Aortic Arteriosclerosis in the Dog After Localized Aortic X-Irradiation

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There is considerable histological evidence that aortic arteriosclerosis in several animal species is initiated by fragmentation followed by reduplication of the internal elastic membrane. This process, observed even in young animals, may be followed by excessive deposition of mucopolysaccharide substance at the site of injury; this change, in turn, is followed by fibroblastic proliferation with the development of fibrous intimal plaques. In most animal species, with the exceptions of human beings and birds, lipid deposition appears late and is relatively insignificant.

Radiation was selected as a physical agent which might injure selectively the internal elastic membrane of the aorta without causing extensive alterations of the other aortic layers, as is the case with other physical agents, including heat and cold, which have been employed to produce experimental vascular injury. Preliminary experiments in which the abdominal aortas of dogs were irradiated with electrons by use of the van de Graaff electron accelerator demonstrated the development of pronounced arteriosclerotic lesions sharply localized to the aortic segment irradiated.

In the present study, segments of the abdominal aortas of dogs were irradiated with 50-kv. x-rays, and the histological appearance of these irradiated aortic segments was compared with that of adjacent nonirradiated, control segments. It is shown here that irradiation of the aorta with x-rays accentuates the development of abdominal aortic arteriosclerosis in the dog in a way that is indistinguishable from the naturally occurring disease in this species.

Methods

SURGICAL PROCEDURE

Under intravenous anesthesia with sodium pentobarbital (U.S.P., 22 mg./Kg.), 18 young adult mongrel dogs (11 females and 7 males, weighing between 7 and 16 Kg.) were subjected to laparotomy through long midline abdominal incisions. The bowel was retracted, and the parietal peritoneum was incised to expose the abdominal aorta. The aorta itself was mobilized for a distance of 12.0 cm., cephalad to the aortic bifurcation by ligature and division of the lumbar arteries. A lead shield, measuring 1.0 mm. in thickness, was mounted around the aorta to form a box-shaped well, on the floor of which lay the aorta. The radiation applicator was projected through the open top of the well so that its tip barely touched the ventral wall of the aorta. The aorta of each animal received irradiation at two points, 1.5 cm. and 3.0 cm., respectively, cephalad to the aortic bifurcation. Each irradiated site was marked with a long suture for later identification. The schedule for dose of irradiation and duration of survival for each animal was determined by the use of a table of random numbers. One dog was subjected to the same operative procedure, but received no irradiation.

Following irradiation, the shield was removed and the abdominal wound closed with two layers of interrupted cotton sutures. The dogs were sacrificed at intervals ranging from 2 to 48 weeks following irradiation.

IRRADIATION OF AORTA

The x-ray source was a Phillips 50-kv. constant-potential mobile unit. The tube housing was fitted with an applicator, 4.0-cm. long, in the end of which was a port, 1.0 cm. in diameter. During an exposure, the port was in gentle contact with the ventral surface of the aorta. The aorta itself in the region of exposure lay within a lead shield, 1.0-mm. thick, to prevent escape of x-rays into the neighboring tissues. The shield extended 1.0 cm. ventral to the aorta to enclose the terminal region of the applicator.

The principal radiological factors were: 50-kv. constant-potential, 1.5 ma.; added filtration, 1.0-mm. Al; HVL, 1.0-mm. Al; target-aorta-surface...
distance, 4.2 cm.; exposure dose rate at ventral surface of aorta, 320 r per minute. Unless specified otherwise, the doses mentioned in the text are based on this surface dose rate, which includes the scattered radiation.

The diameter of the aorta was measured in 18 dogs at the time of irradiation; the mean and standard deviation were 7.9 ± 1.28 mm. On the basis of the manufacturer's depth dose curve, the relative exposure dose received by the aorta as the x-ray beam passed from its ventral to its dorsal surface varied as follows: depth 0 mm. (ventral surface), 1.00; 2.0 mm., 0.83; 4.0 mm., 0.68; 6.0 mm., 0.59; 8.0 mm., 0.51. For practical purposes, it was estimated that the aortic wall was about 2.0-mm. thick. The relative average doses were, therefore, as follows: ventral wall, 0.91; lateral walls, 0.65; dorsal wall, 0.55. Thus, although the exposure dose rate to the surface of the ventral wall was 320 r per minute, on the average the ventral wall received 291, the lateral walls 218, and the dorsal wall 176 r per minute. The dose to the dorsal wall was, therefore, only 60 per cent of that to the ventral wall.

PREPARATION OF TISSUES

The abdominal aorta, including the common iliac arteries, was removed for study. After fixation in a 10 per cent solution of formaldehyde U.S.P., transverse blocks of tissue were removed from each aorta as follows: (1) at each irradiated site which had been marked with a suture; (2) midway between the two irradiated sites; and (3) approximately 1.0 cm. above the more cephalad irradiated site. Contiguous frozen sections from each block were stained (1) with Sudan IV and hematoxylin, (2) with Nile blue, and (3) by the Schultz reaction for cholesterol. An unstained frozen section was examined with polarized light. These blocks were then embedded in paraffin, and contiguous sections were treated with hematoxylin and eosin stain, phosphotungstic acid hematoxylin, a combined Verhoeff–van Gieson stain, and a colloidal iron–Prussian blue stain for mucopolysaccharides. Results

HISTOLOGICAL OBSERVATIONS

The earliest evidence of disease of the intima was an alteration of the internal elastic lamina. This consisted of hyaline swelling, vacuolization, and segmental beading, often associated with fragmentation and rupture of this structure. Replication as a process of regeneration of elastic tissue was often observed, and it appeared that new layers of elastic material had bridged gaps in the lamina resulting from fragmentation. At times, several layers of elastic lamina appeared in these lesions (fig. 1). In some instances, however, elastic regeneration had not occurred (fig. 2). As a rule, these sites of injury and repair of the internal elastic lamina were characterized by increased deposits of acid mucopolysaccharides. These appeared as localized accumulations of the same mucoid material which normally enveloped the intact internal elastic lamina. The newly formed elastic fibers appeared to
FIGURE 3
Early intimal thickening due to fibroblastic proliferation. Control site, two weeks after irradiation. Hematoxylin and eosin, × 250.

FIGURE 4
Early intimal thickening. Note degeneration and partial loss of internal elastic membrane. Four weeks after irradiation with 1,500 r. Hematoxylin and eosin, × 250.

FIGURE 5
Intimal plaque with irregular arrangement of fibroblasts and intercellular fibers. Eight weeks after irradiation with 1,500 r. Hematoxylin and eosin, × 250.

have regenerated from the mucoid ground substance.

The reduplicated segments of internal elastic lamina and mucopolysaccharide deposits elevated the endothelium, thus forming either small intimal plaques or causing diffuse-intimal thickening. No other significant alteration of the endothelium was observed. As the plaques enlarged, they were characterized by proliferation of fibroblasts appearing to originate from the endothelium (figs. 1 and 3). In the smallest plaques, these cells had a loose arrangement and were oriented at right angles to the endothelial surface (fig. 3). In larger plaques, the cells had an irregular arrangement (figs. 4, 5, and 6), and in the largest plaque, lay parallel to the endothelium in a circumferential pattern (fig. 7). The earlier plaques were very cellular, whereas the fully developed ones contained relatively few fibrocytes (figs. 6 and 8).

The smaller intimal plaques had a high content of acid mucopolysaccharide (fig. 9), but as the intimal thickening with or without plaque formation increased, this ground substance gradually was replaced by intercellular fibrillary material which consisted of reticulum, collagen, and elastic fibers. At first, these fibers were delicate, were observed mainly surrounding the fibroblasts, and appeared to have been formed by those cells.

In larger plaques, the fibers were coarser, mainly collagenous, and appeared as wavy bundles arranged circumferentially in the aortic intima (fig. 10). The thinner margins of large plaques were, as a rule, more cellular and contained less fibrillar material than did the thicker, central, and presumably older, portions of the thickened intima. Some larger plaques consisted of two layers: a deeper, compact, collagenous, and presumably older layer, and a superficial cellular layer that contained abundant mucoid sub-
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FIGURE 6
Cellular intimal plaque with irregular arrangement of cells. Two weeks after irradiation with 1,500 r. Hematoxylin and eosin, × 125.

FIGURE 7
Intimal plaque with circumferential arrangement of fibrocytes and coarse collagen fibers. Twelve weeks after irradiation with 5,500 r. Hematoxylin and eosin, × 250.

FIGURE 8
Diffuse intimal thickening characterized by relatively acellular connective tissue. Note loss of segment of internal elastic membrane. Twelve weeks after irradiation with 1,500 r. Verhoeff-van Gieson stain, × 125.

Lipid material was found in only a few of these intimal lesions and appeared as finely divided droplets adherent to the internal elastic membrane, especially beneath intimal plaques. In a few instances, small amounts of lipid were present in the deeper layers of plaques or in the thickened intima, and in one instance, in the media beneath. These sparse lipid deposits stained with Sudan IV and appeared violet with Nile blue, but they were neither visible with polarized light nor reacted with the Schultz stain for cholesterol. None of the intimal lesions, early or late, contained fibrin, as demonstrated by the phosphotungstic acid hematoxylin stain.

No significant abnormalities were noted in the media at any site in any of the dogs. The elastic layers and enveloping mucopolysaccharide and the smooth muscle had not been altered. The adventitia, however, was fibrotic, and aortic branches contained organized thrombi, presumably the result of the surgical mobilization of the lower aortic segment.

At the irradiated sites, intimal lesions, as evidenced by elastic-tissue degeneration and intimal thickening with or without plaque formation, were more pronounced on the ventral wall in approximately the same number.
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FIGURE 9

Early intimal plaque consisting mainly of mucopolysaccharide. Few collagen fibers are present. Eight weeks after irradiation with 1,500 r. Colloidal iron—Prussian blue stain, × 125.

FIGURE 10

Diffuse intimal thickening. Collagen is abundant and few fibrocytes are present. Large segments of the internal elastic membrane are absent. Twenty-four weeks after irradiation with 2,500 r. Hematoxylin and eosin, × 125.

of instances as on the dorsal wall. Also, at the control, nonirradiated sites, the intimal lesions were more pronounced on either the ventral or dorsal aortic walls in an equal number of instances.

Intimal lesions of the aorta observed at the sites of irradiation had characteristics identical to those at the nonirradiated control sites and in the aorta of one dog which had been sham-irradiated, although lesions in the irradiated sites seemed to be more pronounced (table 1).

HISTOPATHOLOGICAL GRADING

In this study, the abdominal aorta of the dog was examined at four sites which will be designated 1 to 4, the lowest number indicating that site nearest the aortic bifurcation; i.e., site 1 - 1.5 cm., site 2 - 2.2 cm., site 3 - 3.0 cm., and site 4 - 3.7 cm. above the aortic bifurcation.

In each animal, sites 1 and 3 were irradiated, but not sites 2 and 4. Each of the irradiated sites received a different dose; in any one dog, these doses were 1,500 and 2,500 r, or 3,000 and 5,500 r. In alternate dogs, site 1 received the higher dose of the pair of doses; in the other dogs, site 1 received the lower dose.

The microscopic lesions were graded by one examiner who did not know the origin of the specimens under examination. The slides were graded for plaque formation, and were then graded again for intimal thickening. The grades ranged from 0 through 4. Each site examined, therefore, had two grades, one for plaque formation and the other for degree of intimal thickening. For almost every site the two grades were identical and, therefore, were summed to give a single grade for the site, ranging from 0 through 8.

When the data for the two irradiated sites were compared dog by dog, it was found that they did not differ consistently or significantly. The average for the two irradiated sites was used, therefore, to characterize each dog. The data for the two control sites (sites 2 and 4) were not averaged. It should be noted that site 2, lying between irradiated sites 1 and 3, presumably would be the best control for them. Control site 4, lying highest on the aorta, might be expected to differ from site 2, since naturally occurring arteriosclerosis in the dog tends to be more pronounced in the lowest segments of the abdominal aorta.

The experimental design for sacrifice was as follows: At each selected interval after exposure, two dogs were sacrificed, one of which had been exposed to 1,500 and to 2,500
Table 1

Histopathological Grade of Aortic Arteriosclerosis in the Dog After X-Irradiation

<table>
<thead>
<tr>
<th>Interval after exposure (weeks)</th>
<th>Site 1 (1 and 3)</th>
<th>Site 2</th>
<th>Site 3</th>
<th>Site 4</th>
<th>Site 1 (1 and 3)</th>
<th>Site 2</th>
<th>Site 3</th>
<th>Site 4</th>
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</thead>
<tbody>
<tr>
<td>3 and 4</td>
<td>6 (5.5, 6.5)</td>
<td>2 (4, 0)</td>
<td>4 (8, 0)</td>
<td>3.5 (1, 6)</td>
<td>0.5 (1, 0)</td>
<td>0 (0, 0)</td>
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<tr>
<td>6 and 8</td>
<td>4.5 (3.5, 5.5)</td>
<td>2 (0, 4)</td>
<td>0 (0, 0)</td>
<td>4.5 (3.5)</td>
<td>4 (4, 4)</td>
<td>3 (2, 4)</td>
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<td></td>
</tr>
<tr>
<td>12 and 16</td>
<td>8 (8, 8)</td>
<td>3.5 (0, 7)</td>
<td>0 (0, 0)</td>
<td>7 (8, 8)</td>
<td>3 (0, 6)</td>
<td>3 (0, 6)</td>
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</tr>
<tr>
<td>24 and 48</td>
<td>7 (7, 7)</td>
<td>3.5 (1, 6)</td>
<td>0.5 (1, 0)</td>
<td>3.5 (4, 3)</td>
<td>3 (0, 6)</td>
<td>4 (8, 0)</td>
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<tr>
<td>12, 16, 24, 48</td>
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That a clear-cut increase in severity of radiation-induced arteriosclerosis with time was not demonstrated may, perhaps, stem from the fact that the number of animals was small. If the data for intervals 3, 4, 6, and 8 weeks are averaged and compared with those for 12, 16, 24, and 48 weeks, a change with time does appear. This is shown by the data in the last two lines of table 1. These average data also show more clearly than those in the body of table 1 that the degree of intimal proliferation or arteriosclerotic thickening tended to be less in the more heavily irradiated animals.

Statistical Analysis

For purposes of this analysis, the grading at each site in each dog is shown in table 2, without averaging as in table 1.

A two-way analysis of variance (at 5 percent level of significance) for the data for dogs which received 1,500 to 2,500 r showed:

1. There were significant differences in the histological grading among the different sites: (a) mean of gradings at site 1 was significantly greater than mean at site 2; (b) mean at site 3 was significantly greater than at site 4; (c) mean at site 1 was significantly greater than at site 4; and (d) means at sites 1 and 3, 2 and 4, and 2 and 3 were not significantly different.

2. There were no significant differences in grading in relation to interval after exposure.

3. There were no significant differences in grading in relation to the combined factors of site and interval after exposure.

A similar analysis of variance for the data...
for the dogs receiving 3,000 to 5,500 r revealed no significant differences in grading in relation to site, interval after exposure, or the combined factors of site and interval after exposure.

When gradings at the combined irradiated sites 1 and 3 were compared with control site 2 and control site 4 by a similar two-way analysis of variance, the following results were obtained for dogs receiving 1,500 to 2,500 r:

1. There were significant differences in the histological grading among the different sites: (a) mean of gradings at combined sites 1 and 3 was significantly greater than mean at site 2; and (b) mean of gradings at combined sites 1 and 3 was significantly greater than mean at site 4.

2. There were no significant differences in grading in relation to interval after exposure nor to the combined factors of site and interval after exposure.

For the dogs which received 3,000 to 5,500 r, there were no significant differences in grading in relation to site, to interval after exposure, or to the combined factors of site and interval after exposure.

**Discussion**

A consistent feature of early arterial disease in a number of animal species, as well as in man, is degeneration and fragmentation of the internal elastic membrane followed by regeneration and formation of one or more new layers of elastic material.1-7 These sites of elastic injury and regeneration contain accumulations of mucopolysaccharide ground substance, a material normally enveloping elastic layers in arterial walls. Indeed, there is histological evidence that the newly formed elastic layers have regenerated and formed directly from the mucoid ground substance, even before fibroblasts have appeared at the site of injury.5 Elastic alterations and mucoid accumulations are then followed by fibroblastic proliferation leading to the development of diffuse intimal fibrosis or localized intimal fibrous plaques. In the dog, these sequences may be regularly observed in the distal segment of the abdominal aorta.1-2 In most species, with the exceptions of the bird, certain primates, and the human being, lipid infiltration in the arteriosclerotic lesion is usually a relatively late occurrence.1-7

The breakdown of elastic laminas of arteries and arteriosclerosis are parallel processes in aging.10 However, elastic fragmentation may be observed often in young animals, but is repaired by elastic regeneration. In certain areas where fragmentation occurs repeatedly, arteriosclerotic lesions eventually appear. These areas include the lower abdominal aorta, particularly on the dorsal wall and on the convex intimal surface of the aortic arch.5 When protein metabolism is deranged, as in pyridoxine deficiency in the monkey, the elastic regeneration seems to be inhibited, mucopolysaccharide material accumulates in the intima, and eventually, arteriosclerotic plaques develop.11,12

Numerous attempts have been made to produce arteriosclerosis by arterial injury with various physical agents.13,14 These have included electrical stimulation, thermal injury by cautery or freezing with carbon dioxide, surgical injury such as crushing, adventitial dissection, or direct intimal tearing, and application of increased gravitational forces. These experimental methods have led to the development of intimal fibrous lesions resembling those of naturally occurring arteriosclerosis, but almost invariably have caused medial necrosis and fibrosis as well.14 Arterial disease produced by these methods thus

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**TABLE 2**

<table>
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<tr>
<th>Interval after exposure (weeks)</th>
<th>1,500 to 2,500 r Site 1</th>
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<th>Site 3</th>
<th>Site 4</th>
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<td>6 8 6 0 0 0 0 0</td>
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<th>Interval after exposure (weeks)</th>
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<th>Site 2</th>
<th>Site 3</th>
<th>Site 4</th>
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<td>48</td>
<td>6 8 6 0 0 0 0 0</td>
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has little real resemblance to the naturally occurring process.

The effects of ionizing irradiation on the vascular system and the development of arteriosclerotic lesions in irradiated tissues are well known. Warren pointed out that the elastic in irradiated human uterine arteries was distorted or absent, whereas in nonirradiated uterine arteries, the elastic structures were usually intact. Although Rhoades believed that injury of collagen secondary to inflammation was the significant change in animal arteries irradiated from internal or external sources, Smith and Lowenthal found ragged fraying of elastic membranes of the media associated with increased amounts of ground substance in arteries of young mice subjected to external irradiation; these lesions closely resembled those observed in old mice. Ellinger indicated that, as a rule, injury of larger vessels was produced only by doses over 500 r, and consisted of endothelial swelling, elastic-fiber degeneration, and vacuolar degeneration of muscle fibers. The thoracic aorta of a patient irradiated for mediastinal lymphoma showed marked thickening of all layers. The elastic tissues appeared well preserved, although they were fragmented. Arteriosclerotic lesions in the aorta and in the coronary and pulmonary arteries of the rat after irradiation of the thorax with 2,50020 r have recently been reported.

The arterial elastic layers consist of protein with characteristics distinct from those of collagen. An unknown, but specific, configuration of amino-acid molecules and their linkages undoubtedly is responsible for the elastic qualities of this macromolecular substance. Another macromolecular elastic material, natural rubber, acquires elasticity when polymerization and bridge formation with sulfur are produced by vulcanization. Weak bonds in the rubber molecule may break, and similar bonds probably are present in other elastic substances as well. That irradiation opens bonds in macromolecular substances has been demonstrated by the depolymerization of hyaluronic acid and other macromolecular mucopolysaccharides by irradiation with electrons or x-rays, which produces small molecular, dialyzable compounds.

In the present study, it would appear that irradiation with the doses employed may have caused selective disruption of the internal elastic lamina, leading to the development of arteriosclerotic intimal thickening, without causing histologically demonstrable injury of the other vascular layers. The lesions at the irradiated sites were similar to those observed at the nonirradiated control sites, but were usually more severe. The lesions at the irradiated sites were also similar in all respects to naturally occurring lesions which appeared with a high incidence in old dogs. It is proposed that the naturally occurring process and sequences in which aging and possible nutritional factors are etiological have been accentuated and accelerated by irradiation.

It is of interest that arteriosclerotic lesions at the sites that received higher doses of irradiation appeared to be less pronounced than those at sites that received lower doses. This finding was consistent with the fact that although elastic degeneration may have been more severe in sites that received higher radiation doses, the proliferative response of the intimal connective tissue was less, an expected result of more intense irradiation.

The evidence also suggests the existence of another factor that appears to influence the magnitude of the local reaction, i.e., the relation between the severity of the lesion and the size of the dose received in a particular segment of the aorta. Owing to the absorption of the x-ray beam as it passed through the aorta, the dorsal wall received only about 60 per cent of the dose received by the ventral wall.

It may be assumed that in the 1,500- to 2,500-r group, the average dose to the dorsal wall was 800 to 1,500 r, and that in the 3,000- to 5,500-r group, it would be 1,800 to 3,300 r. Thus, the dorsal wall of the high-dose group received about the same dose as the ventral wall of the low-dose group. However, the histological data indicate that the irradiation employed in this experiment caused the same...
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degree of injury of the ventral and dorsal walls of the aorta, as evidenced by the development of arteriosclerosis, since the arteriosclerotic lesions were more pronounced on either the ventral or dorsal walls in an equal number of instances, both in the low-dose and high-dose groups of dogs.

Summary

Localized segments of the abdominal aortas of 18 dogs were irradiated with 50-kv. x-rays in doses ranging from 1,500 to 5,500 r (at the ventral surface of the aorta), and were examined histologically at intervals ranging from 2 to 48 weeks after irradiation. Arteriosclerosis developed at the irradiated sites and was significantly more severe than that which occurred in nonirradiated control sites in the abdominal aorta. There was evidence that severity of arteriosclerosis increased with time following irradiation of the aorta. There was less pronounced arteriosclerosis after 3,000 to 5,500 r than after 1,500 to 2,500 r. It appeared that the larger doses of x-rays inhibited the full development of the late lesions, although presumably causing more initial primary damage. X-irradiation appeared to be followed by the development of arteriosclerotic lesions similar to those that occur naturally in old dogs. It is proposed that irradiation may selectively cause injury of the internal elastic membrane, and that this degenerative phenomenon is followed by the development of intimal fibrosis and plaque formation.

Acknowledgment

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