Arterial Lesions in Repeatedly Bred Spontaneously Hypertensive Rats

BERNARD C. WEXLER, PH.D., SAMUEL G. IAMs, PH.D., AND JOSEPH T. JUDD, PH.D.

SUMMARY Repeatedly bred male and female rats of many strains develop hyperglycemia, hyperlipidemia, hypertension, and arteriosclerosis spontaneously. The intensity of their arterial disease and related metabolic derangements appears to be related to their reproductive activity. Repeatedly bred spontaneously hypertensive rats (SHR) were found to have severe hypertension, hyperglycemia, hyperlipidemia, elevated creatine phosphokinase (CPK), serum glutamic oxaloacetic and glutamic pyruvic transaminase (SGOT, SGPT), and lactate dehydrogenase (LDH), as well as high circulating corticosterone levels. Despite these atherogenic metabolic derangements and their severe hypertension, the breeder SHR did not develop the severe, generalized arteriosclerosis found in other strains of breeder rats. Instead, the arterial lesions, consisting of intimal and arterial disease progress in parallel, the aortic lesions remain microscopic during the first two to three breedings and consist of intimal ground substance swellings capped over by collagen followed by elastolytic and calcific changes in the media. As breeding and arterial disease progress in parallel, the aortic lesions remain microscopic during the first two to three breedings and consist of intimal ground substance swellings capped over by collagen followed by elastolytic and calcific changes in the media. This is suggested that the severe hypertension, genetic influences, or differences in hypothalamic-pituitary-adrenal-gonadal function in breeder SHR may not have been conducive to the development of arteriosclerosis in this particular strain of rats.

REPEATEDLY BRED male and female rats of several strains, e.g., Sprague-Dawley, Long-Evans, Wistar, and others, have been shown to develop hyperlipidemia, hyperglycemia, hypertension, arteriosclerosis, premature aging, and other degenerative changes spontaneously. The incidence and severity of these metabolic and pathophysiological changes have been shown to be related to the number and frequency of breedings as well as, in the case of female breeders, to the number of young suckled and the time of weaning. The arterial lesions remain microscopic during the first two to three breedings and consist of intimal ground substance swellings capped over by collagen followed by elastolytic and calcific changes in the media. As breeding and arterial disease progress in parallel, the aortic lesions become grossly visible by the third or fourth breeding. The lesions appear first in the abdominal aortic segment, progress in an anatomical order to the arch and thoracic aortic segments, and eventually spread into the coronary, carotid, mesenteric, renal, and peripheral arteries. Although male breeder rats develop less complicated arterial lesions than female breeders, they die significantly earlier than the females, most often as a result of myocardial infarction.

The Japanese investigators, Okamoto and Aoki, have raised an inbred strain of rats which manifest pathophysiological changes spontaneously, i.e., the SHR strain. These genetically hypertensive rats are normotensive at birth but as they mature show increasingly elevated levels of blood pressure with time. A special breeding colony of these SHR was established in our laboratory to determine whether repeatedly bred SHR would manifest, in addition to hypertensive rat strains, the usual pathophysiological sequelae, e.g., arteriosclerosis, hyperglycemia, hyperlipidemia, etc., commensurate with the number and frequency of their breedings, as we have found for several other strains of rats.

Methods

The original spontaneously hypertensive rats (SHR) with which we established our SHR Breeding Colony were obtained from the National Institutes of Health, Bethesda, Maryland. These SHR were obtained from the original Kyoto-Wistar strain developed by Okamoto and Aoki. These SHR develop increasing blood pressure after weaning and, by 8 to 10 weeks, stable high blood pressure is established.

Male and female SHR were paired at 60 days of age. Record was kept of the number of pregnancies, young born, suckled, and weaned after 21 days of nursing. When the female breeders had completed four to five pregnancies, both the male and female breeders were killed after the last litter of young had been weaned, i.e., a total of 35 pairs of SHR breeders. For purposes of comparison, 24 pairs of Sprague-Dawley breeder rats from our Research Breeding Colony were autopsied after they had completed four to five breedings on a similar basis. In addition, 24 male and female virgin SHR and Sprague-Dawley rats of the same age as the breeder rats (6-7 months) also were killed for purposes of comparison. All of the rats were kept in our Research Animal Colony where temperature, humidity, and light were carefully controlled and monitored. The rats were fed a commercial rat chow (Purina) which has a relatively low fat content (4%) and were given tap water to drink ad libitum.

Prior to autopsy, blood pressures were recorded under light secoarabital (Seconal) anesthesia using the Friedman-Freed microphonnic manometer and indirect tail cuff method which measures systolic blood pressure only. Immediately thereafter and prior to autopsy, blood samples were withdrawn from the aorta, centrifuged (refrigerated) and assayed for creatine phosphokinase (CPK), glutamic oxaloacetic and glutamic pyruvic transaminase (SGOT and SGPT), lactate dehydrogenase (LDH), glucose, free fatty acids, triglycerides, cholesterol, and blood urea nitrogen.
(BUN), using the automated techniques prescribed for the Auto-Analyzer (Technicon Instruments). Corticosterone (compound B), as an index of adrenocortical secretory activity, was measured by the fluorometric method of Guillemin et al. 14

In searching for the presence of spontaneous arteriosclerosis in breeder rats, we exposed the aorta so that the heart, carotid, mesenteric, iliac, and proximal portions of the femoral arteries were visualized. In the case of the female breeders of most strains of rat, the arterial lesions often can be seen on gross inspection by the time the rats have given birth to three or four litters. Rats with no grossly visible plaques in their aorta are classified as “clear,” those with raised plaques in only the abdominal aorta as “minimal,” those with plaques only in the abdominal and aortic arch segments as “moderate,” and those with plaques throughout the aorta as “severe.” For microscopic confirmation of the presence or absence of arteriosclerosis, we routinely took representative samples from prescribed segments of the systemic aorta. The arch of the aorta was taken so that it included the base of the innominate and common carotid arteries. The thoracic aorta was removed from a level just caudal to where the azygos vein crosses the aorta to where the aorta leaves the thorax between the folia of the diaphragm. The abdominal aorta was taken from the level of the diaphragm down to and including portions of the iliac arteries. The aortas of male breeder rats were examined and sampled in the same manner. The iliac arteries of male breeders of most strains of rat occasionally show sclerotic plaques that can be detected by gross examination. 1, 11-14

All segments of the aorta were fixed in 10% buffered neutral formalin (Lillie) for histological study. The brains, hearts, kidneys, and carotid arteries of these rats were removed so that the cerebral, renal, mesenteric, and the main carotid artery and its branches could be examined microscopically. Pertinent organs from each rat were trimmed and weighed. The hearts were dropped into saline and allowed to pump out residual blood, blotted, and weighed, i.e., as a gravimetric index of cardiac hypertrophy. Organs and tissues were embedded in paraffin and sectioned at 3 μm. Frozen sections used for lipid studies were cut at 5-10 μm. Adjacent sections were stained with hematoxylin-eosin for routine analysis; Verhoeff’s, Van Giessen’s, and Gomori’s aldehyde fuchsin stains for elastic tissue; Alcian Blue and toluidine blue for metachromasia; the Hale stain for mucopolysaccharides; the von Kossa method for calcium. Sudan II and III, oil red O, and Sudan black B were used to demonstrate lipids in both frozen and paraffin sections. Statistical analysis of results was performed using a one-way analysis of variance, chi square test, or Student’s t-test. 17

Results

GENERAL OBSERVATIONS

The breeder SHR appeared to be as fecund as Sprague-Dawley breeder rats. However, the average number of pups per litter was eight for SHR dams, whereas the average for Sprague-Dawley female breeders was 12. The SHR dams do not lactate as copiously as the Sprague-Dawley and the average body weight of weanling SHR (21 days postparturition and nursing) was 35.0 g vs. 45.0 g for Sprague-Dawley weanlings.

BLOOD PRESSURE

The arteriosclerotic male and female Sprague-Dawley, breeder rats had significantly elevated blood pressure compared to nonarteriosclerotic virgin rats, as did the breeder vs. virgin SHR (P < 0.001) (Fig. 1). The blood pressures of the SHR were significantly greater (ranging from 175 ± 5 to 220 ± 5 mm Hg) than that of Sprague-Dawley rats (ranging from 80 ± 2 to 120 ± 3 mm Hg).

GRAVIMETRIC DATA

Breeder rats are characteristically more obese than virgin rats of the same age, as was observed here for both the Sprague-Dawley and SHR strains (Table 1). The SHR were generally of shorter head to tail length and were less heavy than the Sprague-Dawley rats. Although the weight of the pituitary glands of most animals is not susceptible to changes except under unusual physiological conditions, there were marked and statistically significant differences in the pituitary gland weights of these rats. Except in the case of the female breeder SHR, the weights of the pituitary glands of all the breeder rats were considerably greater than those of their virgin counterparts (Table 1). Similarly, with the exception of the female breeder SHR, the puitary glands of the SHR were heavier than those of the Sprague-Dawley rats, as were the pituitary glands of female vs. male rats (Table 1). The weights of the adrenal glands of virgin and breeder SHR were statistically much less (P < 0.001) than those of their Sprague-Dawley counterparts (Table 1). Although the weight of the thymus gland is usually inversely proportional to the weight (and secretory activity) of the adrenal gland, the Sprague-Dawley rats with significantly

\[ \text{Figure 1 Systolic blood pressure of male (n = 24) and female (n = 24) vir} \]

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TABLE 1  Gravimetric Comparison of Male and Female, Nonarteriosclerotic (Virgin) vs. Arteriosclerotic (Breeder) Sprague-Dawley Rats with Nonarteriosclerotic (Virgin) and Arteriosclerotic (Breeder) Spontaneously Hypertensive Rats (SHR)

<table>
<thead>
<tr>
<th></th>
<th>Final body wt (g)</th>
<th>Pituitary gland wt (mg)</th>
<th>Adrenal gland wt (mg)</th>
<th>Heart wt (mg)</th>
<th>Testes ovary wt (mg)</th>
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<tbody>
<tr>
<td><strong>Males</strong></td>
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<tr>
<td>Virgins</td>
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</tr>
<tr>
<td>Nonarteriosclerotic, Sprague-Dawley</td>
<td>380 ± 10</td>
<td>6.5 ± 0.5</td>
<td>19.5 ± 1.6</td>
<td>1010 ± 10</td>
<td>2036 ± 25</td>
</tr>
<tr>
<td>Nonarteriosclerotic, SHR</td>
<td>382 ± 13</td>
<td>7.0 ± 0.3</td>
<td>16.1 ± 1.0*</td>
<td>1705 ± 15*</td>
<td>1506 ± 48*</td>
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<tr>
<td>Breeders</td>
<td></td>
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<tr>
<td>Microscopic arteriosclerosis, Sprague-Dawley</td>
<td>425 ± 12</td>
<td>8.5 ± 0.4</td>
<td>28.0 ± 2.0</td>
<td>1300 ± 40</td>
<td>1906 ± 21</td>
</tr>
<tr>
<td>Microscopic arteriosclerosis, SHR</td>
<td>415 ± 11</td>
<td>10.4 ± 0.4*</td>
<td>19.0 ± 1.0*</td>
<td>1650 ± 25*</td>
<td>1630 ± 26*</td>
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<td><strong>Females</strong></td>
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<td>Virgins</td>
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<tr>
<td>Nonarteriosclerotic, Sprague-Dawley,</td>
<td>248 ± 8</td>
<td>8.1 ± 0.3</td>
<td>34.2 ± 1.0</td>
<td>905 ± 2</td>
<td>60.0 ± 20</td>
</tr>
<tr>
<td>Nonarteriosclerotic, SHR</td>
<td>220 ± 4*</td>
<td>14.2 ± 1.1*</td>
<td>22.4 ± 1.0*</td>
<td>945 ± 10*</td>
<td>28.2 ± 15*</td>
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<tr>
<td>Breeders</td>
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<td>Grossly visible arteriosclerosis, Sprague-Dawley</td>
<td>310 ± 10</td>
<td>10.5 ± 0.8</td>
<td>35.0 ± 1.5</td>
<td>1105 ± 15</td>
<td>63 ± 18</td>
</tr>
<tr>
<td>Microscopic arteriosclerosis, SHR</td>
<td>255 ± 8*</td>
<td>10.0 ± 0.5</td>
<td>27.3 ± 1.0*</td>
<td>1230 ± 25*</td>
<td>46 ± 11</td>
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Results are given as mean ± SE. The numbers in parentheses denote the number of rats.
* Statistically significant differences, P < 0.001.

FIGURE 2  Intratubular arteries of a male breeder SHR. The tunica media is hypertrophied and the tunica intima contains extensive quantities of hyalin. These hyalin deposits stain very positively for mucopolysaccharide and collagenous material. H & E; 150x.
heavier adrenal glands had the heaviest thymus glands and the SHR with smaller adrenal glands had the least heavy thymus glands ($P < 0.001$). The heart weights of the SHR were much greater than those of the Sprague-Dawley strain (Table 1), consistent with their more severe hypertension. Although increased weight of the kidney also is a good index of elevated blood pressure, there was no consistent correlation between blood pressure levels, heart weight, and kidney weight, between virgins vs. breeders, or between SHR vs. Sprague-Dawley rats. A marked difference was found in gonad weight between Sprague-Dawley rats and SHR. The testes and ovaries of SHR were greatly reduced in size and weight, as compared to the Sprague-Dawley strain (Table 1).

GROSS AND MICROSCOPIC PATHOLOGY

The repeatedly bred male and female Sprague-Dawley breeder rats displayed their characteristic pattern of grossly visible arterial disease, i.e., clear, minimal, moderate, and severe aortic sclerosis in female breeders and clear aortas in male breeders, with a small number of male breeders (9%) having raised, grossly visible plaques in their common iliac arteries. Of the Sprague-Dawley female breeders, 78% had grossly visible aortic sclerosis: 24% minimal, 41% moderate, and 13% severe.

Microscopically, the arterial lesions in the Sprague-Dawley breeder rats were typical of what we have consistently found in the past, i.e., focal intimal accumulation of mucopolysaccharide capped over by collagen in early lesions. In the more advanced lesions there was medial pooling of mucopolysaccharide about the internal elastica and inner medial elastic lamellae, dystrophic calcification, and, in the most advanced lesions, cartilaginous and osseous metaplasia. Because the morphological nature of the arterial lesions of Sprague-Dawley breeder rats has been reported in detail, they will not be repeated here. Male and female breeders were devoid of any pathological changes. Despite their severe hypertension, no virgin SHR displayed signs of arterial damage or pathological change. Contrary to our previous experience, neither male nor female breeder SHR demonstrated gross evidence of arterial disease. However, on microscopic examination, only male breeders (12%) were found to have arterial lesions confined to their testes. In the smaller, intratubular arteries, there was extensive intimal hyalinization and fibrosis with medial hypertrophy and occlusion of the lumen (Fig. 2).

Although male and female Sprague-Dawley breeders display grossly visible hepatic steatosis, none of the breeder SHR presented any grossly visible evidence of hepatic involvement. Histologically, however, the livers of SHR breeders of both sexes displayed focal, but advanced, fatty infiltration of the liver (Fig. 3) unlike the more diffuse
parenchymatous distribution of lipid found in Sprague-Dawley breeders but equally as severe on the basis of lipid infiltration. The hypertrophied, hemorrhagic, and thrombotic adrenal glands generally found in Sprague-Dawley breeder rats also were found in the Sprague-Dawley breeders used in the present experiment. Although the adrenal glands of the breeder SHR were red in color, they were not hemorrhagic. Further, unlike the adrenal glands of Sprague-Dawley breeder rats, the breeder SHR adrenals showed extensive lipid depletion from the zona fasciculata and zona reticularis (Fig. 4). Also, the zona glomerulosa of SHR breeder rats was especially narrow but full of lipid, whereas this zone in Sprague-Dawley breeder rats was greatly hypertrophied and greatly depleted of lipid.

The myocardium of the SHR showed definite evidence of marked hypertrophy and numerous, scattered, healed foci of myocardial infarction, as did the Sprague-Dawley breeder rats. The islets of Langerhans were hypertrophied in the breeder rats of both strains and their beta cells were degranulated, indicative of sparse insulin reserve. The kidneys of the Sprague-Dawley breeder rats displayed their characteristic glomerulosclerosis and arteriolosclerosis, numerous colloid casts, and kidney stones as previously described. The kidneys of breeder SHR manifested hyalinized glomerulosclerosis, colloid casts, and occasional kidney stones (males only), but the SHR renal pathology was much less extensive and less severe than that found in Sprague-Dawley breeders.

The enlarged pituitary glands of virgin SHR contained no distinctive characteristics. However, breeder SHR, like Sprague-Dawley breeders, displayed definite basophilia, frequent adenomas, and colloid-filled cysts. Although the testes and ovaries of the SHR were greatly reduced in size, aside from the testicular arterial lesions found in male breeder SHR, there was no distinctive evidence of histopathological change except that the ovaries of female breeder SHR, like Sprague-Dawley female breeders, showed numerous hyperplastic corpora lutea with very few Graafian follicles.

**BIOCHEMISTRY**

Concomitantly with their progressive development of spontaneous arteriosclerosis, breeder rats of all of the strains tested by us also develop progressively worsening hyperglycemia, hyperlipidemia, serum enzyme changes, and, most outstanding, marked changes in adrenal steroidogenesis. Because of this, the same serum parameters were measured for the SHR to determine whether repeated breeding in this spontaneously hypertensive strain also would be accompanied by similar endogenous metabolic alterations.

**Enzymes.** The serum levels of CPK, SGOT, SGPT, and...
and LDH serve as an index of myocardial infarction in man and in animals. We have found these enzymes to be a good index of the myocardial damage frequently found in repeatedly bred rats, regardless of whether the myocardial damage is acute or chronic.

In this particular experiment, the characteristic, greater circulating levels of CPK were observed in the male, but not female, Sprague-Dawley breeder rats (Table 2). The SHR showed an inverse relationship in that the CPK levels were observed in the male, but not female, Sprague-Dawley breeder rats (Table 2). However, the circulating glucose levels of the SHR were comparatively greatly elevated compared to SHR breeders and particularly when compared to their Sprague-Dawley virgin sisters and brothers (Table 2). The same was true of the breeder SHR compared to virgin SHR (Table 2). However, the SHR did not exhibit any particular evidence of deranged protein metabolism (Table 2).

Protein. The BUN levels are consistently elevated in breeder vs. virgin Sprague-Dawley rats and especially in the female. The same was true in the Sprague-Dawley rats used in this experiment (Table 2). However, the SHR did not exhibit any particular evidence of deranged protein metabolism (Table 2).

Steroids. Female rats have larger adrenal glands and produce much more corticosterone (compound B) than do male rats. Although the female Sprague-Dawley breeder rat initially secretes considerably greater quantities of corticosterone, by the time she has delivered and nursed four to five litters of young and has developed advanced arteriosclerosis and the other pathophysiological changes described, corticosterone production becomes greatly reduced (Fig. 5), whereas the male Sprague-Dawley breeder increases its ability to produce corticosterone (Fig. 5). In these experiments we found that the Sprague-Dawley breeder rats to be definitely hyperglycemic compared to their virgin sisters and brothers (Table 2). The same was true of the breeder SHR compared to virgin SHR (Table 2). However, the SHR did not exhibit any particular evidence of deranged protein metabolism (Table 2).
Discussion

The major finding in this investigation is that although repeatedly bred SHR manifest essentially the same spontaneous pathophysiological sequelae as Sprague-Dawley breeder rats (as well as other strains), they do not develop advanced arterial disease despite their more severe hypertension. It is of special interest that although SHR have severe hypertension and other atherogenic metabolic changes, the virgin SHR remain resistant to arterial disease. Further, unlike other strains of breeder rats for which the female displays the most advanced arterial disease, it is only the male breeder SHR which, thus far, have been found to have spontaneous arterial lesions of any kind, and interestingly, these lesions were found exclusively in their testes.

It is of interest that breeder SHR become obese, as do Sprague-Dawley breeder rats. It is true that SHR are smaller than Sprague-Dawley rats. However, regardless of how the organ weight data are expressed, i.e., on the basis of absolute weight or as organ weight to body weight ratio, the marked organ weight differences remained statistically highly significant. It is remarkable that despite the obesity, hyperlipidemia, and fatty liver observed both in arteriosclerotic Sprague-Dawley and breeder SHR, the arterial lesions contained very little lipid and were of the connective tissue and ground substance variety.

The fact that SHR pituitary glands were heavier than those of Sprague-Dawley rats points to the possibility that there may be fundamental hormonal differences between these strains, since it is well established that the weight of the pituitary gland is seldom altered except under unusual hormonal conditions. The possibility of hormonal differences between SHR and Sprague-Dawley breeder rats is also reflected in the adrenal glandular histopathology of these two strains. The adrenal glands of breeder SHR did not show any of the extensive hyperplasia, hemorrhage, thromboses, or pheochromocytomas observed in Sprague-Dawley breeder rats. Further, the histopathological significance of a narrow and lipid-rich zona glomerulosa in the adrenal glands of SHR breeders vs. the extensively hypertrophied and lipid-free zona glomerulosa of Sprague-Dawley breeder rats suggests that the Sprague-Dawley breeder rats are very actively synthesizing and releasing mineralocorticoids, e.g., aldosterone, whereas the breeder SHR are less actively synthesizing and releasing mineralocorticoids. Our consistent finding of pituitary basophilia, adenomatosis, and colloid-filled cysts and changes in the ovaries and testes of breeder SHR as well as in repeatedly bred rats of other strains, is in keeping with our recent report of deranged hypothalamic-pituitary releasing factors and trophic hormone interrelationships in Sprague-Dawley breeder rats and suggests that the same may be true for SHR breeders.

In our investigations of spontaneous and drug-induced myocardial infarction in nonarteriosclerotic vs. arteriosclerotic rats, we have found that the serum enzymes CPK, SGOT, SGPT, and LDH are a good index of the mass of myocardium infarcted or repaired and that arteriosclerotic breeder rats show definitely less change in these serum enzymes and other associated metabolic parameters than nonarteriosclerotic, virgin rats. The seemingly paradoxical and considerably greater elevation of serum enzymes in nonarteriosclerotic virgin SHR is in keeping with our previous experience. Our finding of more severe hyperlipidemia in breeder vs. virgin SHR also coincides with our previous experience with virgin vs. breeder rats of other strains. Because the SHR and Sprague-Dawley breeder rats were fed a relatively low fat diet, we believe that their hyperlipidemia was due to the lipid-mobilizing effects of endogenous adrenocortical steroids produced during repeated breeding. Similarly, the greater hyperglycemia found in breeder vs. virgin SHR and Sprague-Dawley rats is in keeping with the greater islet hyperplasia and beta cell degranulation in breeder vs. virgin rats. We have found progressively worsening islet hyperplasia, beta cell degranulation, glucose tolerance, and serum insulin changes to parallel repeated breeding and progressively worsening arteriosclerosis. We believe that these abnormalities, like the aforementioned abnormalities in lipid metabolism, are due to the gluconeogenic or beta cell reserve depleting effects of the abnormal glucocorticoids produced by repeatedly bred rats. We have no ready explanation for the unusually greater hyperglycemia found in the virgin hypertensive SHR. The absence of any increased BUN levels in SHR suggests that good renal function is maintained despite their severely elevated blood pressure. Corticosterone is the predominant steroid produced by the rat adrenal cortex. The decreased production of corticosterone by breeder SHR vs. virgin SHR indicates that repeated breeding leads to reduced or impaired steroidogenesis. Of special interest is the fact that SHR produced much more corticosterone than Sprague-Dawley rats despite the smaller size of their adrenals.
Acknowledgments

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