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LONGEVITY IN SPONTANEOUSLY HYPERTENSIVE MICE*

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INTRODUCTION

IT HAS been known for some time from insurance surveys that in human populations untreated blood pressures in excess of 140/90 are associated with significant life shortening and that pressure below 110/70 are optimum with regard to longevity (Lew, 1973). Life span has not been studied in many of the existing animal models for hypertension, nor in the few models for hypotension. If the models mimic hypertension in man one would expect the same association between life span and blood pressure in the model as in human populations. This study examines longevity in mice of a line developed by selective genetic breeding for elevated blood pressure. About half the mice in this colony have systolic blood pressures in excess of 150 mm Hg. Life span was also studied in a second line selectively bred for low blood pressure in which many of the mice routinely have pressures below 75 mm Hg systolic.

MATERIALS AND METHODS

The mice were samples from the BPI lines genetically selected for high and low systolic blood pressure and from a random-mated control line. The original base population for the two-way selection was produced by an eight-way cross of inbred strains (LP/J, SJL/J, BALB/cJ, C57BL/6J, 129/J, CBA/J, RF/J, and BDP/J) and selection for extreme blood pressures was practiced in the two closed lines for 18–20 generations. A random-bred control derived from the same base population was maintained throughout the study (Schlager, 1974).

Two longevity studies were undertaken. In the first, breeders from the 18th generation of selection were maintained as mated pairs for their lifetime. Earlier litters were left with the parents until weaning, while later litters were removed during the first week after birth. Lifetime reproduction was recorded for all cages, as was age at death. In the second study, virgin mice were set aside at weaning and observed for their lifetime. In this study only cages containing three like-sex litter mates were used to assure initial equal densities. As animals died they were not replaced so densities varied as the study progressed. Female mice could have been combined to maintain three to-a-cage but non-littermate males will fight if introduced into another male's home cage. Consequently, in order to have a valid comparison between the lifespan of males and females, neither was regrouped to maintain equal densities throughout the study. Data in this study were limited to those animals where death was due to natural causes. A few mice were killed for humane reasons (badly injured in fighting, etc.) and a few disappeared during the three year period of the study. The cages were checked at least weekly and generally two or three times a week. The major differences between the two studies were: (1) The differences in average blood pressure between the High and Low line were greater in the first study since only the more extreme mice are used to propagate the line. (2) The variation of blood pressure was greater within the lines in the second study, although there was no overlap of the Hypertensive (HBP = high blood pressure) and Hypotensives (LBP = low blood pressure) distributions. (3) The randombreds were not included in the first study but were set out in a similar manner as the selected lines in the second study. (4) Litter sizes were recorded as soon after birth as practical in the first study; the mice in the second study were not mated.

The systolic blood pressure (SBP) of all mice was taken when they were 100–150 days of age. The method used involved an occluding cuff on the tail and electronic/pneumatic detection of pulse distal to the cuff while the mice were restrained but not anesthetized (NARCO BIOSYSTEMS Physiograph; method described by Schlager, 1974). Five individual blood pressures (BP) were taken on each of three separate days about a week apart.

Although genetic selection was practiced on systolic blood pressure, diastolic pressures changed proportionally. In the 14th generation of selection diastolic blood pressures measured directly from the femoral artery under ether anesthetic was 99 ± 5 mm Hg in the HBP and 59 ± 8 mm Hg in the LBP.

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The mice were housed in stainless steel cages 11 in × 5 in × 6 in and fed Purina Laboratory Chow and provided with water *ad libitum*. Constant light cycle of 12 h and temperatures of 70–80°F were maintained throughout both studies.

Comparisons between LBP and HBP in the first study were made by a *t*-test. In the second study a one-way analysis of variance followed by a studentized multiple comparison of means was used.

RESULTS

Bred mice

The average lifespan was higher in the LBP for both sexes; in each case about one half of the LBP mice lived longer than all of the HBP (Figs. 1 and 2, and Table 1). For females this difference is striking as the entire survival curve of the HBP is below LBP. In males there is some early crossing of the two survival curves. The survival curve also shows a more precipitious drop in the HBP than the LBP in both sexes, although somewhat more pronounced in the males. Within the lines, there was a positive correlation between age at death and systolic blood pressure in the LBP line but a negative correlation in the HBP line (Table 1). None of these correlations were statistically significant although that within the LBP males approaches $p = 0.05$.

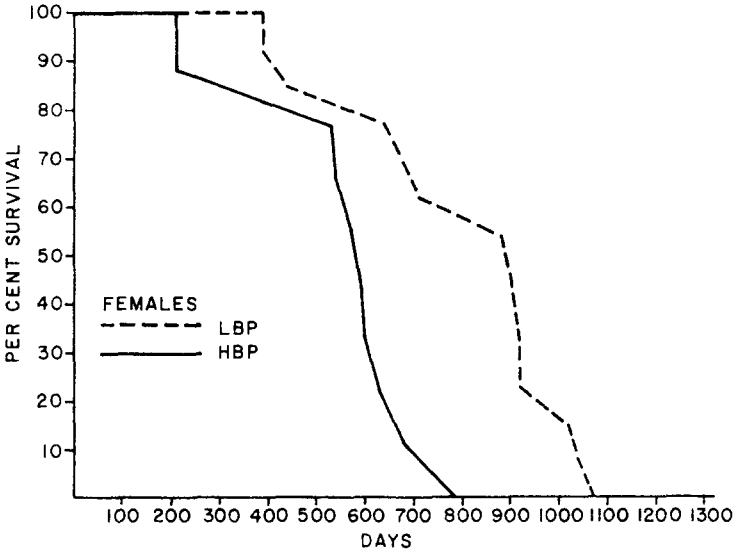

FIG. 1. Survival curves of bred females of the LBP and HBP lines. Mice housed together as a mated pair for life.

The influence of lifetime reproductive history on lifespan was also examined. The mean number of offspring produced by the HBP females was almost twice that of the LBP although the average number of litters was about five in each line. There was a negative association between number born and lifespan and between number of litters and lifespan in the LBP females, and a positive correlation in the HBP females. The correlation coefficient for number of litters and lifespan was statistically significantly different from zero in the HBP females; none of the other correlations were statistically significant.

Unmated mice

The LBP females outlived those of the HBP line by about 200 days (Fig. 3, and Table 2). The LBP males also lived longer than those of the HBP lines, about 300 days longer

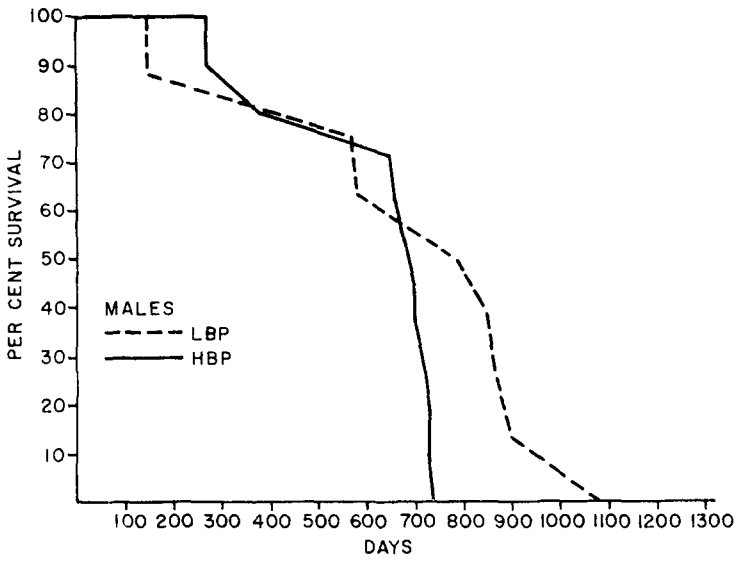

FIG. 2. Survival curves of bred males of the LBP and HBP lines. Mice housed together as a mated pair for life.

TABLE 1. MEANS AND STANDARD ERRORS FOR LIFESPAN, SYSTOLIC BLOOD PRESSURE (SBP) AND REPRODUCTIVE PARAMETERS FOR THE BRED MICE OF THE FIRST STUDY

Line	Sex	Sample size	Age at death (days)	SPB at 100–150 days (mm Hg)	Number of offspring per female	Number of litters per female	Correlations between lifespan and SBP	Number born	Number of litters
HBP	♀	9	571 ± 52*	166 ± 4†	43 ± 7*	5.2 ± 0.6	−0.093	0.562	0.679‡
LBP	♀	13	808 ± 62	76 ± 2	25 ± 4	4.9 ± 0.8	0.128	−0.360	−0.308
HBP	♂	11	628 ± 46	165 ± 4†			−0.220		
LBP	♂	8	719 ± 100	76 ± 3			0.542		

*A significant difference exists between HBP and LBP of the same sex at $p < 0.05$.
†$p < 0.01$.
‡Correlation coefficient significantly different from zero at $p < 0.05$.

(Fig. 4). Both the LBP and randombred had significantly longer lifespans than the HBP in both studies. The correlation between blood pressure and lifespan was negative in both the LBP and HBP. These correlations were not statistically significant.

DISCUSSION

The data support the hypothesis that elevated blood pressure does not favour long life. The average lifespan was higher in the Hypotensive line than in the Hypertensives in both studies in both sexes. Extensive actuary studies in human populations demonstrated that high blood pressure (both hypertension and borderline hypertension) is associated with significant life shortening, while pressures 10–15 mm Hg below average are optimal with regard to longevity (Lew, 1973). For the retired breeders in our study, the LBP mice lived 15 to 40 per cent longer than the HBP. Among the nonbreeders the HBP again had shorter lifespans. However, the extreme blood pressure individual among breeders tended to be at a disadvantage with respect to longevity within both lines, since there was a positive association between blood pressure and lifespan in the LBP but a negative association in the HBP.

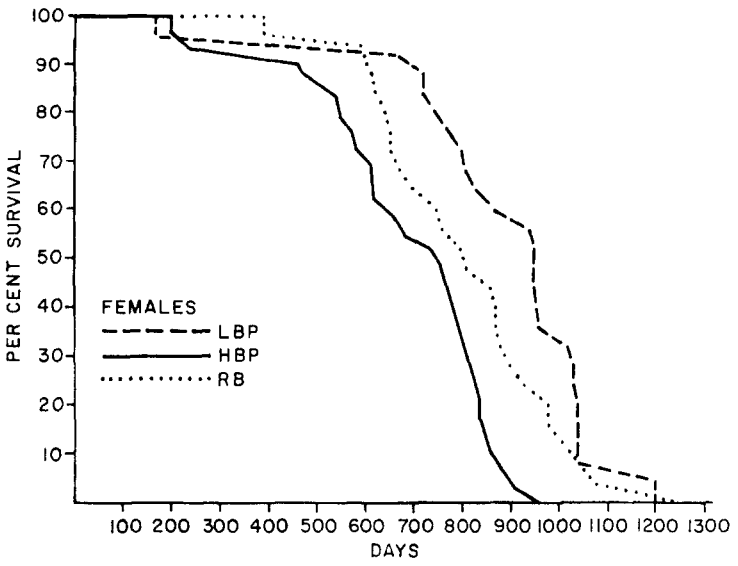

FIG. 3. Survival curves of the unmated females of the LBP, HBP and randombred lines. Initial density was three like-sexed mice per cage.

TABLE 2. MEANS AND STANDARD ERRORS FOR LIFESPAN, SYSTOLIC BLOOD PRESSURE (SPB) OF UNMATED MICE OF THE SECOND STUDY

Line	Sex	Sample size	Age at death (days)	SPB at 100–150 days (mm Hg)	Correlation between lifespan and SBP
HBP	♀♀	29	691 ± 35*	122 ± 4†	−0.18
LBP	♀♀	25	902 ± 42	68 ± 3	−0.16
RANDOM	♀♀	25	814 ± 38		
HBP	♂♂	31	551 ± 38*	131 ± 5†	−0.09
LBP	♂♂	25	853 ± 39	83 ± 3	−0.10
RANDOM	♂♂	24	842 ± 28		

*HBP significantly different from LBP and randombred at $p < 0.05$.
†HBP significantly different from LBP at $p < 0.01$.

Bred females did not have as long a lifespan as the unmated females in either LBP or HBP. Male mice of the HBP lived longer when allowed to mate throughout their lifetime than when unmated. On the other hand unmated LBP males had somewhat longer lifespans than bred LBP males. These comparisons must be made with some caution since these experiments were not designed to be compared to one another and were not run concurrently. Since only mice with extreme blood pressures are used to propagate the lines, the differences between the HBP and LBP were greater in the first study involving bred mice than in the second involving unmated mice. The longer life span of the unmated females of the HBP compared to the bred female may reflect the higher BP of the bred females rather than reproductive stress. Similarly, the longer life span of the unmated LBP compared to bred LBP may be due to the lower BP in the bred mice and the positive association between BP and life span.

There are a number of confounding variables in this study which may contribute to the differences in survival between the HBP and LBP lines. For the bred mice the stress of reproduction could have had an effect on lifespan. On average the LBP female produced 25 offspring in five litters while the HBP produced 43 in about the same number of litters. The smaller litter sizes in the LBP line has been observed for a number of generations and has led to near extinction of the line on at least two occasions. This reduction in litter size has been considered an effect of natural selection where the lowered blood pressure may not suffice to physiologically support larger litters. Virgin female mice tend to have significantly longer lifespans than bred females (Russell, 1966) but not consistenty so (Hrubrant, 1964). The size of litters and longevity appear to be genetically correlated in mouse strains when one omits strains with known specific diseases (e.g., leukemia) and examines only females that have had five or more litters (Roderick and Storer, 1961). There has also been some evidence presented to show that the albino locus may be associated with shorter lifespan, but this has been refuted by other (Goodrick, 1975). Single gene substitutions at the agouti locus also seems to affect survival by nine to fourteen per cent (Hrubrant, 1964). The albino locus was fixed in the HBP line for several generations while tans, brown and dilute alleles are noticeably segregating in the LBP line. It is more likely that the differences in longevity observed in our study are due in large measure to the two-fold difference in blood pressure rather than the reproductive history or pleiotrophic effects of single gene differences for coat color.

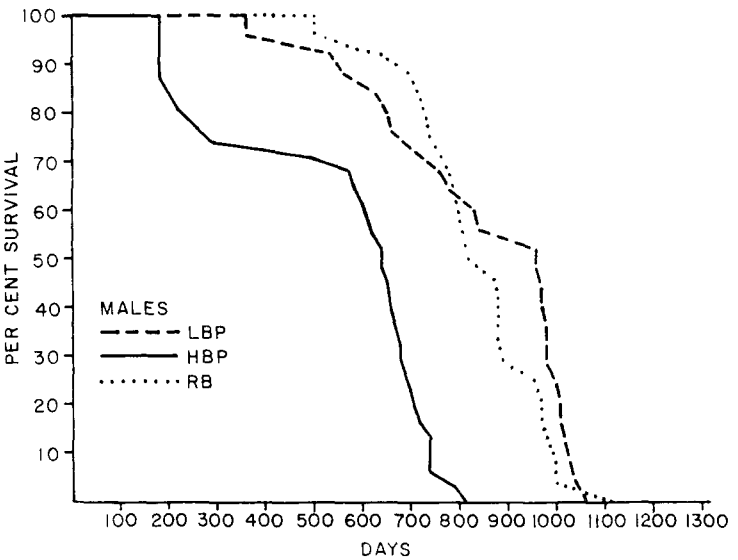

FIG. 4. Survival curves of the unmated males of the LBP, HBP and randombred lines. Initial density was three like-sexed mice per cage.

In rats, Drori and Folman (1969, 1976) have demonstrated that mated males live significantly longer than their unmated littermates although forcing a male rat to run in a revolving steel drum for 2 min a day produced a similar survival curve (Drori and Folman, 1976). Although the experiments reported here were not designed to test a hypothesis of longer life for mated male mice, a comparison of the survival data for the males of the LBP line in the two studies suggest that the mated males did not live

as long as unmated males. However, our nonmated data comes from males caged with two other males while the mated data comes from males caged with one female and their periodic litters. Ebbesen (1972) has shown that unmated single male mice in a cage live considerably longer than males housed with five or six other males.

Our findings in the spontaneously hypertensive mouse parallel those of the spontaneously hypertensive rat (SHR) which also has a significantly shorter lifespan when compared to Wistar controls. Nagaoka *et al.* (1972) found a significant decrease in longevity of the SHR when compared to WK controls. About 60 per cent of the male SHR and 30 per cent of the female SHR died before any of the Control rats. The blood pressure levels in the spontaneously hypertensive mouse are not as elevated as those of the SHR, but it is evident that even mild elevation of blood pressure can lead to life shortening.

Dupont *et al.* (1975) reported significantly shorter life span in rats selected for high blood pressure of the Lyon strain compared to normtensive and hypotensive rats. All male hypertensive rats in this study died by age 32 months at which time approximately 80 per cent of the female hypertensive rats were dead. Among females of the other two lines, fewer than 25 per cent died by 32 months. Lifespan was shorter in the males where approximately 70 per cent of normotensives and 50 per cent of the hypotensives died by 32 months.

In three independent studies of potential animal models for human hypertension, animals with elevated blood pressures had significantly shorter lifespans. In the Lyon hypotensive rat and the LBP mouse the effect of low blood pressure is less clear, but appears to be associated with somewhat increased lifespan.

SUMMARY

Longevity was investigated in three lines of mice with genetically selected differences in systolic blood pressure. Lifespan was shortest in the line with elevated blood pressure and significantly longer in the normotensive and hypotensive lines. In unmated animals this difference in lifespan between the low blood pressure line and high blood pressure line was 200–300 days. The difference in the bred mice was somewhat less but was confounded by differences in reproductive capacity.

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