Psychosocial Stress Can Induce Chronic Hypertension in Normotensive Strains of Rats

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We report on five 6-month experiments during which five colonies of four male and four female rats were exposed to psychosocial stress. Monthly blood pressure measurements by a tail-cuff method showed a modest (10 mm Hg) increase in two studies using Sprague-Dawley rats. In two further studies using the more aggressive Long-Evans strain, terminal direct carotid arterial pressures were taken as well, and in one study the differences exceeded 20 mm Hg. A fifth study used the Wistar-Kyoto, hyperactive (WKHA) strain developed by Hendley, and no differences were observed. Heart and adrenal weights; adrenal catecholamine synthetic enzymes; and heart, aortic, and kidney histology were measured and showed significant changes, which for the most part paralleled blood pressure changes. Social instability and the associated blood pressure changes were made more severe by periodic mixing of males from different colonies. This had no effect on the peaceable WKHA rats, some effect on the Sprague-Dawley rats, and a severe effect on the Long-Evans rats. The WKHA rats failed to show blood pressure changes despite stress-induced increases in heart and adrenal weights. Thus, different types of psychosocial stress and different genetics combine to induce a variety of neuroendocrine changes, not all of which necessarily lead to increased blood pressure. (Hypertension 1993;21:714–723)

KEY WORDS • stress, psychological • hypertension, essential • rat studies • kidney diseases • catecholamines

It is currently doubted whether it is possible to induce chronic psychosocial hypertension in normotensive strains of rats.1 Yet, as Lever has recently pointed out, the gradual development of Folkow’s structural cardiovascular adaptation is not restricted to particular strains or species, and despite the brevity of individual emotional responses, repetition of the appropriate stimulus slowly changes the structure of the mammalian cardiovascular system. In a discussion of etiological components of psychosocial hypertension, Folkow2 points out that the intensity of a stress is not critical but only that it should be persistently repeated and of the right type, such as arousal of the fight-flight response. The defeated state, when the attacker, is not so clearly associated with a rise in blood pressure. Indeed, Adams and Blizard3 have shown that the blood pressure of the SS/JR strain of the Dahl salt-sensitive rat actually falls in this state, although there is the expected rise when the same rat is exposed to inescapable shock. Furthermore, the pressure falls despite the fact that defeat fully meets the criterion of a potent stress.6 Indeed, defeat-induced pathophysiological changes are frequently fatal.7

The strength of the stimulus is not the controlling factor, because different emotions have different neuroendocrine characteristics. As has been discussed in a recent review of the biological basis of the stress response,8 the stimulus most effective in raising blood pressure is a continuing activation of the conflict-based fight-flight response. This results from a degree of instability that prevents the establishment of a stable dominance hierarchy.8 Wexler and Greenberg,9 Ely and Weigand,10 Szilagyi,11 and Mormede et al12 have together shown that constantly changing the composition of groups of male rats living in large cages with sexually active females will result in chronic competition with a rise in blood pressure. Indeed, Adams and Blizard6 have shown that the blood pressure of the SS/JR strain of the Dahl salt-sensitive rat actually falls in this state, although there is the expected rise when the same rat is exposed to inescapable shock. Furthermore, the pressure falls despite the fact that defeat fully meets the criterion of a potent stress.6 Indeed, defeat-induced pathophysiological changes are frequently fatal.7

Work with mice shows that, in addition to the need for the right sort of stress, there are genetic and early environmental factors. Our studies at the University of Southern California13 and those of Lockwood and Turney14 have contrasted the very peaceable AJ mice with the more aggressive DBA and CBA strains and a highly
aggressive strain of BALB, i.e., a rough progression in a scale of readiness to fight. This genetically determined bias is not fixed and can be readily modified by early experience. The AJ mice gave striking evidence of this. When the males were raised with each other, they did not fight, and there was no elevation of blood pressure when they were placed with females in a population cage. However, 4-month-old AJ mice that had been isolated during development were aggressive in the cage and remained hypertensive for several weeks before gradually reverting to their normal peaceable low blood pressure state.13 Thus, there are genetically determined variations in the propensity for the fight-flight response. Some rat strains never fight; some squabble but do not bite each other; some bite each other aggressively on the usual targets, the tail and back, avoiding the more vulnerable belly and neck, which are "out of bounds" in normal competition. The Blanchards12 have detailed this behavior. We have followed Folkow's hypothesis that hypertension will develop when there is frequently acted out, evenly matched competition involving the fight-flight response rather than outright defeat of subordinate by dominant rats.6 The frequently repeated arousal of this competition is aggravated by a constantly changing group composition, which prevents the development of a stable social hierarchy and peaceful dominant/subordinate relations.

In 1988, a new group was formed at Drew Medical School to study whether normotensive rats will develop psychosocial hypertension. The results of 6-month exposures of various rat strains to long-term psychosocial interaction in stable and unstable social arrangements follow. They show that if the genetic strain is appropriate, the social instability resulting from repeated changes of the males will indeed induce sufficient chronic competition to result in frequent activation of the fight-flight response, an increase in blood pressure, and early cardiovascular pathology.

Methods

Experimental Design

Five studies each lasting several months were completed. The procedures followed were in accordance with institutional guidelines. Each study used five or more large communal cages; the area of each was approximately one-half square meter. Four males (250-300 g) or four or more mature females (200-250 g) occupied each of the five cages. All the experiments had aimed to induce the hypertension and pathophysiology reported by Wexler and Greenberg,9 and the eventual relative success with the unstable Long-Evans groups was the outcome of a slow trial-and-error process. The recorded lesions on the tail and rump showed that it made a difference whether the social environment provided a stable or an unstable milieu and whether the genetically determined behavior was what we have called "very peaceable," "peaceable," or "aggressive."

Three rat strains that differ in "aggressiveness" were chosen. The first was the Wistar-Kyoto, hypertensive (WKHA) strain developed from the spontaneously hypertensive rat by Hendley et al.16,17 They are deficient both in the "allogrooming" of the opponent that precedes aggression and in active aggression itself. Repeated observations in these laboratories over a period of months confirmed Hendley's failure to detect any fighting by the males. Because no bites were observed at any time either on the tail or rump, we called them "very peaceable." The second strain was the familiar Sprague-Dawley albino commonly used in psychological studies. We observed that Sprague-Dawley rats placed in the communal cages did not bite, but the males did scratch each other. Although brief fights broke out, especially among mixed groups of males and females, they did not harm each other. We therefore called them "peaceable." The third strain was the Long-Evans rat. Adams and Blizzard6 used them as "fighters" to intimidate Dahl salt-sensitive SS/JR rats because of their "proven level of aggression." We found that they lived up to their reputation, becoming involved in serious fights. For example, each of the males in a first trial group we studied had been selected by the supplier as the dominant in his sibling group. They were so aggressive that after a month in the communal cages, half had killed each other, died of inanition, or been killed by us because of injury. The next group survived with fewer losses. They had been bred from the survivors in our laboratories, and unlike the first group there were few lethal fights. Each male was scored for bites and scars: +, a few small scars on the rump or fewer than three bites on the back; + +, one third of the back scarred or three to five bites on the back; + + +, more than half of the back scarred or more than five bites on the back. Because rats of this strain bite each other readily and can have many nonfatal lesions, we called them "aggressive." The WKHA rats were obtained from the laboratory of Dr. E.D. Hendley, Department of Physiology, University of Vermont, Burlington. The Sprague-Dawley and Long-Evans rats came from the Simonson Laboratories, Gilroy, Calif.

Husbandry

As noted, the experimental animals were randomly assigned to five or six large stainless-steel breeder cages (51×61×18 cm), each housing four males. In the two sets of blood pressure observations shown in Figure 1 that used Sprague-Dawley rats, Wexler and Greenberg's design was closely followed, and 10 females were housed in each cage. In the other three studies, the same number of males as females was used, i.e., four. Because of attrition due to fighting, six cages were used to start the unstable Long-Evans rat study and five cages for the other studies.

Control groups were housed in large polyethylene cages (47×25×21 cm), each of which held one male and one female. The males remained in the same cage with the same partner while she nursed and was weaned at 3 weeks. Each set of communal females was forced bred; i.e., they remained in their assigned cages throughout the experiment, the young being removed shortly after delivery.18 When the composition of the males in these forced breeder groups was changed, the males were assigned to fresh cages in accordance with a prearranged code using the principle of simple random sampling as described by Kelsey et al.19 They were fed a regular commercial chow (Purina 5001) in a single feeder and were given tap water to drink ad libitum from a single bottle. They were housed in a small 3×3×3-m room lit from 8 AM to 5 PM, and a constant
temperature of 22°C was maintained. The animals were observed daily for condition of the pelage, bites, scratches, and scars, as well as their behavior and extent of squeaking and fighting. Body weights were measured once a month, and at that time bites and scars were noted according to the scoring code mentioned above.

**Blood Pressure**

Systolic blood pressure was measured initially and then once a month. Uniform moderate vasodilation was attained by 30 minutes of warming in 32°C air from a commercial hair dryer. The reasons for using this moderate environmental warming procedure are detailed in a report on experimental studies of psychosocial hypertension in mice. 

In the two experiments with the Long-Evans strain, the arterial pressure was also measured at the end of the studies by direct carotid artery catheterization. After installation of the catheter with rats under anesthesia (combination of ketamine, 100 mg/kg body wt, and xylazine, 2 mg/kg body wt, i.m.), the animals were placed under a heat lamp–warmed, shaving-filled 29×18×13-cm polycarbonate shoebox cage for 24 hours before measurement. A PE 50 heparin-filled tube connected via a transducer to an oscillograph resulted in a pressure display with a well-defined dicrotic notch and a pulse pressure of 25–30 mm Hg. Peak systolic pressures were determined by averaging by hand repeated 5–10-second recordings that had been made during 15-minute observation periods. To compare the two methods of pressure determination, we made repeated simultaneous direct and indirect pressure recordings on five control Long-Evans males. They were 124±5 and 127±4 mm Hg, respectively; i.e., they did not differ significantly.

**Autopsy**

Care was taken not to forewarn the animals before they were killed. Their familiar handler took them individually from their respective cages, and within less than 1 minute, they were decapitated. Heart and adrenal weights were determined, and the adrenals were refrigerated at -60°C until assay.

**Endocrine Parameters**

Assays of adrenal tyrosine hydroxylase and phenylethanolamine-N-methyltransferase (PNMT) were made by two of us (V.L. and P.M.) on one Sprague-Dawley and one Long-Evans group at the INRA INSERM Laboratory of Behavioral Biology at Bordeaux (logistic problems caused the loss of two other groups). Tyrosine hydroxylase was determined by a micromethod adapted from the technique described by Okuno and Fujisawa, and PNMT activity was determined by the classic micromethod derived from Axelrod.

**Histology**

The thoracic aorta and hearts were examined for evidence of deposition of mucopolysaccharide and myocardial fibrosis under the supervision of a coauthor (D.E.). Picro-Ponceau with hematoxylin and a modified Lillie's periodic acid-Schiff alcian blue were used. Kidneys were stained by hematoxylin and eosin. The slides were scored blind by two independent observers. Scoring was 0, +, ++, and +++ when severe. For the aorta, scores of + and ++ indicated the presence of discrete and larger more confluent deposits of mucopolysaccharide, respectively. For hearts, the presence of fibrous tissue strands was scored; + indicated significant numbers of such strands, and ++ indicated small patches of fibrous tissue. In the fifth experiment, the kidneys were evaluated for extent of glomerulosclerosis, i.e., loss of capillaries and atrophy of the glomeruli and of the lining of Bowman's capsule; ++ indicated moderate but unequivocal damage and +++ indicated severe destruction. The method was the same as the one we used to evaluate the development of complications in mice with psychosocial hypertension.

**Statistics**

Means and standard deviations were derived, and the data were subjected to analysis of variance (ANOVA), with a value of p≤0.05 considered to be significant. A coded χ² test was used to evaluate the combined results of the histological observations. Six-month longitudinal body weight and blood pressure observations were also analyzed with a repeated-measures ANOVA using software for a Macintosh computer.

**Results**

**Behavior and Indirect and Direct Blood Pressure**

The top panel of Figure 1 shows that the blood pressure of the psychosocially stressed WKHA rats did not differ from that of the control rats. Despite the twice-weekly changes imposing continuous disorder, inspection confirmed that there was no fighting; rats had no bites or scars. The second study showed that, despite their aggressivity, when the composition of the groups of Long-Evans rats was maintained constant, there was only a modest increase of pressure, which vanished during the fourth month. A repeated-measures ANOVA measurement was significant (F=9.9, p≤0.005) and was accompanied by significant individual ANOVA measurements on the second, third, and sixth months. The record of bites and scars paralleled blood pressure. Figure 2 shows that bites had been inflicted in the last month, when blood pressure rose slightly and some conflict was observed.

In both studies with the Sprague-Dawley rats, there was weekly randomization with ensuing social instability. Conflicts and scratching occurred, but as in the WKHA rats, there was no biting, and no scars were found when the regular inspections of fur condition were made. However, as Figure 1 shows, a consistent (10 mm Hg) blood pressure elevation gradually developed, and in study No. 1 the repeated-measures ANOVA gave values of F=18 and p=0.0003. Significant individual ANOVAs were found on the fourth, fifth, and sixth months. In the second Sprague-Dawley study, the repeated-measures ANOVA gave values of F=17
and $p=0.0003$. Again, significant individual ANOVAs were found on the fourth, fifth, and sixth months. The pathophysiological changes in the first study had been so modest compared with those reported by Wexler and Greenberg\textsuperscript{9} that it was repeated. As can be seen, the replication was excellent, indicating that there had not been an uncontrolled technical error.

In the fifth study, the Long-Evans rats were kept in an unstable social state by carefully randomizing male group composition. This was only done monthly and only if the fighting was not too severe; otherwise, randomization was omitted for that month. Figure 2 indicates that competition was vigorous, and by 5 months, almost all the males had back and tail scars from bites. The males also showed a gradual progressive rise of blood pressure, which attained a highly significant 20 mm Hg differential in the later months. The repeated-measures ANOVA for this second Long-Evans study gave values of $F=64$ and $p=0.0001$. The individual ANOVAs for the 6 months of observation indicated highly significant differences between the experimental and control groups for each of the 6 months of observation.

In addition to the observations of blood pressure by the indirect tail-cuff method, direct arterial pressure data was gathered using the favored carotid artery catheterization technique\textsuperscript{29} (Figure 3). Both the stable and unstable Long-Evans colonies of Figure 1 were evaluated. As noted, the animals were removed from the colonies and implanted and left in a quiet, warm cage for a day until they had recovered from surgery. These pressures, taken 24 hours after separation from the colony, were a little higher than those taken indirectly. They differed very significantly from the controls, attaining a 25 mm Hg differential. The ANOVA comparing the nonrandomized groups gave values of $F=1.1$ and $p=0.001$. The randomized group ANOVA values were $F=1.2$ and $p=0.0001$. This group had a mean systolic pressure that was significantly higher (152 mm Hg) than that of the nonrandomized group (143 mm Hg; $F=1.6$, $p=0.05$). Thus, there is independent support of the repeated indirect blood pressure observations and evidence that the blood pressure elevation persisted for at least 24 hours after rats were removed from the social stimuli.
Body Weight

The peaceable WKHA rats showed no difference in body weight between the socially unstable groups in the population cages and the control groups (Figure 4). This contrasts sharply with the Long-Evans rats. Both in the stable and unstable states, the body weights of the males of this aggressive strain were significantly less than those of controls. The repeated-measures ANOVA for the stable group gave values of $F=6.93$ and $p=0.016$, with ANOVAs for individual months 1 to 6 that were all significant. The corresponding data for the unstable Long-Evans groups yielded repeated-measures ANOVA values of $F=21$ and $p=0.0002$. The second to sixth month individual ANOVAs were all significant. Although the Sprague-Dawley rats were also socially unstable and showed a consistent difference in blood pressure, their body weights differed only slightly from those of controls. The individual ANOVAs did not differ, but a repeated-measures ANOVA test of the first Sprague-Dawley group indicated that the pattern of minimal weight loss in the experimental animals was significant ($F=8.8$, $p=0.001$). In the second experiment, the weights of the two groups did not differ significantly.

Heart and Adrenal Weights

Regardless of the rat strain or blood pressure, the hearts of the communal animals were consistently heavier than those of the paired control males (Table 1). Figure 5 details the contrasting data for the Long-Evans groups. The left panel presents milligram of heart weight per gram body weight of the stable groups. The hearts of the stable groups were slightly heavier than those of controls ($F=2.6$, $p=0.02$). The corresponding ANOVA for the unstable groups gave values of $F=1.0$ and $p=0.001$. The weights of the hearts of the unstable groups were also significantly greater than those of the stable groups ($F=1.0$, $p=0.001$). The adrenals presented the same picture. The stable groups were significantly heavier than the control group ($F=1.2$, $p=0.02$). In the case of the unstable group, the values were $F=1.8$ and $p=0.001$. The weights of the adrenals of the unstable group were also significantly greater than those of the stable group ($F=2.8$, $p=0.05$).

Adrenal Catecholamine Synthetic Enzymes

Studies could be completed on only one Sprague-Dawley group and one Long-Evans group. The results are presented in panel A of Figure 6. There was no significant difference between the levels of tyrosine hydroxylase in the communal and paired groups. However, PNMT was significantly elevated in these socially stressed animals ($F=6.2$, $p=0.025$). On the other hand, in the Long-Evans rats, the situation was reversed; tyrosine hydroxylase was significantly elevated ($F=10.3$, $p=0.004$), but there was no difference between the adrenal PNMT in the communal and paired groups (Figure 6B). There was strikingly less tyrosine hydroxylase and PNMT (nanomole per hour per milligram protein) in both the communal and paired peaceable Sprague-Dawley rats compared with the more aggressive communal and paired Long-Evans rats. However, these
differences were not associated with significant differences between the adrenal weights or blood pressures of the three strains.

Pathophysiological Changes

Histological observations were made in the two Sprague-Dawley studies, and the incidence of early myocardial fibrosis and mucopolysaccharide deposition in the aortas was determined using two independent scorers of the slides. The changes were minor but unequivocal, and the combined data yielded a χ² test with a significance of p<0.03 for the hearts and p<0.001 for the aortas.

Figure 7 presents data from the unstable groups of Long-Evans rats; data from the stable group were not available. Again, there were significant changes. A measure of renal glomerulosclerosis had been added to the adrenal and heart observations of the Sprague-Dawley rats. The myocardial fibrosis and mucopolysaccharide deposition were at the same early stages. However, glomerulosclerosis in these Long-Evans rats was quite severe. Approximately a third showed a well-defined atrophy and loss of glomerular capillaries, and in one animal the destruction was severe.

Discussion

End-Organ Specificity of the Stress Response

The twice-weekly changes in the colony composition of the peaceable WKHA rats failed to lead to any fighting, nor were any changes in body weight or blood pressure observed. However, Figure 8 shows they had been affected by the psychosocial stress, for their adre-
nal and heart weights had significantly increased. Similar changes were seen in the hearts of the Sprague-Dawley rats (Table 1). As Figure 5 shows, this also applied to the Long-Evans rats. In so far as these organ weight increases reflect psychosocial stress, there is evidence that in all five studies cardiovascular and adrenal physiology were significantly affected (Table 1). Our data confirm the detailed observations of Harrap et al, who also reported adrenal hypertrophy, with gastric ulceration and elevated plasma renin and norepinephrine (i.e., evidence of stress), despite a failure of blood pressure to rise. Currently, Gelsema et al report similar results. Like Harrap et al, they used borderline hypertensive rats. They found that 3 months of psychosocial stress induced both adrenal and cardiac hypertrophy, with a 7% increase in the ratio of left ventricular wall thickness to lumen but no hypertension. Similar changes have been reported by Henry and Stephens in the organs of psychosocially stressed mice. Although the blood pressure, adrenal tyrosine hydroxylase, and

FIGURE 5. Bar graphs show comparison of heart and adrenal weights of stable and unstable colonies of aggressive Long-Evans rats. Unstable groups differ more from control values of stable groups. Vertical bars show standard deviation.

FIGURE 6. Bar graphs show that levels of adrenal catecholamine synthesizing enzymes tyrosine hydroxylase (TYOH) and phenylethanolamine-N-methyltransferase (PNMT) were lower in adrenals of Sprague-Dawley rats (panel A) than in the more aggressive Long-Evans strain (panel B). Social instability significantly increases PNMT in the former and TYOH in the latter. Vertical bars show standard deviation.
plasma renin of mouse colonies were all brought back to normal by the β-blocker metoprolol, adrenal weight, plasma corticosterone, and adrenal dopamine remained elevated.82

The generally accepted view is that during stress there is uniform arousal of both the fight-flight sympathoadrenal and the pituitary adrenal cortical systems. Discussing the neurobiology of stress, Gold et al83 see the two systems as together involved in the stress response, and in 1984 Dunn and Kramercy84 commented on the need to find if the two systems are ever dissociated. De Boer et al85 have recently answered this with quantitative studies showing that the brain can activate the neurosympathetic outflow of norepinephrine, the "fight" hormone, independently from the more purely endocrine catecholamine "flight" component that is based on epinephrine and the adrenal medulla; these in turn can be differentiated from the corticosterone response. The significance of this and related work is discussed in the above-mentioned recent article by the senior author on the biology of the stress response.8 In this context, Folkow86 has emphasized the all-important role of the defense reaction in the development of pathophysiological states involving high blood pressure. He differentiates it from the defeat reaction involving corticotrophin releasing factor and the pituitary adrenal cortical system. Koolhaas and Bohus87 as well as Benus88 speak of the former as active and the latter as passive responses, respectively. They too have emphasized the neuroendocrine and behavioral contrasts between the two stress modes.

The failure of the WKHA rats to develop high blood pressure and the limited success with the Sprague-Dawley rats reflect these animals' perceptions of and responses to their social environment. Their neuroendocrine responses and pathophysiological patterns of vulnerability, including blood pressure, differ from the more aggressive Long-Evans strain, whose defense reaction is more strongly aroused. Our experience with the WKHA rats supports the idea that there are physiologically...
control of food can affect group body weight

The body weight data merits discussion because of the sharp contrast between the Long-Evans and Sprague-Dawley rats. Even the stable Long-Evans groups, which fought little, had a considerable weight loss; the Sprague-Dawley rats had almost none. Alexander39 details the intensity with which dominant rats will fight to keep others away from the food box, and Gehsma has made similar observations (personal communication). We used a single food box in each of the communal cages and suggest that difficulty of access induced by social conflict may have been the reason why the weight loss was seen only in the aggressive Long-Evans strain.

Increased Adrenal Catecholamine Synthetic Enzymes

The level of adrenal catecholamine synthetic enzymes observed in the two groups we studied fits with previous data from psychosocially stressed mice. Work in the 1970s with Axelrod and Ciarenello,33,39,40 contrasted the peaceable AJ mouse strain with the much more active CBA/USC strain and these again with a highly aggressive strain of BALB. The series showed a progressive increase in both adrenal PNMT and tyrosine hydroxylase, particularly the latter. With exposure to long-term psychosocial stress, overall enzyme level increased, whereas interstrain differences were maintained; those fighting the most had the highest enzyme levels.33,39 The following year, Kessler et al41 published similar data. They contrasted the BALB, CBA, and C57BL strains. As in the previous studies,33,39 the aggressive BALB mice had the most elevated levels of these enzymes. Two years later in a study of the inheritance of this trait, Ciarenello et al42 reported that fighting behavior parallels the level of the enzymes, both being greater in an aggressive strain of BALB. The series showed a progressive increase of the enzyme synthesizing the "flight" hormone, whereas for the aggressive Long-Evans rats, the "fight" hormone enzyme tyrosine hydroxylase was increased. These differences appear to hold for humans. Woodman43 has demonstrated that psychopaths convicted of violent crimes consistently have higher-than-normal norepinephrine/epinephrine ratios in their urine.

Differences Between Early and Later Stages of Hypertension

Although the catecholamine synthetic enzyme data are compatible with increased sympathetic activity throughout the months of psychosocial stimulation,40 work on the renin-angiotensin mechanism points to the gradual development of changes in the neuroendocrine set. Sympathetic mechanisms may be more important during the early phases of stress-induced hypertension than during the long-term maintenance of the state. Just as in humans,44 despite high normal levels of plasma renin and sensitivity to sympathetic β-blockade,30 psychosocially stressed mice remain unresponsive to an angiotensin converting enzyme inhibitor such as captopril for about 1 month.45 By then, they have become sensitive to angiotensin II, and the blood pressure responds as well to an angiotensin converting enzyme inhibitor as it had to sympathetic blockade.31,42 It remains to be seen whether this also occurs in the rat.

Repeated observations in mice showed that the increase in blood pressure induced by psychosocial stress persisted for months despite removal of the social stimuli.29 Our rats showed no decrease during the critical first 24 hours, and we expect them to follow the same pattern.

Different Psychosocial Responses in Different Strains

Wexler and Greenberg3 used Sprague-Dawley rats, and their experimental design, including the size of their communal cages, was carefully followed in the present experiments. Unlike the present observations, they reported very severe histological changes and an impressive increment of blood pressure.9 The conflict may be resolved by the report of File and Velucci.46 They found marked differences in the social responses of Long-Evans rats obtained from different suppliers, and Lockard7 warns against underestimating the genetic diversity of the various commercially available rat strains such as Long-Evans or Sprague-Dawley. Current genetic studies calculating nucleotide divergence between spontaneously hypertensive and Wistar-Kyoto rat strains have led Johnson et al47 to comment that substantial divergence may exist between rats of the same strain maintained in different colonies. Certainly, File and Velucci46 have shown that animals from different sources will differ greatly in their emotionality. Our rats came from a different source, and this may be the reason why we did not find changes as severe as those reported by Wexler and Greenberg.8

Our observations of behavior such as fights and the scoring of bites and scars give solid evidence of the extent to which WKHA rats differed in their behavior from the Sprague-Dawley rats and these in turn from the Long-Evans rats. Figure 2 is based on this data and shows that the unfamiliarity induced by randomization significantly increased agonistic behavior. The experimental records suggest that different types of psychosocial stress are at work in the differing experimental arrangements. The records provide a behavioral counterpoint to the variations in neuroendocrine responses. The enlargement of most of the adrenals (Figures 5 and 8) and all of the hearts (Table 1) indicates that a stress response was aroused in all five studies, but the degree of blood pressure elevation appears to be related to agonistic behavior, i.e., aggression as expressed by the extent of fighting and biting.
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