Spontaneous Coronary Arteriosclerosis in Repeatedly Bred Male and Female Rats

By Bernard C. Wexler, Ph.D.

The spontaneous development of generalized arteriosclerosis in several strains of repeatedly bred male and female rats has been reported. The arterial lesions remain microscopic in the male but in the female breeder the lesions become more prominent and can be easily recognized grossly. Of particular importance is the fact that these arterial lesions develop spontaneously although the rats are fed a diet which has a low fat content (4%). Further, the development of the arterial lesions can best be correlated with the number and frequency of breedings. In addition, the arterial changes appear in anatomical sequence. That is, after the lesions have developed throughout the length of the main aorta, the coronary arteries then begin to show evidence of degenerative change. When arteriosclerosis has become advanced in both systemic and coronary artery beds, the cerebral arteries begin to show arterial damage. The changes in the carotid and cerebral arteries have been reported.

In this paper, the changes in the coronary arteries and hearts of these breeder rats will be described.

Methods

Several strains of breeder rats have been examined: Sprague-Dawley, Holtzman, Mead- Johnson, Long-Evans, Wistar and Lewis. Our experience has been most extensive with the Sprague-Dawley rat of the Sprague-Dawley Farms, Madison, Wisconsin. This strain of rat is bred in a closed colony established forty years ago from litters delivered by Caesarian section. When male or female rats have outlived their usefulness as breeders they are discarded. Our laboratory has been receiving these discarded breeder rats for study and experiment for the past six years during which time several thousand such male and female rats have been examined. These shipments of commercial breeder rats are not uniform in that no exact record is kept of the number of breedings for each rat. However, most of the male breeder rats have sired at least four to five litters and the female breeders average four to five litters before discard. Extensive histological observations have been made on 2800 of these animals.

In addition to this material, several long-term controlled breeding studies involving young Sprague-Dawley rats obtained from the identical strain as the discarded breeder rats have been conducted in our own animal colony and more precise records of breeding history have been maintained. In each of these long-term breeding experiments, approximately 400 male and female rats were paired and each pair was housed undisturbed in a separate breeding cage throughout the breeding period. Because of the large number of animals, a minimum of 24 animals of each sex could be removed for sacrifice after each breeding. A history was compiled to record the vascular and other changes which occurred with repeated breeding, i.e., after one, two, three, four, five and six breedings. Male and female virgin rats of identical strain and source were sacrificed at proper intervals along with the breeders to serve as controls for breeding and age. The material from these studies is included in this report. Finally, in order to confirm the spontaneous occurrence of coronary arteriosclerosis in other strains of breeders, the strains mentioned above were also included. Studies pertaining to the hearts and coronary arteries are included in this present report. For each strain other than Sprague-Dawley, approximately 100 male and 100 female breeders were autopsied.

All animals were sacrificed by decapitation as soon as possible after arrival in this laboratory. At autopsy, the heart, carotid arteries, main aorta with the iliac bifurcation, and proximal portions of the iliac arteries were exposed. After gross examination, the heart and aorta were dissected. The heart was separated from the aorta at the base of the ascending portion of the arch of the.
CORONARY ARTERIOSCLEROSIS IN BREEDER RATS

1.3

FIGURE 1

Normal coronary artery of a virgin female control rat. Lumen is of the usual diameter and the media of normal width. Note that the tunica intima is extremely delicate. (There is essentially no difference between the coronary arteries of male virgin rats and female virgins.) Compare with coronary arteries of breeder rats. Hematoxylin and eosin stain \( \times 250 \).

Aorta, and both the heart and aorta were fixed in 10% buffered neutral formalin.

The tissues were embedded in paraffin and sectioned at 3\( \mu \). Frozen sections were cut at 10\( \mu \). Adjacent sections were stained with hematoxylin and eosin for routine analysis; both Verhoeff van Gieson and Gomori’s aldehyde fuchsin stains for elastic tissue; alcian and toluidine blue for metachromasia; the Hale stain for acid mucopolysaccharides; the von Kossa stain for calcium; and Sudans II and III, oil red O, and Sudan black B were used to demonstrate lipids on the frozen sections.

The term “arteriosclerosis” is used throughout this paper to describe all of the different types of lesions found in the coronary artery. The term “atherosclerosis” has not been used because of the paucity of lipid in these lesions. 3

Results

LESIONS OF THE CORONARY ARTERY

A variety of coronary artery lesions have been found to be common in the hearts of all strains of repeatedly bred male and female rats. The nature of the lesion appeared to be dependent upon its location within the coronary artery. The character of the arterial lesions of the epicardial coronary arteries was distinct and different from that of the myocardial and smaller subendocardial branches of the coronary arteries.

Small-Sized Subendocardial Branches

Arteriosclerotic changes begin first in the small subendocardial branches which are about 50 to 75\( \mu \) in diameter. (figs. 1 and 2). Subendocardial arteries show no deposition of basophilic material and the elastic tissue is so delicate that it is difficult to visualize. Individual muscle cells in these arteries appear to swell and often cause virtually complete occlusion of the lumen (fig. 2). The arterial wall frequently contains large vacuoles. Vacuoles are consistently negative to lipid stains but stain positively for mucopolysaccharides. This lesion frequently escapes detection un-
less serial sections of the heart are examined. Therefore, no precise record has been made of its incidence. However, our experience to date indicates that this type of lesion appears earlier and more frequently in male breeder rats (table 1). Lesions of the same kind were found in several strains of breeder rats of both sexes with early arteriosclerosis.

**Medium-Sized Myocardial Branches**

The medium-sized myocardial branches are next to develop arteriosclerotic changes. These arteries are approximately 100 to 300 μ in diameter. The normal tunica intima of the myocardial coronary artery of the rat is very thin and consists of one layer of cells with a potential subintimal space (fig. 1). In normal coronary arteries mucopolysaccharide cannot be detected. The lesions which develop in these arteries show degenerative changes which are more severe than those found in the subendocardial branches. First, the subintimal basophilic, metachromatic and Hale stain positive material is less copious in lesions of the main myocardial branches than in the epicardial arteries. Second, this material is distributed most frequently in clumps or as granules. And, third, no calcium is detected by the von Kossa stain. The myocardial arterial lesions are also characterized by more prominent involvement of the internal elastic membrane. Elastic tissue involvement is most often focal rather than circumferential. These arteries do not show the great distension that the larger branches display. Further, the myocardial arteries show focal hyperplasia of intimal cells so that endothelial cushions are frequently found (figs. 3 and 4). These intimal cushions contain mucopolysaccharide material but no lipid. In the media, the smooth muscle cells become swollen and often appear vacuolated. Rounded clear spaces are found in the intima and media of the myocardial branches. They are negative to lipid stains, nonmetachromatic and Hale stain positive (fig. 5). The intimal cushions eventually are replaced by

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**TABLE 1**

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<tr>
<th>Strain</th>
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* Hearts of 100 male and 100 female breeder rats of each strain were examined in this particular survey, i.e., a total of 400 males and 400 females. Two sections of each heart were examined microscopically. Each of the breeder rats had sired or given birth to four to five litters.

† Only those arteries showing reduction of the lumen to a slit-like opening accompanied by definite swelling of smooth muscle cells were recorded.

‡ Arteries of this caliber showing either definite intimal cushions, granular basophilia about elastic fibers or elastolytic lesions were recorded.

§ Epicardial branches showing any deposition of mucopolysaccharides, calcium, elastolytic changes or intimal cell proliferation were recorded.

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CORONARY ARTERIOSCLEROSIS IN BREEDER RATS

FIGURE 3
Medium-sized myocardial artery showing intimal endothelial cushion subtended by a contorted and broken internal elastic membrane (see arrows). The contour of this membrane is accentuated by the deposition of basophilic material. (Sprague-Dawley female breeder, bred four times.) Hematoxylin and eosin stain x 250.

fibrous material (fig. 5). This lesion has been found with about the same frequency in both male and female breeder rats after the 4th to 5th breeding (table 1).

Larger Epicardial Branches
The larger epicardial branches of the coronary artery in the rat by definition are those which lie just beneath the epicardium. These arteries, when normal, range from 250 to 500 μ in diameter. However, when abnormal, they may become distended three to nine times their normal size. These arteries are least prone to develop arteriosclerosis. They usually do not show degenerative involvement until arterial degeneration has become extensive throughout the subendocardial and myocardial branches. Therefore, it appears that coronary arteriosclerosis is a retrogressive process in the breeder rat. It starts first in the smallest coronary arteries and extends proximally toward the main epicardial branches (table 1).

The first change observed in the epicardial branches is a subintimal deposition of an intensely basophilic material between the delicate endothelial cell layer and the internal elastic membrane (fig. 6). This substance is intensely hematoxylin-positive, metachromatic, Hale stain positive, and reacts positively to the von Kossa stain. It appears to be an admixture of calcium and acid mucopolysaccharides. With the lipid stains employed thus far, this material consistently fails to stain. In certain foci, cushions of endothelial proliferation are encountered. This is especially evident in those areas where the internal elastic membrane is fractured (fig. 6). The endothelial cell boundaries within the intimal cushions become prominent by virtue of an

FIGURE 4
Medium-sized coronary artery showing intimal cushion of larger proportions than that shown in figure 3. Also, the granular basophilia (this material is also metachromatic and stains positively for acid mucopolysaccharides) surrounds the internal elastic membrane (see arrows) about the entire circumference of the artery. Note the increased diameter of this artery (fig. 3) with more extensive involvement. Hematoxylin and eosin stain x 250.
increase of mucopolysaccharide material. In time, these endothelial cells are replaced by fibrous tissue (figs. 6 and 7). The epicardial branches showing this type of lesion are always dilated so that they may be seen grossly protruding through the surface of the heart. With advancing arteriosclerosis, the lumens of the epicardial branches become even more enlarged with distension and thinning of the arterial wall. With distension of the epicardial branches, an even greater content of Hale stain positive, metachromatic, and basophilic material is evident. This material is probably largely composed of acid mucopolysaccharides. Like the earlier changes described above, calcium also can be detected in the more advanced lesions. These changes occur in female breeder rats usually after they have borne five or six litters. Only a few male breeders have been observed to develop these advanced coronary lesions in the epicardial coronary branches. Most male breeders die before this stage of the coronary arteriosclerosis is reached (table 1).

MYOCARDIAL LESIONS ASSOCIATED WITH CORONARY ARTERIOSCLEROSIS

A variety of myocardial degenerative changes appear when the process of coronary arteriosclerosis has become well established. Therefore, it is assumed that the myocardial degenerative changes are in some way connected with the development of coronary arteriosclerosis. Myocardial scarring, endocardial fibrosis, valvular degenerative changes, calcification of the bases of the papillary muscles, and disappearance of myocardial mast cells have been observed in the several strains examined.
Myocardial Scarring

Evidence of infarct-like lesions of the myocardium in the hearts of rats with advanced arteriosclerosis is common (fig. 8). However, most of the lesions are old and so well-healed that they consist of small areas of scar tissue (table 2). Occasionally, large areas of acute myocardial necrosis are found at autopsy. These necrotic sites are characterized by heavy infiltration with white blood cells dominated by the polymorphonuclear granulocyte followed by a marked increase of acid mucopolysaccharide material and rapid healing. The infarct-like lesions frequently occur within the subendocardial layer. In the more fulminating cases, they may extend to the pericardium. They are found most often in the apex and body of the left ventricle, either as consolidated areas or in splotchy arrangement. The scars and infarctoid lesions show no recognizable anatomic relationship to the coronary arteries which display arteriosclerotic alterations.

Endocardial Fibrosis

On occasion, massive endocardial fibrosis has been found in both the left atrium and ventricle of the hearts of breeder rats with advanced coronary arteriosclerosis (fig. 9). It has appeared in both male and female breeder rats (table 2). It bears some resemblance to organized thrombi, however fresh mural thrombi in these sites have not been observed.

Valvular Degenerative Changes

Degenerative valvular damage is frequently observed in rats with advanced arteriosclerosis (table 2). The observed changes have not been seen in nonbreeder control rats. The valves often stain very intensely with the Hale stain and are, at the same time, intensely metachromatic with alcian and toluidine blue. Many of the valve bases are heavily scarred (fig. 10). Although the rat normally shows increasing calcification of the annulus fibrosis with age, this process is definitely accelerated in these breeder rats. The annulus is transformed into large bars of cartilage. Cartilaginous metaplasia can be detected radiating from the valve base into the leaflets and into

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* Hearts of 100 male and 100 female breeder rats of each strain were examined in this particular survey, i.e., a total of 400 males and 400 females. Two sections of each heart were examined microscopically. Each of the breeder rats had sired or given birth to four to five litters.
† Both large and small scars are included.
‡ Any abnormal deposition of mucopolysaccharide, collagen, extensive cartilaginous metaplasia or calcification was considered as evidence of valvular degeneration.

Circulation Research, Volume XIV, January 1964
FIGURE 7
Same artery as figure 6 showing extensive deposits of acid mucopolysaccharides (deep black material in photo) interlacing between endothelial cells and inundating the media. Light grey areas are collagen deposits (see arrows). Hale stain × 150.

the truncus of the aorta away from the semilunar valves (fig. 11).

Papillary Muscles
In advanced cases of coronary arteriosclerosis, the proximal portions of the papillary muscles become calcified (fig. 12 and table 2). Morphologically, the cartilaginous material is arranged in a manner resembling spicules of bone. The spicules of cartilage are intensely metachromatic and Hale stain positive. A positive von Kossa stain indicates that these areas contain calcium. These changes appear to be limited to the base of the muscle and are found in both ventricles. The muscle cells of the myocardium contain no abnormal calcium deposits.

Myocardial Mast Cells
Myocardial mast cells are fairly numerous in the rat and are found clustered about the precapillary vessels. In the controlled breeding studies, the myocardial mast cells disappear concomitant with developing systemic and coronary arteriosclerosis (to be published).

FREQUENCY OF OCCURRENCE OF CORONARY ARTERIOSCLEROSIS IN BREEDER RATS
The frequency of occurrence of coronary arteriosclerosis in arteriosclerotic breeder rats is difficult to determine with any degree of reliability. Since the earliest coronary lesions appear in the small subendocardial branches, a diagnosis of coronary arteriosclerosis may be missed unless serial sections of each heart are examined. To date, only random sections (usually two or three) of each heart have been studied (table 1). An animal was considered to have coronary arteriosclerosis even when the coronary arteries contained slight microscopic lesions. The approximate incidence of coronary arteriosclerosis in breeder

FIGURE 8
The two large grey areas, A and B, are myocardial scars. These scars are believed to be sites of repair of infarct-like lesions which develop spontaneously and are most frequently found in the apex and left ventricle of the heart. Hematoxylin and eosin stain × 50.
Coronary arteriosclerosis in breeder rats, males and females combined, was found to be: Sprague-Dawley breeders, 28%; Holtzman breeders, 40%; and Long-Evans breeders, 48%. In general, the incidence of lesions of coronary arteries in male rats is twice that in females. However, coronary lesions in the male breeders are usually confined to the subendocardial branches (vide supra) whereas the female breeders display much more severe lesions in the myocardial and epicardial branches (table 1).

In the controlled, long-term breeding experiments, the earliest coronary lesions were found after the second breeding. These early lesions were confined to the small subendocardial branches. The frequency with which these lesions were found increased with each breeding. After the second breeding, the frequency was only 2%, after the third breeding 5%, after the fourth breeding 12%, and by the fifth breeding the frequency increased to 20%. None of the control male or female virgin rats developed arteriosclerosis or coronary artery lesions.

Discussion

The spontaneous development of coronary arteriosclerosis in breeder rats has special interest because the rat is reputed to be highly resistant to this disease. Coronary arteriosclerosis appears spontaneously in senile male and female virgin rats. The disease appears to be accelerated by breeding since coronary arteriosclerosis develops in the breeders as early as 9 to 12 months. Furthermore, the coronary lesions develop without hormonal and dietary manipulations.

The order of development of the arterial lesions appears to follow a pattern which is similar to that found in man. The appearance of arteriosclerosis in the abdominal aorta and main aorta first, followed by sclerosis of the coronary arteries and eventually the cerebral arteries, would reinforce the contention that...
the factors which influence the physiological regulation of these arterial beds are not identical.\textsuperscript{7-9}

In this connection, it should be pointed out that there are striking differences in the morphological appearances of the arterial lesions in the coronary, cerebral, main aorta, and peripheral arteries of these breeder rats. This variegated pattern of lesions according to the particular arterial bed has been found consistently in breeder rats of several strains.\textsuperscript{1,10}

The outstanding variant encountered in these studies has been the severity of these lesions as they develop in the different strains. The severity of the arterial lesions is believed to be related to the frequency with which the animals are bred; i.e., animals bred repeatedly without rest have more intense arteriosclerosis than animals allowed to rest between breedings. Further, the marked sex differences in the morphology and pathogenesis of arteriosclerosis in breeder rats indicate that sex hormones may condition the response of the arterial wall to the arteriosclerosis-inciting mechanism.

It is interesting that the subendocardial branches of the coronary artery are the first coronary arteries to show abnormalities. In the myocardial arteries a relationship may exist between the appearance of clumps of basophilic material orientated about the elastic fibers and the prevalence of elastolytic changes in the media. Mucopolysaccharides are known to play a vital role in the maintenance of elastic tissue and normally serve as structural binding elements in the elastic tissue.\textsuperscript{11,12} In the initial phases of elastosis this material imbibes water and aggregates into hydrophilic clumps. As the degeneration of elastic tissue proceeds, these clumps coalesce and the mucopolysaccharide material becomes more diffuse.
This is characteristic of the more advanced lesions. It is in these foci of degenerative changes, especially in the inner media, that the overlying endothelial cells proliferate to form intimal cushions. The endothelial proliferations contain intracellular mucopolysaccharide. They do not contain demonstrable lipid. Like other endothelial proliferative sites elsewhere in the aorta, these coronary endothelial cushions become fibrosed.

In contrast to the medium-sized coronary arteries, the larger epicardial branches were found to contain calcium, in sufficient amounts to be demonstrable, in association with mucopolysaccharides. Some mechanism is indicated which imparts a greater tendency towards calcification in the epicardial coronary arteries than in the myocardial arteries. This occurs despite their close similarity in structure and the presence of mucopolysaccharides common to both. Hass has written an excellent review on pathological calcification in which such a concept of a calcification potential or gradient is explored. One wonders if the physical pressure of the surrounding myocardium may decrease the need for maintaining the structural rigidity of these medium-sized arteries by calcification. In the case of the larger epicardial branches, however, the presence of calcium could promote increased polymerization of mucopolysaccharides. The increased polymerization would provide the turgor or rigidity required by the exposed epicardial arteries.

The absence of lipid, especially in the early coronary lesions, is typical of early lesions in the other arterial beds of these rats. Lipid is found only in the more advanced lesions which show necrosis or medial calcification. The coronary arteries, therefore, resemble the other arterial branches in that they first show mucopolysaccharide accumulation, followed by fibrosis.

Recently, Gresham et al. conducted a comparative histopathological study of the early atherosclerotic lesion in man and other species and found that the lesion was predominately fibrous with quantities of extracellular mucopolysaccharide and little lipid. The lesions described here in the breeder rat bear close resemblance to those described by Gresham et al., Moon, and Levene. The tentative interpretation is that the mucopolysaccharide is laid down by mesenchymal elements and is subsequently converted to collagenous material which caps and eventually replaces the endothelial cushions.

The marked sex difference in the severity of arteriosclerosis observed in the main aorta is also reflected in the case of the epicardial coronary branches. That is, the female breeder develops more severe and fulminating arteriosclerosis than the male breeder and also develops more complicated lesions in the epicardial branches. Epicardial arteries of female breeders with advanced systemic arteriosclerosis usually show marked calcification. A similar observation was made by Gillman and Hathorn with female breeders of the Glaxo strain. Severe coronary arteriosclerosis has seldom been encountered in male breeders. Perhaps this is so because, paradoxically, the male breeders do not survive long enough for their lesions to become severe.

The author has been particularly impressed with the severity of the calcification and the elastolytic and other degenerative changes which occur in the epicardial branches. Many of these arteries were distorted and stretched and portions of the artery appeared flaccid at necropsy. An artery deprived of its normal elasticity and resiliency would be expected to dilate and become flaccid in vivo and remain patent. Therefore, the author wonders if the finding of myocardial infarct-like lesions in these animals is more probably due to compromising of blood flow in smaller coronary arteries. The well organized, small scars in the myocardium of arteriosclerotic breeder rats have been interpreted as healed sites of myocardial necrosis. Apparently, the infarct-like lesions are rapidly repaired because of the rich collateral coronary circulation in the rat. In this connection, Wexler and Kittinger have found that massive myocardial necrosis induced by the drug isoproterenol in the Sprague-Dawley rat undergoes very rapid repair. Neither the drug-induced, nor the spontaneous myocardial necrosis can be linked with thromboses or any...
significant alteration in the structure of adjoining coronary arteries. Perhaps, in the rat the death of myocardial tissue is due to spasm of the coronary arteries (particularly smaller arteries) rather than to sclerotic occlusion of the coronary arteries.

Degenerative changes in the heart valves and the general phenomenon of arteriosclerosis in these comparatively young breeder rats is interpreted as an acceleration of the aging process. It is well known that many species have increasing cartilaginous deposits in the annulus fibrosis of the heart with age. However, the premature character of the cartilaginous change and the marked mucopolysaccharide deposit and scarring in these valves indicate an acceleration of the normal aging process. Valvular lesions of almost identical morphologic and histochemical character have been found by Robertson et al. in the hearts of “spawning” salmon which also develop arteriosclerosis and show premature aging.18

Cartilaginous alterations in the bases of the papillary muscles are reminiscent of membranous bone formation. Gillman and Hathorn have found similar lesions in the papillary muscles of breeder rats of the Glaxo strain.10 These calcific alterations are not similar to lesions described in experiments in which rats have been given large doses of parathyroid hormone or Vitamin D,19 since intramyocardial fiber deposits of calcium are not found in breeder rats. The parathyroids of these breeder rats appear normal histologically and their serum calcium is either normal or subnormal.20

It may be of interest to mention that the progressive disappearance of mast cells from the myocardium is the only evidence gathered, thus far, that mast cells may participate in the arteriosclerosis observed in breeder rats (to be published).

Summary

Repeatedly bred male and female rats of several strains develop arteriosclerosis spontaneously, irrespective of diet. The severity of the lesions differs between male and female breeders. The morphology and pathogenesis of these lesions have been found to be the same in all of the strains examined. Once the process of arteriosclerosis has been initiated within the abdominal aorta, the subendocardial and medium-sized myocardial coronary arteries also show degenerative changes. The large epicardial coronary arteries become arteriosclerotic only when the process of arteriosclerosis has become severe and generally distributed throughout the aorta.

The smaller subendocardial lesions are characterized by occlusive swelling of medial muscle cells and by the presence of vacuoles. These vacuoles react negatively to lipid stains but stain positively for mucopolysaccharide. The myocardial arteries show endothelial hyperplasia, elastosis and accumulations of mucopolysaccharides, especially in the region of fragmented elastic elements. The mucopolysaccharide-rich endothelial cushions eventually become fibrosed. The epicardial arteries show intense accumulations of calcium-mucopolysaccharide complexes. These arteries become greatly distended and can be detected grossly because of their size and tortuosity.

Acute and chronic myocardial infarct-like lesions are found but these cannot be associated with specific coronary thrombi or arteriosclerotic lesions. Valvular scarring, calcification of the papillary muscles and disappearance of myocardial mast cells has been correlated with advancing arteriosclerosis.

The relation between the intensity of coronary arteriosclerosis and the frequency of breeding, the sex of the animal, and the strain indicates that the pathogenesis of this disease in breeder rats is probably governed by hormonal factors, e.g., sex and adrenal steroids, as well as by genetic factors.

References

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