Genetic Control of Blood Pressure by More than One Pair of Alleles[1] (35381)

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Blood pressure and hypertension are genetically determined to some degree in humans and laboratory animals. Investigation of the relative importance of genetic and environmental factors on blood pressure levels has suggested that the percentage of the total variation due to inherited genetic causes may be as high as 33% in humans (1), 15% in rats (2), and 20% in mice (3). There is considerable controversy about the number of loci affecting hypertension in humans. Platt (4) has suggested that a single gene difference accounts for a large amount of the variation in blood pressure. Pickering (5) on the other hand challenges this hypothesis since blood pressure is the result of the interaction of many anatomical, physiological, and epidemiological factors and is consequently multifactorial in nature. Under this opposing "polygenic" hypothesis the genetic determination must be due to the action of several genes and their modification by environmental factors. As Miall *et al.* (1) have pointed out, epidemiological studies in human populations have been primarily conducted on the assumption of polygenic inheritance with the belief that "if the inheritance of hypertension was not polygenic this would be revealed in long-term studies by the accumulation of incompatible findings." In laboratory animals, this assumption need not be imposed since specific kinds of matings can be made to follow the transmission of particular sets of genes with known effects on blood pressure.

Inbred strains of mice show a wide range of average systolic blood pressures (6) and the effects of these genes can be followed in crosses between strains and subsequent intercrosses and backcrosses. The A/J strain has relatively low systolic blood pressure (mean about 80 mm Hg at 100–150 days), while the BALB/cJ (105 mm Hg) and SWR/J (110 mm Hg) strains exhibit the highest pressures of 40 inbred strains measured. Crosses between the low and high strains demonstrated intermediate inheritance of blood pressure levels and this finding was further corroborated by the F_2 and backcross means (6, 7). It was apparent that the BALB/cJ and SWR/J strains were not genetically identical for the alleles contributing to blood pressure differences since the two strains were consistently different in average systolic blood pressure. This genetic difference could be due to a single locus with a multiallelic system, *e.g.*, A_1A_1 in A/J, A_2A_2 in BALB/cJ, and A_3A_3 in SWR/J, with the A_3A_3 homozygotes exhibiting slightly more elevated pressures than A_2A_2 homozygotes. This genetic difference could also be due to allelic differences at two or more loci. To resolve the question, selection for elevated pressures was begun in a base population containing genetic contributions from the two highest strains (an F_2 from BALB/cJ $\times$ SWR/J). If the maximum response was no higher than the original SWR/J mean, then the results would support the single locus hypothesis since the selected genotype would be the A_3A_3 homozygote. If the response exceeded the SWR/J mean, then the two strains contributed alleles from more than one locus since the selected line has more alleles for elevating blood pressure than either homozy-

[1] This investigation was conducted at The Jackson Laboratory, Bar Habor, Maine, and was supported in part by NIH Research Grant HE-09331 from the National Heart Institute, by an allocation from NIH General Research Support Grant RR-05545 from the Division of Research Resources to the Jackson Laboratory, and by an allocation from the Biomedical Sciences Support Grant RR-07037 at the University of Kansas.

gous parental strain.

Materials and Methods. The BALB/cJ and SWR/J were mated reciprocally and the resulting F_1 hybrids were intercrossed to produce an F_2. Selection was initiated in this F_2 population of 66 mice by choosing 7 males and 7 females with the highest blood pressures. Of 45 F_3 mice, 6 pairs with the highest blood pressures were used to continue the line; 3 pairs out of 46 mice in the F_4, and 7 pairs out of 33 mice in the F_5. Mice of the SWR/J strain were reared and measured concurrently with the F_4 and F_6 generations to serve as controls. Rather intensive inbreeding was practiced throughout the four generations of selection since only a few matings were made in each generation and most matings were between sibs. Attempts to breed the F_7 generation are now being hampered by poor fertility and it is doubtful that the line can be continued.

The mice were reared under standard laboratory conditions with 12 hr of light. No more than 3 mice of the same sex were weaned into stainless steel cages (11 × 5 × 6 in.). Food and water were continuously available to the mice.

Systolic blood pressure was determined by an occluding cuff on the tail with a pneumatic pulse transducer to detect the return of pulse distal to the cuff upon deflation (Physiograph, E and M Instrument Co.). Simultaneous direct and indirect determinations have shown this technique to be valid although the pressure in the tail is recorded at about 10 mm Hg lower than in the carotid artery (6). Blood pressures were determined when the mice were 100, 125, and 150 days old and were taken betewen 1 and 3 p.m. to avoid "time of day" effects (8).

Results and Discussion. The difference in blood pressure between the selected F_4 line (100 ± 4, $n = 45$) and the control SWR/J (108 ± 4, $n = 54$) was not significant. By the F_6 generation, after 4 generations of selection, the selected line had statistically higher systolic blood pressures than the controls. The means of systolic blood pressure by sex and line in the F_6 are shown in Table I. The higher systolic blood pressures in the SWR/J controls are undoubtedly due to unexplainable environmental influences, quite possibly seasonal variation as evidenced by other long-term investigations of blood pressure in mice. Apparent seasonal fluctuations are noticeable in another selection experiment for high and low blood pressure lines during a 5-year period. Similar increases and decreases are present in the two selected lines and a random-mated control. This variation should affect both selected and SWR/J controls equally since the concomitant controls were exposed to the same environmental conditions as the selected mice in F_6. The variance in the selected line was larger than that of the highly inbred SWR/J controls suggesting that the selected line was not yet homozygous for the alleles affecting blood pressure levels. This difference in variance was not significant by an F_{max} test and therefore should not interfere with the conclusions reached from the analysis of variance. However, the data were reanalyzed using a transformation to logarithm (base 10) to overcome this disparity in variances; the F ratios of the new analysis were essentially the same as those shown in Table II and will not be presented.

TABLE I. Means and Their Standard Errors of Systolic Blood Pressure (mm Hg) of the Selected F_6 and Control Groups.

Twenty-three mice per sex per group were measured.

	Selected	Controls (SWR/J)
Males	128 ± 4.0	121 ± 2.5
Females	132 ± 4.0	115 ± 2.9

The analysis of variance in Table II did not detect a significant difference in systolic blood pressure between males and females, nor was there any indication that there was a

TABLE II. Analysis of Variance of Systolic Blood Pressure.

Source of variation	*df*	Mean square	*F*
Selected vs control	1	3408.70	12.72[a]
Males vs females	1	25.04	0.09
Sex × line	1	595.17	2.23
Error	88	267.95	

[a] $p < 0.001$.

TABLE III. Estimates of the Minimum Number of Loci Determining the Response to Selection for Elevated Blood Pressure.

Sex	Variance F_2 (V_p)	Cumulative response F_2–F_6 [R (mm Hg)]	Realized heritability[a] (h^2)	Minimum no. of loci (n)[b]
Males	125	19	0.379	3.8
Females	226	33	0.406	5.9
Av	175	26	0.392	4.9

[a] h^2 calculated from the regression of cumulative response on cumulative selection differential.

[b] $n = (2R)^2/(8 \cdot h^2 \cdot V_p)$.

significant interaction between sex and line. The bulk of the differences between subgroups was due to a highly significant difference between the selected line and the SWR/J control. There is only one chance in a thousand that a difference of this magnitude is due to chance. None of the mice in the SWR/J strain had systolic blood pressures exceeding 145 mm Hg while 12% of the selected line were hypertensive by this criterion.

An estimate of the minimum number of loci can be obtained from the response to two-way selection and the additive genetic variance (9). In this experiment selection was practiced in one direction only, but if we assume that the response would have been reasonably symmetrical, the calculation can be made using the formula given in footnote *b* in Table III. These calculations assume that the extreme range of response was reached, that there is no directional dominance, and that the effects of the loci are equal. Violation of these assumptions tend to underestimate the number of genetic "factors" (loci or groups of closely linked loci). Selection limits for blood pressure differences were probably not reached in this experiment before the line was lost so the number of loci will be underestimated by this formula. Previous genetic studies with these strains found no evidence for dominance of alleles for elevated pressures among the males (6, 7) and an apparent dominance in the female data was attributed to physiological factors rather than gene action (7). Estimates of the minimum number of loci affecting the blood pressure differences between the BALB/cJ and SRW/J strains are given in Table III. These calculations suggest that at least three loci are involved.

Summary and Conclusion. This experiment was designed to determino whether the genetic differences in blood pressure found between the A/J and BALB/cJ and between the A/J and SWR/J strains were due to different loci in the BALB/cJ and SWR/J strains or due to different alleles carried at the same locus. It was found that after four generations of selection the mean blood pressure of the SWR/J was exceeded by 7 mm Hg in males and 17 mm Hg in the females. The results could not be due to different alleles at the same locus since the selected genotype would be the same as the SWR/J genotype at that locus and should not have a more elevated blood pressure than the SRW/J strain. Since the blood pressure in the selected line exceeded that of the SRW/J, each of the two strains (BALB/J and SWR/J) must have contributed different alleles at more than one locus to the original gene pool in the F_1 and F_2. It is also concluded on the basis of genetic selection theory, that the difference between mean systolic blood pressure of the two inbred strains is due to the action of at least three loci.

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Received Sept. 8, 1970. P.S.E.B.M., 1971, Vol. 136.