated with bone resorption.

D. Sixty-four days after the extraction. Epithelial and bony healing. Bony reconstruction of the area and formation of hematopoietic marrow tissue.

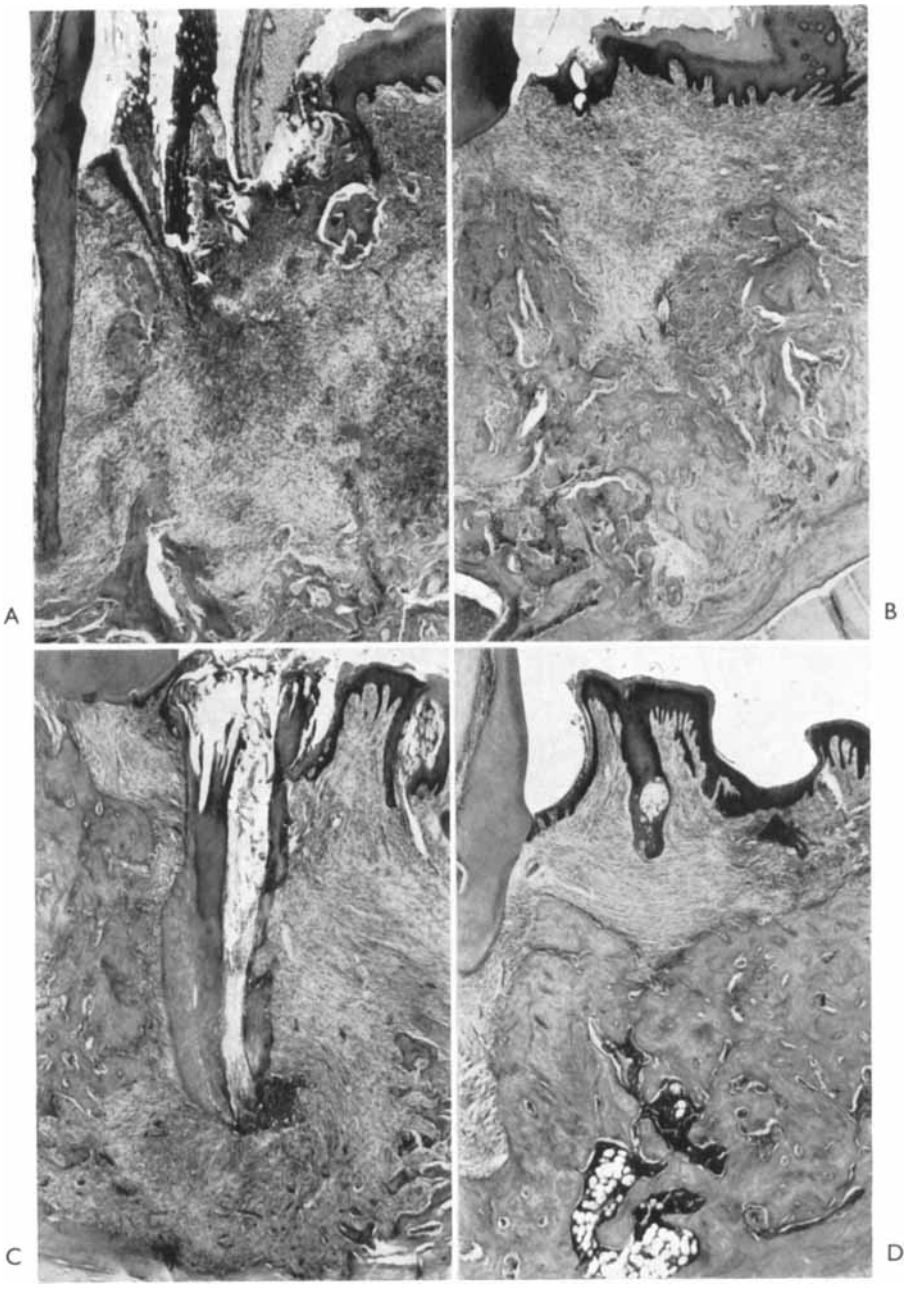
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Plate 5.

Socket healing in irradiated rats from Group III. Hematoxylin-eosin stain. Original magnification X 26.

A. Two days after the extraction. Partly organized blood clot in the socket.

B. Twelve days after the extraction. Socket only partly covered by epithelium. Inflammatory exudate in connection with small sequestrum. Scarcity of fibroblasts in the organized clot and no new bone formation.

C. Twelve days after the extraction. A root has been left in the socket and is surrounded by sequestra and inflammatory exudate. No epithelium and no new bone formation.

D. Forty days after the extraction. Resorption or sequestration of all bone in the socket area.

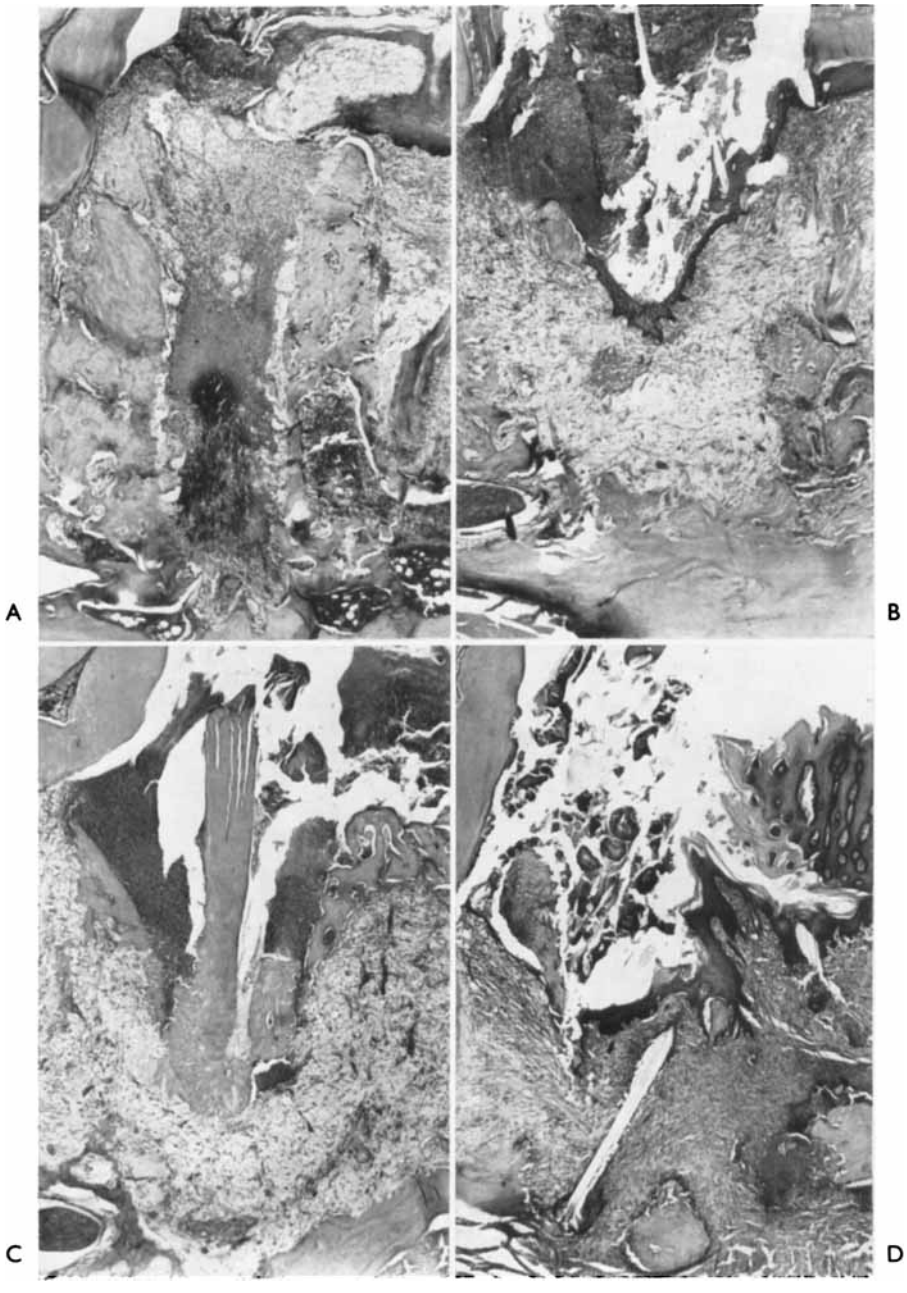
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Plate 6.

Left mandibles of irradiated rats from Group III. Hematoxylin-eosin stain. Original magnification X 11.

A. Five days after the extraction. Hematoma covering the first molar area and a root left in the distal socket. No epithelial proliferation, and no organization of the clot.

B. Forty days after the extraction. Healing of the socket area. Progressive periodontitis around second and third molars.

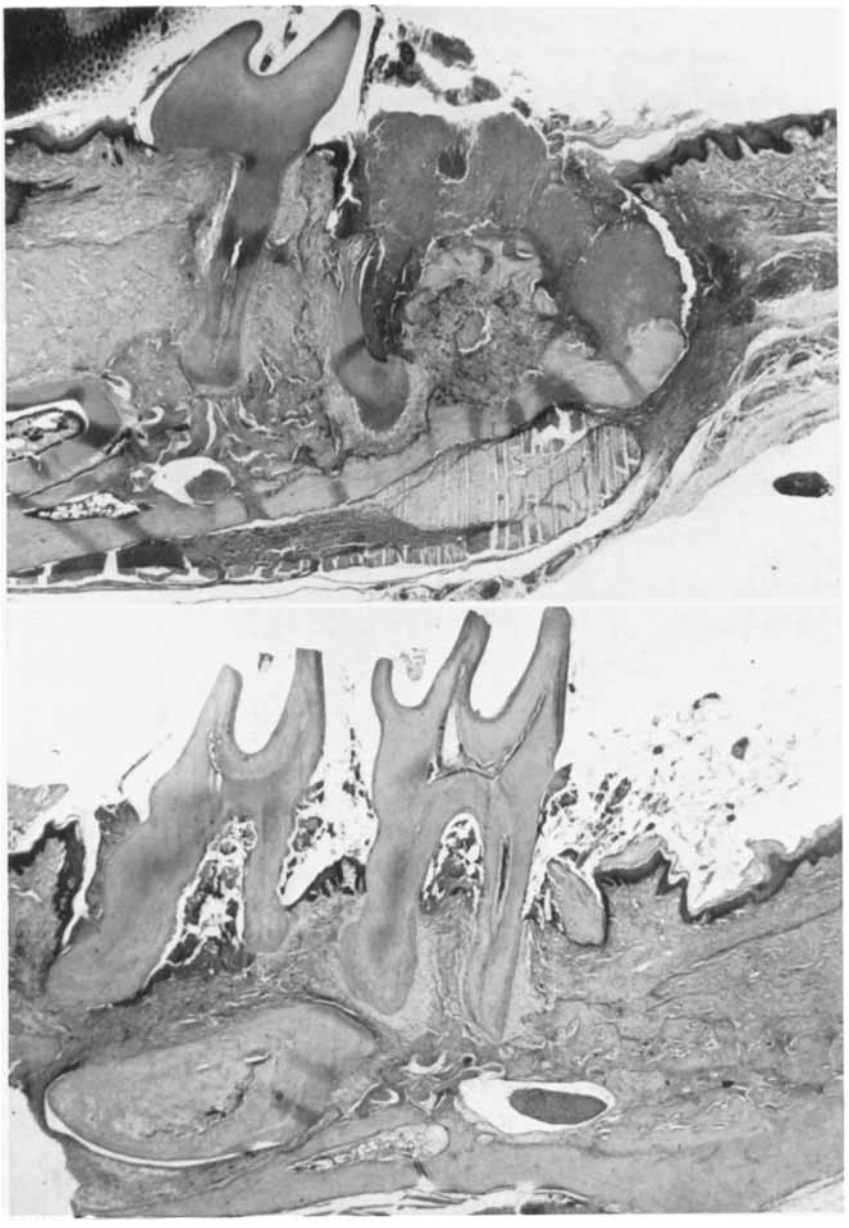

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Plate 7.

Bone changes in irradiated rats from Group I. Hematoxylin-eosin stain.

A. Two days after the extraction. Portions of alveolar bone, periodontal membrane, and blood clot are illustrated. Resorption of alveolar bone from the marrow cavities. Original magnification X 64.

B. Higher magnification of enclosed area from Fig. A. Necrotic changes of alveolar bone and periodontal membrane. Original magnification X 260.

C. Twenty-six days after the extraction. Anterior wall of socket after healing. Original magnification X 64.

D. Higher magnification of enclosed area from Fig. C. New bone deposited on necrotic bone. Original magnification X 260.

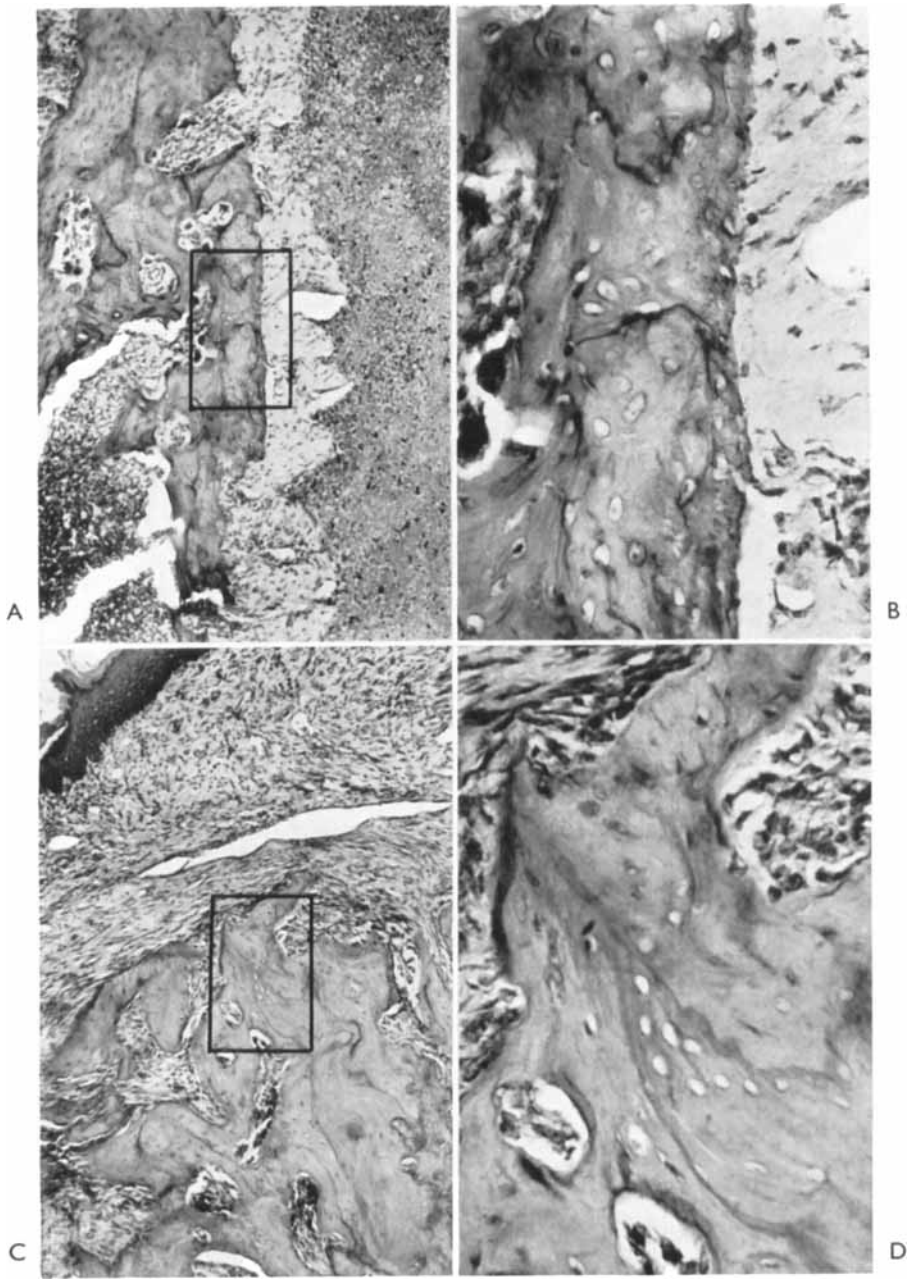
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Plate 8.

Bone resorption and bone formation in irradiated rats from Group I. Hematoxylin-eosin stain.

A. Five days after the extraction. Resorption of osseous periodontium of second molar associated with loss of principal fibres. Original magnification X 64.

B. Twenty-six days after the extraction. Area of new bone closely lined with osteoblasts from fundus of socket dominated by osteoclastic activity. Original magnification X 64.

C. Twelve days after the extraction. Part of the mandible apically to second and third molars illustrated. To the right radio-osteomyelitis undermining the second molar and reaching the incisor. To the left vivid formation of new spongy bone. Original magnification X 11.

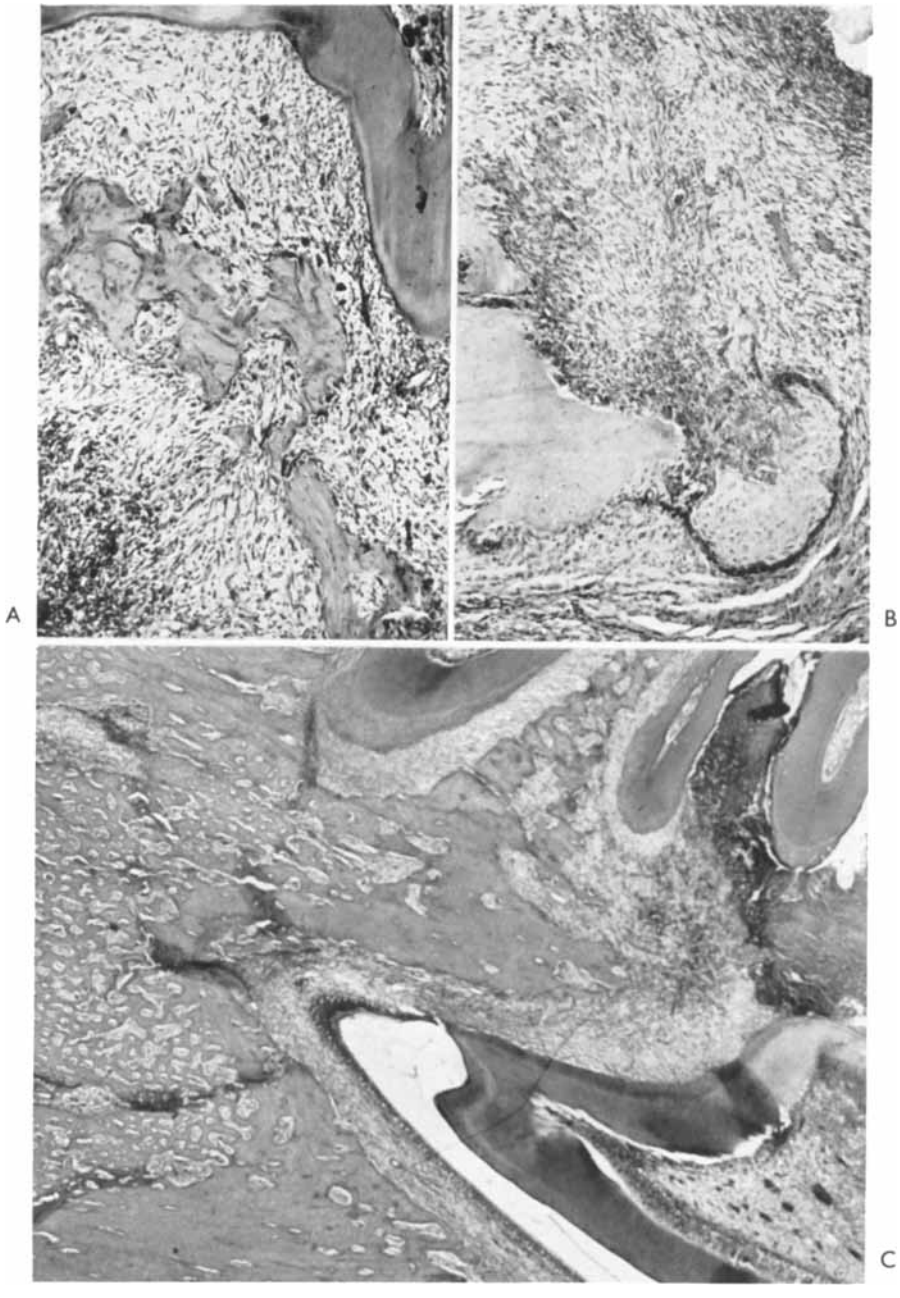
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Plate 9.

Granulation tissue in irradiated and control rats. Hematoxylin-eosin stain. Original magnification X 64.

A. Five days after the extraction (Group I). Low cellularity of fibrous tissue in fundus of socket. No bone formation.

B. Twelve days after the extraction (Group III). Degenerative changes of fibrous tissue in socket. No bone formation.

C. Twelve days after the extraction (Group I). Lack of inflammatory reaction to sequestrum mesial to second molar.

D. Twelve days after the extraction. Normal inflammatory reaction in control animal.

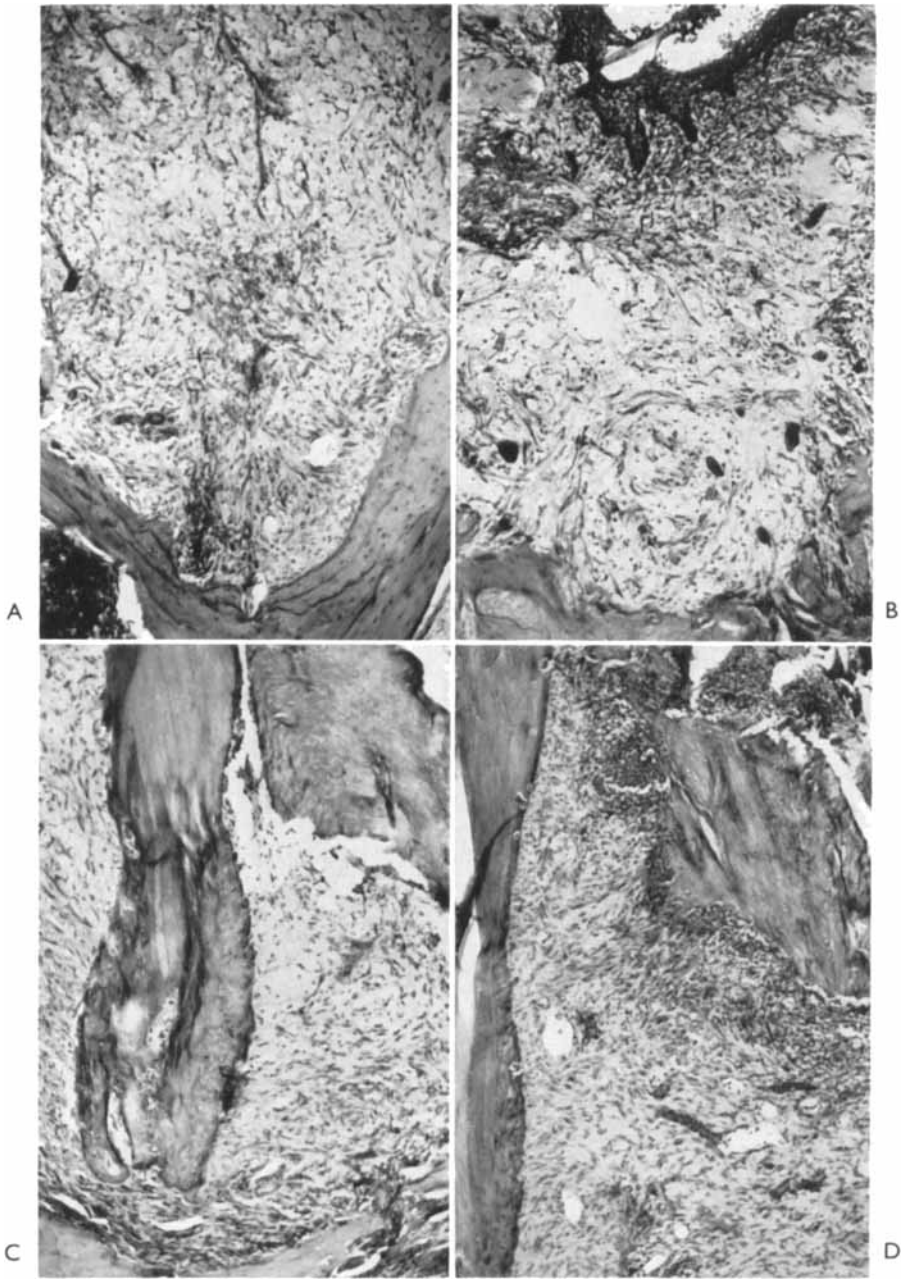
A
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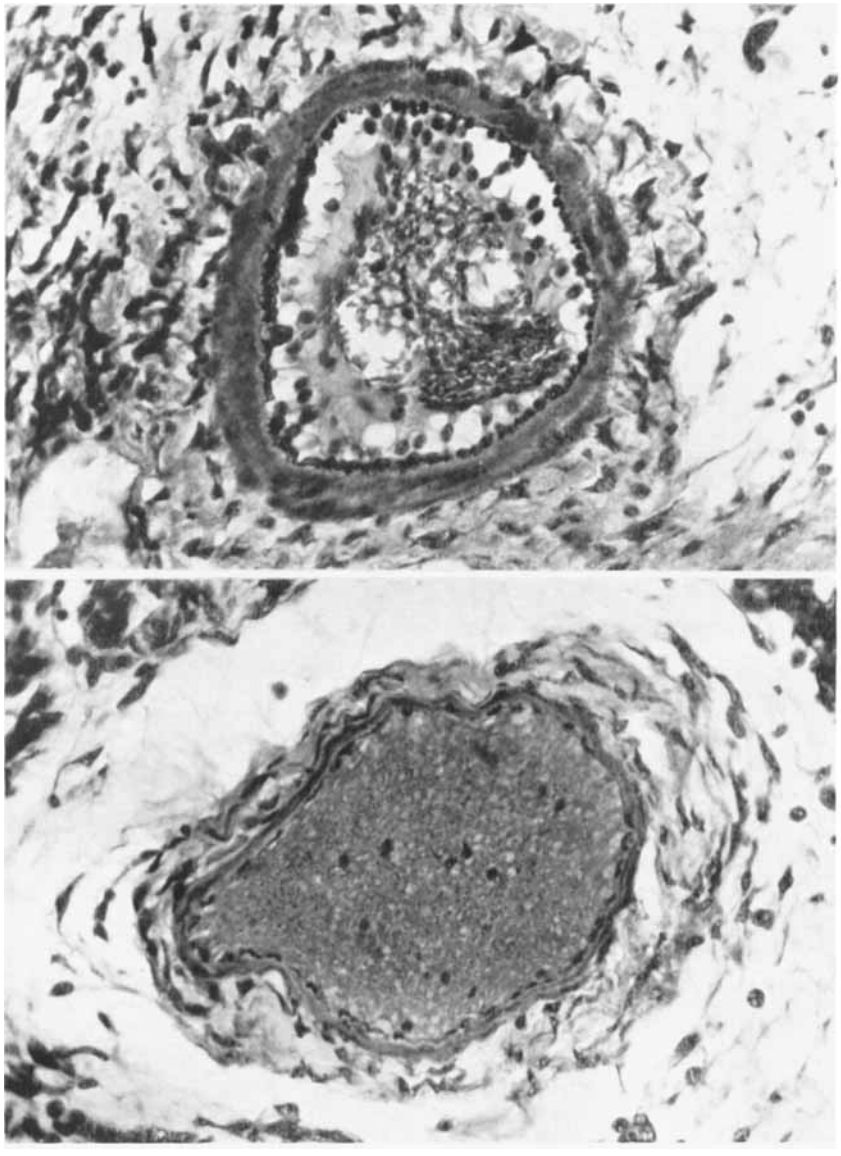
Plate 10.

Vascular changes. Hematoxylin-eosin stain. Original magnification X 260.

A. Thirteen days after the irradiation .Small artery anterior to the socket area in an irradiated rat from Group III. Proliferation of endothelial cells with large round nuclei.

B. Corresponding artery in control rat. Normal endothelial cells.


A
B