Pathophysiological Differences between Paired and Communal Breeding of Male and Female Sprague-Dawley Rats

BERNARD C. WEXLER AND BRUCE P. GREENBERG

SUMMARY Sexually mature, male and female Sprague-Dawley rats were housed in large communal breeding cages or in smaller paired breeding cages. Virgin control rats of the same age were housed similarly but segregated by sex. Breeders became obese, developed a fatty liver, and showed elevated levels of triglycerides, free fatty acids, and cholesterol. Breeders had high blood pressure, enlarged hearts, hyperglycemia, and islet beta cell degranulation. Serum enzymes, creatine phosphokinase, serum glutamic oxalo-pyruvic transaminase, serum glutamic pyruvic transaminase, lactate dehydrogenase, and blood urea nitrogen levels were elevated in breeder rats. The adrenal glands of male breeders appeared hyperactive; the adrenal glands of female breeders were thrombosed and appeared to be hypoplastic. Male breeder rats developed microscopic aortic lesions only; female breeders developed advanced calcific aortic sclerosis. Male breeders kept in active stud service manifested the most abnormal metabolic and pathophysiological changes. Female breeders developed similar pathophysiological changes after four pregnancies, irrespective of their paired or communal breeding environment. Virgin rats were normal regardless of housing conditions. Our findings suggest that repeated breeding in male and female rats causes resetting of the hypothalamic-pituitary-adrenal-gonadal axis. This may lead to disturbed hormonal and metabolic changes which culminate with the development of accelerated cardiovascular degenerative changes.

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hypothalamic-pituitary-adrenal-gonadal axis associated with the reproductive effort leads to resetting of hypothalamic-pituitary-interaction and disruption of normal hormonal processes that eventuates in a Cushingoid spectrum of degenerative changes.7,8

We have found that longer periods of rest between pregnancies or mating (in the male) will attenuate greatly the usual incidence and severity of the Cushingoid degenerative changes which attend active and repeated breeding. Males placed in large breeder tanks, e.g., designed to hold as many as 50 rats (40 females, 10 males) without crowding, develop much more severe changes than those placed in smaller laboratory cages for paired breeding. In order to evaluate further these earlier findings, we compared the pathophysiological changes that occurred in male and female breeder rats after four consecutive breedings during the time they were housed in a large, com-
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Methods

Sexually mature, 90-day-old Sprague-Dawley rats were placed randomly either in large breeder cages (20 x 25 x 7 inches) housing four males with 10 females (i.e., communal breeding), or in standard-sized cages (16 x 9 x 7 inches) housing one male and one female (i.e., paired breeding). When the females in the large breeder cages became pregnant, they were removed and housed separately so they might nurse their young unmolested. They were returned to the breeding cages when their young were weaned at 20 days postpartum. The male breeders assigned to communal breeder cages were transferred to other communal breeder cages which kept them in constant reproductive activity. The male breeders paired with one female remained in the same cage with the same partner while she nursed and was weaned of her young. This comparison of communal vs. paired breeding continued from April through October until all of the females had borne and nursed four litters of young. Virgin males and females of the same stock were housed in large breeder cages, i.e., 14 males/cage or 14 females/cage, and in the smaller cages, i.e., two males or two females, to control the possible effect of animal density as a factor in the pathogenesis of the cardiovascular degenerative changes. All of the rats were fed a regular commercial rat chow (Teklad) which is relatively low in fat and were given tap water to drink ad libitum. Light, heat, and humidity were controlled carefully.

Blood pressure was recorded three times each week by the indirect tail cuff microphonic manometer method which measures only systolic pressure.

Autopsies were performed during the early morning hours in deference to the diurnal rhythm of adrenal steroids. The rats were anesthetized lightly with Secobarbital, 250 mg/kg, ip, for their final blood pressure determination and then were exsanguinated by laparotomy and insertion of a needle into the abdominal aorta. Arterial lesions (gross and microscopic) were scored on a blind and random basis, using a scoring system detailed in a previous report. 4 Organs from each rat were weighed and fixed in 10% neutral formalin for histopathological analyses. Blood from each rat was centrifuged (refrigerated) and analyzed by automated methods in the Auto-Analyzer (Technicon) for creatine phosphokinase (CPK), transaminases (SGOT, SGPT), lactate dehydrogenase (LDH), triglycerides, total cholesterol, free fatty acids, glucose, and blood urea nitrogen (BUN). All of the automated procedures are described in the manual published by the Technicon Co. ("Automation in Analytical Chemistry," Technicon, Mediad, Inc., New York). The level of serum corticosterone (compound B) was measured by a fluorometric method as an index of adrenocortical secretory activity. All data were subjected to statistical analysis by Student's t-test or the analysis of variance, as appropriate. 5 P values <0.05 were considered to be significant.

Results

General Observations

Occasionally a female breeder would canibalize her young after the first or second pregnancy. These rats were excluded from the experiment. By the time the female breeders had completed their third or fourth pregnancy, 19% of the males (in the large breeder cages) that had been kept in constant reproductive activity had died, usually during the night. At autopsy, the hearts of these male breeders often displayed extensive myocardial infarction accompanied by hydrothorax. None of the other male or female breeders died. Because of the high mortality rate among the communal male breeders, the experiment was terminated when all the females had completed at least four pregnancies. There were no differences, i.e., gravimetric, metabolic, or histopathological, between the virgin controls housed in small or large cages. Therefore, all of the virgin control data cited in this report have been combined into two groups, one for males and one for females.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Final body weight (g)</th>
<th>Adrenal weight (mg)</th>
<th>Thymus weight (mg)</th>
<th>Heart weight (mg)</th>
<th>Kidney weight (mg)</th>
<th>Testes/ovary weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virgins; no arteriosclerosis</td>
<td>318 ± 6</td>
<td>20 ± 2</td>
<td>300 ± 18</td>
<td>1025 ± 10</td>
<td>1206 ± 21</td>
<td>1856 ± 19</td>
</tr>
<tr>
<td>Paired breeders; microscopic arteriosclerosis</td>
<td>465 ± 11*</td>
<td>24 ± 1</td>
<td>198 ± 12*</td>
<td>1305 ± 26*</td>
<td>1489 ± 8*</td>
<td>1895 ± 11</td>
</tr>
<tr>
<td>Communal breeders; microscopic arteriosclerosis</td>
<td>504 ± 10††</td>
<td>29 ± 2††</td>
<td>171 ± 14††</td>
<td>1442 ± 33††</td>
<td>1403 ± 28††</td>
<td>1989 ± 30††</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virgins; no arteriosclerosis</td>
<td>205 ± 7</td>
<td>30 ± 1</td>
<td>230 ± 16</td>
<td>803 ± 5</td>
<td>703 ± 11</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Paired breeders; grossly visible arteriosclerosis</td>
<td>307 ± 11*</td>
<td>31 ± 2</td>
<td>171 ± 17*</td>
<td>1065 ± 36*</td>
<td>989 ± 12*</td>
<td>48 ± 4*</td>
</tr>
<tr>
<td>Communal breeders; grossly visible arteriosclerosis</td>
<td>340 ± 21††</td>
<td>25 ± 2††</td>
<td>76 ± 13††</td>
<td>1069 ± 12††</td>
<td>909 ± 33††</td>
<td>63 ± 4††</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE; n = 24.

* Significant difference, at the 0.05 level of confidence (paired breeders vs. virgin controls).
† Significant difference, at the 0.05 level of confidence (communal breeders vs. virgin controls).
‡ Significant difference, at the 0.05 level of confidence (communal breeders vs. paired breeders).
Figure 1

Systolic blood pressure levels of male and female Sprague-Dawley rats bred on a communal or paired basis compared with virgin control rats that were housed in large communal or smaller paired breeding cages. No record was kept of the copulatory activity of the male breeders; the female breeders had completed four pregnancies including 21 days of lactation and weaning of their young on the 21st day postpartum. Each point depicts the mean ± SE. The same protocol was followed in Figures 2 and 3.

Gravimetric Findings

Both male and female breeders were significantly ($P < 0.05$) heavier than their virgin counterparts (Table 1). Breeders in the communal breeding cages were more obese than those kept in smaller cages. Although the breeder rats manifested marked thymus gland involution, only the male breeders showed an appropriate concomitant increase in adrenal weight. The adrenal glands of some of the breeder females were reduced significantly in weight ($P < 0.05$) (Table 1). Hearts, kidneys, testes, and ovaries were heavier in breeders than in virgins ($P < 0.05$). The kidneys appeared to be larger and heavier in the breeders that had been paired ($P < 0.05$) (Table 1). The gravimetric data were comparable whether they were calculated on an absolute or body weight-organ weight basis.

Blood Pressure

The systolic blood pressure of the male breeders that were in active stud service (communal breeding) manifested a substantial increase soon after they were placed in the communal breeder pool (Fig. 1). Their blood pressure increased steadily and reached hypertensive levels after 2–3 months of reproductive activity, i.e., blood pressure levels over 135 mm Hg are considered to be abnormally high in the Sprague-Dawley rat (Fig. 1). The male breeders that had been paired with females showed a more gradual increase in blood pressure which did not rise as high as that for communal breeders. Initially, blood pressures of the communal female breeders remained well below those of their male counterparts. After the fourth pregnancy, their blood pressures rose to a hypertensive level regardless of whether they were in a communal or paired breeding status (Fig. 1). The virgin male and female rats were normotensive. Frequent blood pressure measurements made during the last 7 days of pregnancy demonstrated no evidence of any reduction in blood pressure levels prior to parturition.

Blood Biochemistry

The biochemical data demonstrated that paired breeding was associated with the least number of untoward metabolic changes and communal breeding was more deleterious to both male and female breeders.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>CPK (µmol/liter)</th>
<th>SGOT (µmol/liter)</th>
<th>SGPT (µmol/liter)</th>
<th>LDH (µmol/liter)</th>
<th>Triglycerides (mg/100 ml)</th>
<th>Free fatty acids (mEq/liter)</th>
<th>Cholesterol (mg/100 ml)</th>
<th>BUN (mg/100 ml)</th>
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<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virgins; no arteriosclerosis</td>
<td>85 ± 10</td>
<td>80 ± 9</td>
<td>40 ± 3</td>
<td>106 ± 8</td>
<td>90 ± 9</td>
<td>450 ± 11</td>
<td>61 ± 4</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>Paired breeders; microscopic arteriosclerosis</td>
<td>158 ± 8*</td>
<td>120 ± 12*</td>
<td>53 ± 5*</td>
<td>125 ± 8</td>
<td>125 ± 8*</td>
<td>650 ± 21*</td>
<td>221 ± 17*</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>Communal breeders; microscopic arteriosclerosis</td>
<td>180 ± 15†</td>
<td>140 ± 9†</td>
<td>70 ± 8†</td>
<td>134 ± 11†</td>
<td>140 ± 6†</td>
<td>786 ± 32†</td>
<td>251 ± 18†</td>
<td>20 ± 2†</td>
</tr>
<tr>
<td><strong>Females</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virgins; no arteriosclerosis</td>
<td>45 ± 3</td>
<td>84 ± 13</td>
<td>38 ± 3</td>
<td>103 ± 5</td>
<td>84 ± 9</td>
<td>540 ± 21</td>
<td>65 ± 8</td>
<td>22 ± 1</td>
</tr>
<tr>
<td>Paired breeders; grossly visible arteriosclerosis</td>
<td>40 ± 4</td>
<td>110 ± 8</td>
<td>46 ± 12</td>
<td>110 ± 6</td>
<td>128 ± 11*</td>
<td>590 ± 26</td>
<td>130 ± 12*</td>
<td>28 ± 2*</td>
</tr>
<tr>
<td>Communal breeders; grossly visible arteriosclerosis</td>
<td>120 ± 16†</td>
<td>160 ± 13†</td>
<td>92 ± 7†</td>
<td>174 ± 12†</td>
<td>146 ± 9†</td>
<td>627 ± 28</td>
<td>185 ± 13†</td>
<td>37 ± 3†</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE; n = 24. CPK = creatinine phosphokinase; SGOT = serum glutamic oxalo-pyruvic transaminase; SGPT = serum glutamic pyruvic transaminase; LDH = lactate dehydrogenase.* Significant difference, at the 0.05 level of confidence (paired breeders vs. virgin controls).† Significant difference, at the 0.05 level of confidence (communal breeders vs. virgin controls).‡ Significant difference, at the 0.05 level of confidence (communal breeders vs. paired breeders).
**Enzymes**

We used serum enzymes CPK, SGOT, SGPT, and LDH as an index of muscle, hepatic, and cardiovascular damage, and we found that communal breeding was associated with the greatest elevation in levels of these enzymes (Table 2).

**Lipids**

Triglycerides, free fatty acids, and cholesterol showed the usual elevation observed in breeder vs. virgin rats (Table 2). Communal breeding was associated with the greatest increase in circulating lipid levels.

**Carbohydrate**

Most remarkable was the severity of hyperglycemia found in male communal breeders (Fig. 2). Breeder rats were consistently hyperglycemic. Although the female breeders were definitely hyperglycemic, there was no statistically significant difference between those bred with one male and those exposed to several males (Fig. 2).

**TABLE 3**  Summary of the Comparative Severity of Key, Naturally Occurring Pathological Changes in Male and Female, Breeder, Sprague-Dawley Rats under Conditions of Paired vs. Communal Breeding

<table>
<thead>
<tr>
<th></th>
<th>Grossly visible aortic sclerosis</th>
<th>Microscopic aortic sclerosis</th>
<th>Myocardial fibrosis or necrosis</th>
<th>Renal pathology</th>
<th>Adrenocortical pathology</th>
<th>Thymic involution</th>
<th>Fatty liver</th>
<th>Pancreatic islet pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virgin (controls)</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>Paired breeders</strong></td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Communal breeders</strong></td>
<td>0</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Virgin (controls)</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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<tr>
<td><strong>Paired breeders</strong></td>
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<td>+++</td>
<td>++</td>
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<tr>
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<td>+++</td>
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<td>+++</td>
</tr>
</tbody>
</table>

Scoring system: + = minimal severity; ++ = moderate severity; +++ = severe.
FIGURE 4 A: Mesenteric artery of a male Sprague-Dawley rat after repeated breeding in a communal cage. The tunica media is hypertrophied, the internal elastic membrane is distorted and fragmented in several places, and there is beginning endothelial hyperplasia (see B) H & E, 150x. B: Some mesenteric artery as in A, showing intense deposition of mucopolysaccharide (black material in photo) in the tunica intima. Collagenous material (light grey) caps these ground substance deposits. Hale stain; 150x.
grossly visible aortic lesions, commencing in the abdomi-
nal aorta and extending into the arch and eventually into
the thoracic aorta. We used a numerical scoring system
for grossly visible aortic sclerosis and found that 81% of
the female breeders had grossly visible aortic sclerosis
ranging from minimal to moderate severity, and there
was no difference in the incidence or severity of aortic
sclerosis between those females bred on a communal or
one-partner basis (Table 3). The livers of the breeder rats
showed grossly visible fatty infiltration and was most
severe in female breeders and much more intense in
communal male breeders than in male breeders paired
with one female (Table 3).

Histopathologically, both male and female breeders
displayed the typical aortic lesions found in breeder rats,
\textit{i.e.}, accumulation of focal, intimal mucopolysaccharide
capped over by collagen (Fig. 4). This ground substance
lesion is typical of the early arterial lesions which develop
spontaneously in breeder rats. Although these micro-
scopic aortic lesions in male breeders are hard to quantify,
there was a strikingly higher incidence of this kind of
lesion in communal male breeders, \textit{i.e.}, 76\% vs. only
47\% in male breeders paired with one female (Table 3).
The aortic lesions in female breeders were more advanced
and complex and consisted of medial elastolytic, calcific,
and cartilaginous metaplasia subtending the intimal foci
of ground substance degenerative changes. Both the
paired and communal female breeders had a similar
incidence and severity of microscopic atheroarterioscle-
rosis of 83\% and 86\%, respectively (Table 3).

Microscopically, the fatty livers observed in breeder
rats exhibited fat droplets intensely and diffusely dispersed
throughout the hepatic parenchyma. The hearts showed
numerous foci of old and new myocardial fibrosis or
necrosis that were most intense in the communal male
breeders (Table 3) (Fig. 5). Female breeders showed
more advanced glomerulo-, arterio-, and arteriolosclerosis
than did male breeders. There was little difference in the
severity of renal damage between paired or communal,
male and female breeders. The thymi of all breeder rats
were severely involuted, but the adrenal glands of the
male breeders showed much less pathological change than
did those of female breeders. The adrenal cortices of
male breeders were hypertrophied and hyperplastic with
extensive lipid depletion, particularly of the zona glomer-
ulosa (Fig. 6A). This was most pronounced in the com-
munal male breeders. The adrenal cortices of female
breeders, irrespective of paired vs. communal breeding,
were distorted equally by frequent foci of hemorrhage
and thrombosis (Fig. 6B). The insulin-producing beta

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image}
\caption{Myocardium of communal male breeder showing an area of fibrosis (white in photo) representative of myocardial damage that has been repaired, subtended by an area of more acute necrosis which is infiltrated by an intermix of white blood cells and fibroblasts. Hematoxylin and eosin stain; 75x.}
\end{figure}
**Figure 6**

A: Adrenal cortex of a communal male breeder which is illustrative of the adrenal cortical hyperplasia and intense lipid depletion of both the zona glomerulosa and reticularis which occurs in these animals. Black material in photo is lipid. Frozen section, Sudan black B stain; 50×.

B: Adrenal cortex of a female breeder rat which has borne and suckled four litters of pups in closely spaced pregnancies. The cortex is hypertrophied, depleted of lipid, with numerous foci of thromboses and infarction. Frozen section, Sudan black B stain; 75×.
FIGURE 7 Pancreas of a communal male breeder rat showing two hyperplastic islets of Langerhans separated by a narrow band of acinar tissue. The insulin producing beta cells are extensively depleted of fuchsin-positive material indicative of severe insulin deficiency and commensurate with the unusual hyperglycemia found in these rats. Aldehyde fuchsin Ponceau stain; 200×.

cells showed extensive degranulation in all breeder rats and particularly in male breeders assigned to communal breeding (Table 3) (Fig. 7). All of the pathophysiological changes described above, gross and microscopic, are identical to what we have found earlier and have described in detail. None of the virgin control rats exhibited any evidence of pathological change.

Discussion

These findings demonstrate that for male breeder rats, the conditions associated with communal breeding are much more conducive to the development of a spectrum of pathophysiological changes than those associated with paired breeding. Repeated pregnancies with little rest between weaning and the onset of the next pregnancy are associated with metabolic and deleterious pathophysiological changes, but there are some metabolic differences between females that are exposed to one or to several males. The lack of pathological changes in male or female virgin rats, whether they were caged in relatively smaller paired breeding cages or larger communal breeder cages, indicates that the stress of population density per se does not incite the development of the spectrum of pathophysiological changes, which develop spontaneously in repeatedly bred male and female rats. It is readily understood why repeated pregnancy and lactation should contribute to the pathogenesis of progressively worsening degenerative changes in female breeders. It is more difficult to reconcile why and how copulatory activity in the male breeder contributes to the development of pathophysiological changes. Since male breeders in the communal breeder cages manifested the most severe degenerative changes, the question arises whether competition between males for females or some interaction between males and females in a communal breeding environment serves as an extra stress mechanism, which induces greater activity of the hypothalamic-pituitary-adrenal-gonadal axis. The development of metabolic changes conducive to cardiovascular disease and associated with parity has been described in the human. One of us (B.C.W.) has described the spontaneous and almost explosive development of atherosclerosis, hypertension, diabetes, premature aging, and death in male and female salmon as they fight their way upstream to the spawning grounds. There are many situations in nature wherein the male of the species dies after mating while the female survives to rear their young. Based on the evidence we have accumulated to date, we believe that increased activity of the hypothalamic-pituitary-adrenal-gonadal axis associated
with the reproductive effort is responsible for the appearance of the pathophysiological changes described. The increased sex dichotomy in the manifestation of these untoward changes is due to a fundamental difference between males and females in hypothalamic-pituitary interaction.

Another intriguing paradox is that male breeders die suddenly, oftentimes due to myocardial infarction despite their less severe aortic sclerosis, whereas female breeders survive significantly longer in spite of their severe, grossly visible, calcific sclerosis. It is of interest that the metabolic changes in the male breeder are often more marked than those found in females, e.g., hypertension, hyperglycemia, and hyperlipidemia, and we have found the male breeder rats invariably to be more susceptible than are female breeders to a variety of stresses, e.g., alloxan diabetes, cerebral ischemia, and myocardial infarction. Apropos of the above, the possibility exists that increased activity of the sympathetic nervous system may also play a role in the pathogenesis of these cardiovascular degenerative changes. Repeatedly bred, male and female rats excrete greater amounts of normepinephrine than do virgin rats; they have higher phenyl-ethanamine-N-methyl transferase enzyme activity, and there is a 10% incidence of pheochromocytomas among female breeders.

During the initial period of reproductive activity, both male and female breeder rats are hyperadrenocortical; i.e., they produce greater quantities of adrenal steroids than do virgin rats. We believe this increased production of adrenal steroids best accounts for the abnormally elevated blood pressure in these breeder rats. The adrenal hypertrophy, hyperplasia, and the specific lipid-depletion of the zona glomerulosa in our male breeders suggest that increased mineralocorticoid activity plays a key role in the induction of their hypertension. The adrenal hemorrhage and thrombosis found in female breeder rats are indicative of adrenal insufficiency and hypotension, which is not in concurrence with the elevated blood pressure found in female breeders. Our investigation of pituitary-adrenal function in female breeders indicates that adrenal function is supernormal during their first few pregnancies, culminating with adrenal hemorrhage and hypofunction or hypertension followed by hypotension. Recently, we reported that adrenalectomized female breeder rats, maintained through four consecutive pregnancies, do not develop arteriosclerosis.

As indicated earlier, repeatedly bred male rats are prone to succumb due to myocardial infarction. In this connection, it is of interest that communal breeder males had the most enlarged hearts and exhibited high circulating levels of the serum enzymes, e.g., CPK, SGOT, SGPT, and LDH, that are indicative of myocardial damage.

The unusual hyperglycemia observed in the communal male breeders is consistent with our previous experience in which we found that active male breeders have marked islet cell hyperplasia, beta cell degranulation, decreased glucose tolerance, and the greatest susceptibility to the diabetes-inducing effects of alloxan. 4 5 6 7 8 We have found that, with each successive breeding, both male and female breeders show hyperinsulinism along with their obesity but decreased glucose tolerance. 3 8 It is noteworthy that male breeders secrete extra insulin up to the time they have sired five to eight litters; those that have sired eight or more litters show a definite reduction in their ability to secrete insulin. This underscores our observation and conclusion that reproductive activity in male rats is associated with definite metabolic derangements.

One of the most salient features of this investigation is that the communal male breeders had a higher incidence of aortic sclerosis (76%), albeit microscopic, compared to that of the paired male breeders (47%), whereas both the paired and communal female breeders had an equal incidence of advanced aortic sclerosis, i.e., 83% and 86%, respectively. This would indicate that, in the male, active breeding is much more conducive to the pathogenesis of arterial disease by whatever mechanism, whereas in the female it is the number of pregnancies that is connected most intimately with the pathogenesis of their arterial disease, irrespective of the social conditions of breeding. The fact that female breeders develop more severe and grossly visible arteriosclerosis but live significantly longer than do male breeders with microscopic aortic lesions only underscores the fact that the morphology and location of the arterial lesion may be of paramount importance. Although arterial lesions in male breeder rats are of microscopic proportions, they appear in such vital places as the carotid, coronary, renal, and mesenteric arteries, suggesting that the earlier demise of male breeder rats may be due to cerebral-mycardial-renal damage.

Acknowledgments
The authors are indebted to D. Conser, K. Cornelius, W. Goodhew, E. Domingo, and J. Wexler for their technical expertise and dedication to the successful completion of this demanding experiment.

References
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Hemodynamic Components of a Cardiogenic Hypertensive Chemoreflex in Dogs

Ferdinand Urthaler, Gilbert R. Hageman, and Thomas N. James

SUMMARY The mechanical and hemodynamic components of a cardiogenic hypertensive chemoreflex were studied in 50 dogs. Within 6 seconds after a single injection of serotonin (100 µg/ml) into the left atrium, mean atrial pressure (mm Hg) rose in the atria from 103 to 197 and in the pulmonary artery from 77 to 176. Aortic and pulmonary arterial hypertension were associated with a profound depression (82%) in atrial contractility; a delayed increase in atrial contractility might represent a kind of "aortic cough." Some possible clinical implications are discussed.

INJECTION of small amounts of 5-hydroxytryptamine (serotonin) into either the left atrium or a small branch of the proximal left coronary artery activates a powerful cardiac chemoreceptor in the dog. This cardiogenic hypertensive chemoreflex is elicited by concentrations of serotonin that may readily occur during life in man. It is characterized by an immediate profound arterial hypertension concomitant with simultaneous vagal and sympathetic efferent discharges to all the atrial and ventricular myocardium including the sinus node and atrioventricular (AV) junctional tissue. In contrast to the spinal sympathetic cardiovagal reflexes, which are activated via the vagus nerve, these afferent sympathetic fibers, the afferent neural traffic of the cardiogenic hypertensive chemoreflex, and before and after bilateral stellectomy, and before and after excluding the adrenal circulation, in order to assess the effect concomitant with simultaneous vagal and sympathetic afferent cardiac sympathic fibers, the afferent neural traffic of the cardiogenic hypertensive chemoreflex, and before and after excluding the adrenal circulation, in order to assess the effect.
Pathophysiological differences between paired and communal breeding of male and female Sprague-Dawley rats.

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