Spontaneous Arteriosclerosis of the Mesenteric, Renal, and Peripheral Arteries of Repeatedly Bred Rats

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Considerable emphasis is given to the investigation of the coronary and cerebral arteries because of the dramatic consequences of arteriosclerosis in these vessels. It is well known that the severity of arterial disease differs from one anatomical site to another. Hence greater emphasis should be placed on understanding the anatomical distribution of arteriosclerosis, particularly since recovery from the acute clinical complications of coronary and cerebral arteriosclerosis may depend largely upon the physiological and anatomical integrity of more peripheral arteries, such as those of the mesentery, kidney, and extremities.

In this laboratory, we have found that male and female rats, bred repeatedly, will develop arteriosclerosis spontaneously. The arterial lesions begin in the abdominal aorta, and, as the disease progresses, arterial degeneration appears in the arch and thoracic segments of the aorta as well. As a later development, the coronary arteries also show evidence of arteriosclerosis. In addition, arteriosclerosis tends to appear earlier in the endocardial than in the epicardial branches of the coronary arteries. The cerebral arteries appear to be the most resistant, or the last to develop arterial disease, because only minimal arterial lesions are found in the cerebral arteries despite severe arteriosclerosis in the carotid arteries. The present paper describes the spontaneous development of arterial lesions in the mesenteric, renal, and peripheral arteries of male and female breeder rats, and relates these lesions to those in the aorta.

Methods

This report is based upon autopsy material taken from several thousand Sprague-Dawley male and female discarded breeder rats purchased from the Sprague-Dawley Farms and sacrificed during the years 1958 to 1963. Breeder rats are on the average eight and one-half to ten months old when discarded. By the time this age is reached the average male has sired four to five litters and the average female has given birth to and suckled four to five litters. Virgin Sprague-Dawley rats, from the same source and of comparable age as the breeder rats, served as controls wherever indicated. All of the animals were housed in air-conditioned quarters and were fed ad libitum on a regular diet (Rockland) which has a relatively low fat content (4%). None of the animals were given treatment of any kind.

The incidence of the spontaneous arteriosclerosis found in discards breeder rats of the Sprague-Dawley Farms has been relatively consistent over the years. However, Sprague-Dawley rats raised and bred in our own animal colony, under controlled conditions, are also included. These animals were sacrificed after 1, 2, 3, 4, and 5 breedings in order to correlate the temporal development of the arteriosclerosis with reproductive activity. In addition, other strains of breeder rats such as Wistar, Long-Evans, Lewis, and Holtzman, were also sampled (100 males and 100 females of each strain).

The approximate age of breeder rats may be determined by the use of this guide. Male and female rats are started as breeders at the age
of four months. Allowing three weeks for gestation and three weeks for nursing, six weeks elapse between each breeding. The number of pregnancies is calculated on the basis of the number of litters a female has successfully raised; for males, breeding activity is based on the number of litters sired.

A special effort was made to correlate arterial changes in peripheral arteries, e.g., brachial and radial, femoral and tibial, with the degree and development of arteriosclerosis in the aorta. To do this, Sprague-Dawley male and female virgin rats and Sprague-Dawley male and female breeder rats were used. The male and female virgin rats and the male breeder rats were eight to nine months old. The female breeders ranged from four to nine months of age and had produced a minimum of one or a maximum of six litters. Male and female virgin rats, under 12 months do not develop arteriosclerosis.1-3 Male breeder rats, under 12 months, develop microscopic lesions only in the aorta.1-3 Female breeders, however, regularly develop grossly visible and easily detectable arteriosclerotic lesions of the aorta. The aortic lesions in the female breeder are classified as follows: none, minimal, moderate, and severe. The details of this scoring system have been published.1-3 In this way, samples of peripheral arteries of the upper and lower extremity could be obtained from animals with known degrees of gross arteriosclerosis found in the aorta at autopsy. Complete sets of the aorta and its peripheral branches (see below) were collected from six or more female breeders having severe gross aortic arteriosclerosis, six or more with moderate, six or more with minimal, and six or more with no grossly visible arteriosclerosis. In addition, complete sets of aorta and peripheral arteries were collected from six male breeders, six male and six female virgin rats. The rats in this special study were all of the Sprague-Dawley strain.

Throughout this investigation, the peripheral arteries of the lower extremity were subdivided into the following categories: common iliac, femoral, popliteal, anterior and posterior tibial; those of the upper extremity into subclavian, brachial, radial, and ulnar. Samples of mesenteric arteries such as the celiac, superior and inferior mesenteric as well as pancreatic and splenic arteries, were also collected along with selected organs during the several years of this study. The renal artery is defined in this report as the segment between the abdominal aorta and the hilus of the kidney. Observations concerning the small branches of the renal artery, i.e., intrarenal arteries, are based on examination of microscopic sections of the kidney.

All tissues were fixed in 10% buffered neutral formalin (Lillie). Paraffin sections were cut at 3μ and samples of each artery were stained with hematoxylin and eosin, toluidine blue, alcan blue, and Hale stain for metachromasia and identification of mucopolysaccharide material. Representative samples of all arteries were stained with oil red O and Sudan black B for the demonstration of lipids. Masson’s trichrome stain was used for the demonstration of connective tissue, Gomori’s aldehyde fuchsin stain and the Verhoeff-van Gieson stain for elastic tissue and the von Kossa stain for the demonstration of calcium.

Results

Abdominal Aorta

The abdominal aorta, particularly that portion just proximal to the bifurcation into the common iliacs, is almost invariably the first site for the formation of arterial lesions. These early lesions consist of subintimal deposition of fibrous material in close association with pools of highly metachromatic material which is believed to be acid mucopolysaccharide.1-3 This type of lesion is found, particularly in the female, soon after the first or second pregnancy. With continued breeding, or as arteriosclerosis becomes more severe, the morphological nature of the arterial lesions in the abdominal aorta becomes increasingly complex and varied. Medial elastic fibers stretch and fragmentize. These sites of elastic tissue degeneration are often demarcated by accumulations of mucopolysaccharide, degeneration or necrosis of ground substance, hemorrhage and calcification. It is at this stage of morphological complexity that the lesions can be detected grossly, i.e., as annular rings, or minimal arteriosclerosis. This type of lesion can be detected by gross inspection in the female breeder after the third or fourth pregnancy, i.e., at eight to nine months. With continued breeding, the single plaques seen in cases of minimal (gross) arteriosclerosis lose their annular arrangement and become confluent, extending along the abdominal aorta up to the level of the diaphragm proximally and down into the common iliacs distally.

Male breeder rats, after having sired four
PERIPHERAL ARTERIOSCLEROSIS IN RATS

to five litters, display microscopic lesions within the abdominal aorta similar to the early lesions described in the female breeder, e.g., after one to two pregnancies. However, these lesions do not reach such proportions that they can be detected grossly. The details of the progression of arteriosclerosis in the aorta with time and repeated breeding have been described.1,2

MESENTERIC ARTERIES

Soon after the microscopic lesions begin to develop in the abdominal aorta, the mesenteric arteries also begin to show microscopic evidence of arterial damage. Arterial damage appears first in the larger mesenteric arteries at their origin in the abdominal aorta and progresses distally into the smaller branches (fig. 1). The complexity and frequency of these lesions lessens midway between the origin and termination of the mesenteric arteries, only to increase in intensity and severity within the serosal layer of the intestines or

in the hilar portions of organs, e.g., spleen (fig. 2).

Microscopically, the lesions consist of linear streaks of subendothelial basophilic material which causes relatively little distention of the subintimal space. This material which is strongly basophilic with hematoxylin stain is moderately metachromatic but reacts intensely to the von Kossa, alcian blue, and Hale stains, indicating the presence of calcium and mucopolysaccharides. No lipid can be detected in these sites.

As arteriosclerosis becomes more advanced in the abdominal aorta, the lesions in the mesenteric branches show concomitant increased severity of degeneration. Although the endothelial cell lining remains intact and the quantity of subendothelial basophilic material increases only slightly, the internal elastic membrane becomes “thickened, stiffened, straightened,” and fragmented in many places. This elastic membrane invariably becomes coated with a substance which is both metachromatic and strongly positive to the alcian blue and Hale stains. In severe cases of arteriosclerosis, medial elastic tissue also fragments, calcification is frequent and in the more proximal portions of the mesenteric arteries, cartilaginous metaplasia may occur.

![Abdominal aorta (upper portion of figure) and mesenteric artery (below). Aorta shows severe medial elastolytic changes, calcification, and marked ground substance degeneration. Deeply black-stained material is mucopolysaccharide and calcium. Mesenteric artery shows endothelial hyperplasia and deposition of moderate amounts of mucopolysaccharide (grey-black). Elastic is becoming distorted. Medial smooth muscle cells are swollen and scattered dark black material throughout the media is mucopolysaccharide. Hale stain.](image1)

![Spleenic artery in hilus of spleen taken from a female breeder after three pregnancies. Note endothelial hyperplasia, fragmented and distorted elastic, swollen media and reduction of lumen. Hematoxylin and eosin.](image2)
Mesenteric artery showing moderate arteriosclerosis. Endothelial ingrowth practically occludes lumen. Endothelium is interlaced with collagenous tissue and contains fragments of elastica. This artery was taken from a female breeder following two pregnancies. Hematoxylin and eosin.

More distally, the intima shows intensive ingrowth of fibrous material which causes reduction of the lumen (fig. 3).

Male breeder rats, although seldom developing arteriosclerosis of the abdominal aorta, do develop lesions within the mesenteric and visceral branches of the abdominal aorta. These lesions resemble the early microscopic lesions found in female breeders, i.e., subendothelial deposition of an admixture of calcium and mucopolysaccharide. The pancreatic, splenic, and adrenal arteries, particularly in their hilar or capsular portions, show frequent arterial damage of the kind described above with equal frequency in both male and female breeder rats.

RENA L ARTERIES

The appearance of arteriosclerosis in the renal arteries of the female breeder parallels the progression and severity of arteriosclerosis in the abdominal aorta. In male breeders, however, arteriosclerosis of the renal artery is more frequent and appears to be independent of arterial degeneration in the mesenteric arteries. Also, in a temporal sense, these lesions in the renal arteries of male breeders are more advanced than in the other arterial branches.

Morphologically, the lesions in the renal artery are quite different from those found in other arteries. In breeder rats of both sexes, the renal artery displays the same subendothelial basophilic admixture of calcium and mucopolysaccharide and fragmentation of the internal elastica seen in other branches of the abdominal aorta. However, in addition to the above, a marked swelling of all of the smooth muscle cells of the media which is distinctive of the renal artery also occurs (fig. 4). The interspaces between the muscle cells of the media are filled either with mucopolysaccharide or with collagen, i.e., fibromuscular dysplasia. This unusual palisading of medial muscle cells with accompanying fibrosis has been found only in the renal artery and disappears abruptly at the point where the renal artery enters the hilus of the kidney. Thus the renal hilar arteries display subendothelial calcium-mucopolysaccharide deposits and fragmentation of the internal elastica only and no fibromuscular thickening of the media (fig. 5).

The renal arterial lesions described above begin to appear soon after the third pregnancy in the female and after the male has sired three to four litters. The lesions increase in frequency and complexity with con-
Hilar renal artery showing an intimal plaque framed by deeply basophilic and stiffened elastica (see arrow). Extending from right side of plaque the elastica is discontinuous and broken. Extending from left side of plaque the elastica is continuous but is deeply basophilic and is beginning to show loss of its normally crenated contour. Plaque and broken elastica are bathed by mucopolysaccharides and metachromatic material. This early lesion in a renal hilar artery should be contrasted with those in other portions of the renal artery (see figs. 4 and 6). Verhoeff-van Gieson elastic tissue stain.

The lesions found in the arteries within the renal parenchyma are entirely different from those observed in the main renal artery (fig. 4) and are distinctly different from lesions in any other renal arteries. The larger intrarenal arteries display intimal cushions of endothelial cells (fig. 6) which are negative to: (1) calcium and mucopolysaccharide stains; (2) metachromatic dyes; and (3) lipid stains. Although there is swelling of medial smooth muscle cells with reduction of the lumen, specimens showing complete occlusion of blood flow have not been encountered.

Arteriolosclerosis is frequent in the kidneys of both male and female breeders which have given birth to or have sired five litters. These animals are often hypertensive and the kidneys show both arterio- and arteriolosclerosis (fig. 6), together with glomerulosclerosis, tubular dilatation, infarction, shrinkage, calculi, marked cast formation, and other obstructive changes associated with arteriosclerosis (to be published).

**PERIPHERAL ARTERIES**

In the female breeder grossly visible arteriosclerosis is often found in the aorta without grossly visible lesions in the common iliac arteries. Conversely, the male breeder often has grossly visible lesions in the iliac arteries although the aorta is grossly normal. Despite the earlier and more advanced arterial degeneration in the iliac arteries of male breeders, their lesions seldom become as severe as those in female breeders (fig. 7). Again, complete study of the development of arterial lesions is hampered by the early death of the male breeder, i.e., after having sired four to five litters.

The special study of peripheral arteries reveals that although medial calcification and elastosis occur in the iliac arteries of male breeders, the more distal arteries of the extremities show only slight change. The only consistent finding in males was swelling of medial smooth muscle cells leading to reduction of the lumen and some deposition of metachromatic material in the subendothelial space. This material reacted positively to alcian blue and to Hale stain and is probably mucopolysaccharide. Similar changes are found in the brachial, radial, and ulnar arteries of the male breeder. However, the subclavian arteries often show subendothelial swelling, proliferation of deeply basophilic mesenchymal cells, and cartilaginous metaplasia, all within the subintimal space. The cartilaginous cells are surrounded by a deeply basophilic halo which also reacts positively to alcian blue and Hale stain. This type of lesion has been described as occurring frequently in the arch of the aorta, innominate, and carotid arteries and its occurrence in the subclavian arteries is believed to be an extension of this same process into the adjacent subclavian arteries.
Although the female breeder ordinarily shows little evidence of gross arteriosclerosis, they, nonetheless, do display severe arterial damage in the peripheral arteries (figs. 7 and 8). Lesions are usually found in the more proximal portions of peripheral arteries such as the femoral and tibial, brachial, radial, and ulnar. The earliest consistent change common to these arteries appears to be a deposition of acid mucopolysaccharide between the internal elastica and the endothelial cells. Swelling of medial smooth muscle cells leads to reduction of the lumen. Later, both the internal elastica and medial elastic fibers swell, accumulate mucopolysaccharide in their immediate vicinity and, finally, break.

In the more proximal portions of the femoral artery, the lining endothelial cells appear to be unusually reactive (figs. 7 and 8). In this region, the endothelial cells undergo active proliferation leading to virtually total occlusion of the lumen. These occlusive masses...
of endothelial cells become fibrosed, and they contain copious amounts of mucopolysaccharide but little or no lipid. Special elastic tissue stains indicate that the internal and external limiting membranes are particularly prone toward fragmentation in arteries of this calibre and location. In addition to hypertension, which occurs frequently in breeder rats, these animals also show muscular degeneration, inflammation, swelling, and gangrene, especially of the lower extremities (fig. 9).

**INCIDENCE AND SEVERITY OF ARTERIOSCLEROSIS IN THE ABDOMINAL AORTA, MESENTERIC, RENAL, AND PERIPHERAL ARTERIES OF BREEDER RATS**

**A. Male Breeders**

As shown in table 1, in male breeder rats the incidence of arteriosclerosis of the abdominal aorta becomes fairly high with repeated breeding but the lesions are of minor grade. Minor changes in the mesenteric arterial branches of the abdominal aorta appear earlier but remain relatively infrequent. The renal artery appears to show a particularly early predilection toward the development of arterial lesions with a lag in the appearance of changes in the intrarenal arteries. The iliac arteries show the most severe evidence of arterial degeneration, often displaying lesions which are grossly detectable. Despite the severity of the arterial lesions in the iliac arteries, the lesions in the femoral and tibial arteries become progressively less frequent and severe but are still much more frequent and severe than those in the arteries of the upper extremity (table 1), giving rise in some to circulatory complications, e.g., gangrene (fig. 9).

**B. Female Breeders**

By direct contrast, arterial degeneration appears promptly and is much more severe in the abdominal aorta and mesenteric branches of the female breeder (table 2). Development of arteriosclerosis of the renal and intrarenal arteries of the female breeder lags behind the male breeder during early breeding activity. However, there is a very sharp rise
Comparison of Incidence (in per cent) and Average Severity (score: 1—5)* of Microscopic Arterial Lesions in the Abdominal Aorta and in Mesenteric, Renal, and Peripheral Arteries of Repeatedly Bred Male Sprague-Dawley Rats

<table>
<thead>
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<th>Number of littera sized</th>
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<td></td>
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<tr>
<td>Abdominal aorta</td>
<td>0%</td>
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<tr>
<td></td>
<td>(0)</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>(0)</td>
</tr>
<tr>
<td>Renal</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>(0)</td>
</tr>
<tr>
<td>Intrarenal</td>
<td>0%</td>
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<tr>
<td></td>
<td>(0)</td>
</tr>
<tr>
<td>Upper extremity, e.g.,</td>
<td></td>
</tr>
<tr>
<td>brachial, ulnar, and radial</td>
<td>0%</td>
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<tr>
<td></td>
<td>(0)</td>
</tr>
<tr>
<td>Iliac t</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>(+1)</td>
</tr>
<tr>
<td>Lower extremity, e.g., femoral and tibial</td>
<td>0%</td>
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<td>(0)</td>
</tr>
</tbody>
</table>

* Scoring system for severity of arterial lesions: (+ 1) = intim- nal lesion only. (+ 2) = intimal + medial involvement but without complications, such as calcification, ulceration. (+ 3) = intimal + medial involvement with elastosis, necrosis and calcification but in isolated foci. (+ 4) = same as above but showing extensive confluence of foci of involvement and complications such as ulceration and cartilagenous metaplasia. (+ 5) = grossly visible lesions, i.e., extension of conditions observed in a + 4 lesion.

† The iliac artery in the male breeder rat is the only site in which grossly visible arteriosclerotic plaques can be readily detected. Data cited for the iliac artery include both gross and microscopic observations.

Discussion

The most significant features in the investigation of the spontaneous development of arteriosclerosis in repeatedly bred rats are the diversity of the morphological nature of the arterial lesions in general, and the characteristic specificity of the morphological nature of the lesions within a particular an-
TABLE 2

Comparison of Incidence (in per cent) and Average Severity (score: 1—5)* of Arterial Lesions (gross and microscopic) in the Abdominal Aorta and in Mesenteric, Renal, and Peripheral Arteries of Repeatedly Bred Female Sprague-Dawley Rats

<table>
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<th>Arteries</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal aorta</td>
<td>13%</td>
<td>25%</td>
<td>67%</td>
<td>73%</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>(+1)</td>
<td>(+2)</td>
<td>(+5)</td>
<td>(+5)</td>
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<tr>
<td>Mesenteric</td>
<td>5%</td>
<td>8%</td>
<td>24%</td>
<td>50%</td>
<td>87%</td>
</tr>
<tr>
<td></td>
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<td>(+2)</td>
<td>(+3)</td>
<td>(+4)</td>
<td>(+5)</td>
</tr>
<tr>
<td>Renal</td>
<td>1%</td>
<td>1%</td>
<td>3%</td>
<td>42%</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td>(±1)</td>
<td>(+1)</td>
<td>(+2)</td>
<td>(±3)</td>
<td>(±3)</td>
</tr>
<tr>
<td>Intrarenal</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
<td>12%</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>(0)</td>
<td>(±1)</td>
<td>(+1)</td>
<td>(+1)</td>
<td>(+2)</td>
</tr>
</tbody>
</table>

| Upper extremity, e.g.,          | 0%  | 0%  | 2%  | 19% | 53% |
| brachial, ulnar, and radial     | (0)  | (0)  | (+1) | (+2) | (+3) |
| Iliac                           | 0%  | 2%  | 3%  | 25% | 69% |
|                                 | (0)  | (±1) | (+1) | (+3) | (+4) |

| Lower extremity, e.g.,          | 0%  | 0%  | 4%  | 21% | 72% |
| femoral and tibial              | (0)  | (0)  | (+1) | (+2) | (+3) |

* Scoring system of severity of arterial lesions: same as given in footnote of table 1.

atomical locale of the aorta or of its branches. Of added significance is the order of precedence in which different portions of the aorta and its branches develop arteriosclerosis. Furthermore, those factors which may initiate arterial degeneration are not necessarily the same as those which are involved in the formation of the more advanced lesions. Breeding appears to accelerate the development of arteriosclerosis since virgin male and female rats do not develop any of the lesions described here until they are well over one year old.1-3 Finally, the sex hormones may play a vital role in conditioning the response of the aortic wall to those factors which both incite and cause complications of arterial lesions.

Because arteriosclerosis begins in the abdominal aorta, the morphological nature of the early lesion is of special import. The sequence of events of subendothelial edema, accumulation of mucopolysaccharide, and eventual replacement by fibrotic material suggests that the fundamental processes involved are alterations in the physicochemical composition of intimal ground substance leading to scar tissue formation. Mesenchymal cells are found in great number in these foci and histochemical tests indicate that these cells are surrounded by, and probably secrete, acid mucopolysaccharides and phospholipids (studies to be published). In this same connection, others have described arterial smooth muscle cells as being responsible for the formation of fibrous material6 or of lipid.7 It is interesting that, with continued development of arteriosclerosis in the abdominal aorta, the smooth muscle cells and elastic fibers of the media also show accumulation of mucopolysaccharide material in their immediate vicinity. Blumenthal et al.8 described accumulations of calcium, and later mucopolysaccharides, in close association with degenerating elastic tissue.

It is particularly noteworthy that although the abdominal aorta in the female breeder is consistently the earliest site for arterial degeneration, it lags behind in the temporal development of more severe arteriosclerosis until other segments of the aorta also develop evidence of degeneration. Thus the intimal changes described above also appear in the...
arch and thoracic portions of the aorta but in these latter sites the lesions, once started, develop more quickly in size and complexity. Subsequently the lesions in the abdominal aorta also increase in size and complexity but seldom become as severe as those in the arch and carotid branches of the aorta.  

In breeder rats the severity of arteriosclerosis of the mesenteric arteries correlates with the severity of arteriosclerosis in the abdominal aorta. A similar correlation is found in man. The mesenteric branches show reduced frequency and severity of lesions as one proceeds distally. Furthermore, the severity of lesions increases as the artery approaches the serosal layer of the intestine or the hilar portion of the organ which it nourishes. Perhaps this pattern is due to changes in blood pressure as well as to the vascular architecture and structure. The mesenteric arteries show a predilection towards intimal calcification and mucopolysaccharide deposition. Calcification of the intima of mesenteric arteries is also frequently found in man. Although the male breeder rat does not develop severe arteriosclerosis of the abdominal aorta it does develop mesenteric arterial lesions which are equal in severity to those found in the female breeder. It has been observed that the ostia of the mesenteric branches within the wall of the abdominal aorta show heavy deposition of mucopolysaccharides both in the intima and media which is associated with narrowing of the origin of the artery and often with thromboses occluding the lumen. This type of occlusion of branching arteries has been observed with equal frequency in male and female breeders. The thromboses, alterations of ground substance, and occlusion of the lumen in both male and female breeders could explain why mesenteric arterial lesions are so frequent in both sexes despite the existence of less severe arteriosclerosis in the abdominal aorta of the male breeder.

The fibromuscular dysplasia observed in the main renal artery may be due to alterations of connective tissue ground substance, i.e., to abnormal production of mucopolysaccharides by smooth muscle cells with subsequent production of collagen. The fibromuscular dysplasia of the main renal artery followed by another type of lesion in its hilar segment, i.e., intimal basophilia and distortion of elastic tissue, and distally by the intimal cushions of the intrarenal arteries indicate that the varied nature of these arterial lesions must be related to structural and functional stresses. Because of the constrictive nature of all of these lesions, it is not difficult to understand why these breeder rats also develop glomerulosclerosis, marked proteinuria, contraction of the renal parenchyma, hypertension, and renal calculi. These renal arterial lesions may also be conditioned by certain hormonal and metabolic conditions which occur after repeated breeding. For example, the breeder rats manifest disturbed adrenocortical function, and may develop a steroid type of diabetes. The vascular complications often associated with diabetes in man, such as gangrene, may be related to the gangrene and peripheral arteriosclerosis seen in these breeder rats (fig. 9).

The paradoxical finding of severe gross arteriosclerosis in the abdominal aorta but none in the iliac arteries of the female, contrasted with no grossly visible arteriosclerosis in the abdominal aorta but gross plaques in the iliac arteries of the male breeder, is perhaps another example of the conditioning effects that sex hormones may have on the development of arteriosclerosis of arteries in various locales. The finding of more severe arterial complications in the proximal portions of the arteries of the extremities with localized areas of involvement, decreasing in severity distally, is much like the pattern of peripheral arteriosclerosis observed in man. It should also be remembered that the terminal portion of the aorta and the proximal portions of the common iliac arteries are the foci in which thromboses are most frequently encountered in breeder rats. This anatomical site presents a logical nidus for thrombosis because of physical factors and the nature of the morphological lesions at this point, i.e., endothelial hyperplasia, the abrupt divergence of
arterial flow, and the tendency toward abnormal clotting of blood observed in breeder rats. The earlier death of the male breeder as compared to the female, despite much less severe arteriosclerosis in the male, is ascribed to the appearance of the seemingly minor arterial lesions which occur, nevertheless, in crucial foci. For example, in the male breeder, arterial lesions occur in the coronary arteries, at the ostia of branches along the entire length of the aorta, in the mesenteric arteries, in the renal arteries, and in the proximal portions of the arteries to the extremities. Male breeder rats are also particularly susceptible to myocardial necrosis and it is believed that their death is often due to heart failure. The female breeder develops severe arteriosclerosis but manages to adapt to or live with the progressing disease.

In conclusion, previous studies have shown that the severity of coronary arteriosclerosis in female breeder rats correlates directly with the severity of arteriosclerosis in the abdominal aorta. In male breeders coronary arteriosclerosis is more closely correlated with arteriosclerosis of the mesenteric arteries. In general, the cerebral arteries appear to lag behind in the development of arterial degeneration but arteriosclerosis in the carotid arteries parallels the severity and temporal development of arteriosclerosis in the abdominal aorta. It appears that mesenteric branches show arterial damage which is also commensurate with arteriosclerosis of the abdominal aorta. These experimental findings are in keeping with what has been observed in man. For example, Mitchell and Schwartz and others have shown that patients with arterial disease in one part are likely to show disease elsewhere and that the severity of the disease in one site may not correlate with the amount or severity of disease in other arteries. These authors as well as Malajatzkaja and Reiner et al. have shown that there is a significant and direct correlation between coronary arteriosclerosis, myocardial infarction, and stroke with the severity of abdominal aorta and mesenteric artery disease and with peripheral artery disease as well. A similar correlation between coronary, mesenteric, and peripheral artery arteriosclerosis seems to obtain in breeder rats.

Summary
Repeatedly bred male and female rats develop arteriosclerosis spontaneously. The arteriosclerosis appears to be accelerated by breeding because virgin rats of comparable age do not develop arterial disease. The arterial lesions begin in the abdominal aorta and consist of subendothelial swelling, mucopolysaccharide accumulation and eventual fibrosis. With continued, active breeding, the arterial lesions continue to increase in severity in the abdominal aorta, becoming grossly visible in the female breeder and of microscopic proportions in the male breeder. Concomitant with the increasing severity of arteriosclerosis in the abdominal aorta, the mesenteric arteries and the visceral branches also show increasing numbers of arterial lesions. The lesions in the mesenteric and visceral branches are of varied morphology. The main renal artery, for example, shows fibromuscular dysplasia, its hilar portion displays intimal basophilia and elastosis and the intrarenal branches develop intimal cushions.

The male breeder develops severe, grossly visible lesions in the proximal portions of the iliac arteries, the lesions becoming less complex distally. The female breeder shows no grossly visible lesions in the iliac arteries but arteriosclerosis is severe throughout the length of the arteries to the extremities, the severity of these lesions being proportional to the arteriosclerosis in the abdominal aorta and its branches.

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Circ Res. 1964;15:485-496
doi: 10.1161/01.RES.15.6.485

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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