Genetic Analysis of Blood Pressure in Spontaneously Hypertensive Rats*

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Spontaneously hypertensive rats (SHR), established now as an inbred strain, were used for the genetic study on hypertension. The genetic mechanism was analyzed from the blood pressure in SHR, several normotensive strains and their F₁, F₂ and backcross generations. The three series of experiments, one of which was independently done, gave similar results, which indicated a great importance of genetic factors and additive mode of inheritance, and further suggested on some assumptions a relatively few number of genes involved in this genetic hypertension.

THERE have been accumulating considerable evidences which indicate that human essential hypertension is a sort of genetic trait, and it can now hardly be doubted that an hereditary factor is important in the pathogenesis of essential hypertension.¹ However, there are still two conflicting views about the genetic mechanisms, especially the number of genes involved. PLATT and several researchers²⁻⁴ basing their observations on the bimodal distribution of blood pressure in human population, suggested that essential hypertension is an entity of hereditary disease caused by a single gene with incomplete dominance. Conversely, a continuous unimodal frequency distribution in blood pressure was also observed by other researchers.⁵⁻⁷ Although the curves demonstrated a positive skew and left the possibility that two distinct populations were presented, PICKERLING et al^{6,7} deriving a hypothesis from this unimodal distribution, concluded that blood pressure level was a multifactorial trait. This question could not be easily solved from the analysis of human pedigree data, comparison in monozygotic and dizygotic twins and

comparison of the different racial groups, and it still remains open to the future long-term study of representative populations by the modern technique of epidemiology.⁸

On the other hand, the importance of hereditary factors in hypertension has been clearly demonstrated by the development of hypertensive strains of animals by selective breeding for high blood pressure. For example, ALEXANDER et al^{9,10} developed a colony of spontaneously hypertensive rabbits by selecting animals with blood pressure over 160 mmHg from New Zealand White, Dutch and Californian rabbits. SMIRK and his coworkers^{11,12} developed several lines with a high incidence of hypertension from New Zealand strain of albino rats, using selective cross breeding and intensive sister-brother mating, and confirmed the effectiveness of selection on hypertension. DAHL et al¹³ noticed a difference in susceptibility to salt ingestion for developing hypertension in SPRAGUE-DAWLEY rats and separated two strains, sensitive and resistant to the development of hypertension due to chronic salt excess. OKAMOTO and AOKI succeeded in

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producing a strain of spontaneously hypertensive rats (SHR)¹⁴⁻¹⁶ by selective inbreeding from a male with mild hypertension and female with a slightly higher blood pressure than the average among Wistar-Kyoto. The successive selective sib-matings have been continued by OKAMOTO and his collaborators in Kyoto, and the F_{21} generation was obtained in October, 1969. The inbred (so-called biologically pure) strain of SHR is now available after 20 generations of full sib-mating. These SHR's uniformly develop moderate or severe hypertension over 200 mmHg at 15 to 20 weeks of age, and are obviously the best materials for the genetic study on hypertension.

Among these animals with hypertension or susceptibility to hypertension, no detailed studies have yet been performed on the mode of inheritance of blood pressure or on the relative importance of genetic and environmental factors, although genetic analysis was done on some of the normotensive animals such as chickens¹⁷ and mice.¹⁸⁻²⁰ A preliminary study on the blood pressure in hybrids between the F_{15} generation of SHR (F_2 in NIH) and randomly bred Wistar (Albino Farm, Redbank, New Jersey) was reported by LOUIS et al.²¹ As they used only a limited number of F_1 hybrids, this was theoretically insufficient and far from any conclusion about the mode of inheritance of genetic hypertension. The extensive analyses of the blood pressure in SHR, control normotensives, cross generations between them (F_1 , F_2) and backcross generations had been done independently by two groups of researchers in Japan. The works of these two laboratories yielded a similar result simultaneously and reached a consistent conclusion. The validity of this conclusion was further confirmed by a recent work using both inbred strains of SHR (F_{21}) and Wistar-Mishima (F_{58}). Therefore, all the results of these three experiments were summarized together and reported here with the cooperation of two groups of researchers, in the hope that analysis on genetic determination of hypertension and on its interaction with environmental factors in SHR would contribute to the elucidation of the mode of inheritance in human essential hypertension.

MATERIALS AND METHODS

The principle of genetic analysis applied in this study is to measure the blood pressure and calculate the variance of the blood pressure in SHR, several normotensive strains of Wistar, F_1 , F_2 and the backcross generations.

Blood pressure was measured weekly in experiments 2 and 3, or biweekly in experiment 1 in unanesthetized rats using a tail-plethysmographic method.^{14,22} The average of three readings was recorded as the blood pressure for each rat.

The degree of genetic determination of the blood pressure in control normotensive strains, that is, the ratio of genetic variance (V_G) to total variance (V_P) was derived from the analysis of the variances of several normotensive strains on the assumption that the variance within a strain corresponded to the variance due to environmental factors while the variance between the strains to that due to genetic factors. This degree of genetic determination (V_G/V_P) is an estimate of the relative importance of all genetic factors in determining the phenotype, the blood pressure, and was calculated as described by FALCONER.²³ The calculation of the standard errors was based on the method of OSBORNE and PATERSON.²⁴

This analysis should not be applied to the data in SHR because the distribution of the blood pressure in this strain was greatly different from that in other normotensive strains. Consequently, the degree of genetic determination of blood pressure in SHR was obtained after cross analysis. The blood pressure in average and the variance in parent strains, F_1 , F_2 and backcross generations between F_1 and the parent strains were calculated at certain periods after birth. Since the distribution of the blood pressure in these non-segregating parent- and F_1 generations as well as segregating F_2 and backcross generations was continuous but tended to be positively skewed, and also because of the inhomogeneity of variances among non-segregating parent- and F_1 generations supposedly due to genotype-environment interaction, the data of the blood pressure was logarithmically transformed. And further biometrical analyses were carried out with the blood pressure values transformed to a thousand times of the logarithmus. Although non-allelic interaction was not completely eliminated with the scale from the results of MATHER's scaling tests,²⁵ the validity of the logarithmic transformation was partially proved so far as inhomogeneity of the variances was removed. The phenotypic variance in F_2 generation (V_{F_2}) can be attributable to both genetic and environmental causes. On the other hand, the phenotypic variance in F_1 hybrids (V_{F_1}) can only be due to environmental

causes. Therefore, the degree of genetic determination of the blood pressure in SHR was estimated by dividing the difference between the F_1 computed phenotypic variance (V_{F_1}) and the F_2 computed phenotypic variance (V_{F_2}) with the latter variance (V_{F_2}): $(V_{F_2} - V_{F_1})/V_{F_2}$.²³

The genetic parameters, relating to additivity (D) and dominance (H), were calculated in the manner described by MATHER²⁵ as follows: The variance of F_2 generation (V_{F_2}) is $\frac{1}{2}D + \frac{1}{4}H + E_1$ where E_1 is environmental variance and calculated from the mean of variances in parent strains and F_1 hybrids. The total of variances of 2 backcross generations is $\frac{1}{2}D + \frac{1}{2}H + 2E_1$. From these 2 equations, D and H were obtained and dominance ratio (average degree of dominance) was calculated as $\sqrt{H/D}$.

On the basis of a number of assumptions which was described by WRIGHT,²⁶ the minimum number of loci affecting one trait was approximately estimated from the following equation: $n = R^2/4D$, where R is the difference between the parent strains and D is the variance attributable to additive effect.

All the rats used in the following series of experiments were reared in the animal rooms with the temperature of $24 \pm 2^\circ\text{C}$ and humidity of $55 \pm 5\%$ and fed on commercial pellets CMF supplied from Oriental Yeast Co., Ltd. in experiment 1 and on OA-2 or CA-1 from Japan Clea Co., Ltd. in experiments 2 and 3. The tap water and food were accessible ad libitum.

The detailed number and the strains of rats used in 3 experiments for genetic analysis are as follows.

Experiment 1: Genetic analysis of blood pressure in 3 normotensive strains of albino rats and cross analysis using SHR (F_{14}) and WISTAR-IMAMICHI.

Four strains of rats were used in this experiment, i.e., WISTAR-IMAMICHI, HOLTZMAN, SPRAGUE-DAWLEY and the spontaneously hypertensive rats (SHR). WISTAR-IMAMICHI rats (WI)²⁷ were obtained from a closed colony maintained at the Institute for Animal Reproduction, and 48 of them were used. SPRAGUE-DAWLEY (SD) and HOLTZMAN (HOZ) rats were obtained from closed colonies commercially maintained at the Japan Central Laboratories for Experimental Animals and KITAYAMA LABES, respectively, and 44 of the former and 40 of the latter were used. SHR (male; 7078, females; 7070, 7087) were separated from the original colony at F_7 generation to Toho University¹⁴ from where

they were introduced to Sankyo Central Research Laboratories in 1966, and they were reproduced by full sister-brother matings. Fifty two of the F_{14} of these SHR were used in this experiment.

For the cross analysis, 65 F_1 hybrids were produced mostly from the crosses of $WI \times SHR$, and they were intercrossed to produce 63 F_2 hybrids and backcrossed with WI and with SHR to produce 54 and 55 backcross generations, respectively.

Experiment 2: Cross analysis between SHR (F_{18-20}) and Wistar-Kyoto.

F_{18-20} generation of SHR in Department of Pathology, Faculty of Medicine, Kyoto University, Kyoto, Japan, and Wistar-Kyoto (WK) were used in this experiment. SHR used for the breeding of cross analysis were the F_{18} and F_{19} offspring of a male 170267 and a female 170270, and 4 rats from F_{20} generation (male; 200028, female; 200034, 200035, 200037). WK were supplied from the closed colony maintained at the Animal Center Laboratory of Kyoto University. These two strains had the same ancestors and SHR were separated from WK by selective sister-brother matings. Forty five of SHR and 32 of WK served for the study, and crosses were made between 8 SHR and 6 WK to produce 51 F_1 hybrids, which were intercrossed to produce 72 F_2 hybrids and backcrossed with WK and SHR to produce 116 and 114 backcross generations, respectively.

Experiment 3: Cross analysis between both inbred strains, SHR (F_{21}) and Wistar-Mishima (F_{58}).

Wistar-Mishima (WM) were introduced to the Department of Pathology, Faculty of Medicine, Kyoto University at the F_{56} generation. Since the inbred strain, F_{21} of SHR was established by OKAMOTO and his collaborators in October, 1969, at the Department of Pathology, Faculty of Medicine, Kyoto University, 41 SHR of F_{21} generations with 46 WM (F_{58}) were used for the analysis. From the crossings between 4 SHR (males; 217502, 217505, females; 217506, 217508, which were the offspring obtained by mating between a male 200030 and a female 200034.) and 4 WM, 41 F_1 hybrids were produced. They were intercrossed to produce 94 F_2 hybrids and backcrossed with SHR and WM to produce 71 and 67 rats of backcross generations, respectively.

RESULTS

1. Genetic analysis of blood pressure in 3 normotensive strains of albino rats and cross analysis using SHR (F₁₄) and Wistar-Imamichi.

The progressive rise in blood pressure with age in SPRAGUE-DAWLEY, HOLTZMAN, WISTAR-IMAMICHI (WI) and SHR was observed and is presented in Tables I and II. At all ages observed, the blood pressure in SHR was significantly higher than that in other normotensive strains. At 19 weeks of age the range between the highest and lowest average blood pressures was about 42 mmHg in females and 60 mmHg in males, respectively. The blood pressure in the males was consistently higher than that in females in all strains as well as in F₁, F₂ and backcross generations. The sex difference in blood pressure was

especially marked in SHR.

On the basis that the variance within a strain is an environmental variance while the variance between strains is genetic plus environmental variance, the degree of genetic determination of blood pressure was estimated in 3 normotensive strains, but SHR was not included because the blood pressure in SHR was greatly different from the other 3 normotensive strains. The results of the comparison of 3 normotensive strains are shown in Table III. The distribution of blood pressure of each strain tended to be slightly positively skewed, but these skews were eliminated by a logarithmic transformation. Since such logarithmic transformation did not affect the results, only the untransformed data were presented. The difference among the strains became evident with age and significant differ-

TABLE I BLOOD PRESSURE IN MALES OF SHR (F₁₄), WISTAR-IMAMICHI, SPRAGUE-DAWLEY, HOLTZMAN AND CROSSES BETWEEN SHR AND WISTAR-IMAMICHI

Weeks of age		5	7	9	11	13	15	17	19
Generations	N	Blood pressure (mmHg) Mean $\pm$ SE							
WI	(P ₁) (22)	110 $\pm$ 1.5	116 $\pm$ 1.4	119 $\pm$ 1.2	122 $\pm$ 1.2	123 $\pm$ 1.4	125 $\pm$ 1.4	127 $\pm$ 1.5	129 $\pm$ 1.6
SD/JCL	(19)	108 $\pm$ 1.1	116 $\pm$ 1.1	124 $\pm$ 1.3	128 $\pm$ 1.3	132 $\pm$ 1.4	134 $\pm$ 1.1	136 $\pm$ 1.1	139 $\pm$ 1.3
HOZ	(20)	108 $\pm$ 1.0	117 $\pm$ 1.1	122 $\pm$ 1.1	127 $\pm$ 1.0	131 $\pm$ 1.0	136 $\pm$ 1.1	139 $\pm$ 1.0	140 $\pm$ 1.1
SHR	(P ₂) (26)	122 $\pm$ 1.5	150 $\pm$ 1.6	161 $\pm$ 1.3	169 $\pm$ 1.4	173 $\pm$ 1.9	179 $\pm$ 1.7	186 $\pm$ 1.9	189 $\pm$ 1.8
WI $\times$ SHR	(F ₁) (35)	113 $\pm$ 1.2	135 $\pm$ 1.2	143 $\pm$ 1.2	146 $\pm$ 1.2	152 $\pm$ 1.2	155 $\pm$ 1.2	157 $\pm$ 1.2	160 $\pm$ 1.3
F ₁ $\times$ F ₁	(F ₂) (30)	112 $\pm$ 1.8	131 $\pm$ 1.9	137 $\pm$ 1.9	141 $\pm$ 1.9	144 $\pm$ 2.0	146 $\pm$ 2.0	148 $\pm$ 2.1	150 $\pm$ 2.2
WI $\times$ F ₁	(BC ₁) (27)	109 $\pm$ 1.3	122 $\pm$ 1.5	126 $\pm$ 1.6	131 $\pm$ 1.6	133 $\pm$ 1.6	135 $\pm$ 1.8	136 $\pm$ 1.9	136 $\pm$ 2.0
F ₁ $\times$ SHR	(BC ₂) (27)	120 $\pm$ 1.5	139 $\pm$ 1.5	149 $\pm$ 1.7	153 $\pm$ 1.7	156 $\pm$ 2.2	158 $\pm$ 1.8	161 $\pm$ 1.9	163 $\pm$ 1.9

N: Number of cases observed SHR: Spontaneously hypertensive rats WI: Wistar-Imamichi
SD/JCL: Sprague-Dawley rats (Japan Central Laboratories for Experimental Animals) HOZ: Holtzman rats

TABLE II BLOOD PRESSURE IN FEMALES OF SHR (F₁₄), WISTAR-IMAMICHI, SPRAGUE-DAWLEY, HOLTZMAN AND CROSSES BETWEEN SHR AND WISTAR-IMAMICHI

Weeks of age		5	7	9	11	13	15	17	19
Generations	N	Blood pressure (mmHg) Mean $\pm$ SE							
WI	(P ₁) (26)	109 $\pm$ 1.4	116 $\pm$ 1.1	116 $\pm$ 1.2	120 $\pm$ 1.1	119 $\pm$ 1.2	121 $\pm$ 1.4	123 $\pm$ 1.0	123 $\pm$ 1.0
SD/JCL	(25)	106 $\pm$ 1.0	114 $\pm$ 1.0	118 $\pm$ 0.8	122 $\pm$ 0.8	126 $\pm$ 0.9	128 $\pm$ 0.9	129 $\pm$ 1.1	131 $\pm$ 1.2
HOZ	(20)	107 $\pm$ 0.9	115 $\pm$ 1.1	119 $\pm$ 1.2	123 $\pm$ 1.1	125 $\pm$ 1.0	127 $\pm$ 1.0	131 $\pm$ 1.0	132 $\pm$ 1.0
SHR	(P ₂) (26)	119 $\pm$ 1.7	141 $\pm$ 1.5	151 $\pm$ 1.4	154 $\pm$ 1.2	157 $\pm$ 1.5	161 $\pm$ 1.5	164 $\pm$ 1.5	166 $\pm$ 1.4
WI $\times$ SHR	(F ₁) (30)	111 $\pm$ 1.1	127 $\pm$ 1.2	132 $\pm$ 1.1	136 $\pm$ 1.1	138 $\pm$ 1.0	140 $\pm$ 1.0	143 $\pm$ 0.9	144 $\pm$ 1.0
F ₁ $\times$ F ₁	(F ₂) (33)	109 $\pm$ 1.4	122 $\pm$ 1.6	128 $\pm$ 1.5	133 $\pm$ 1.5	135 $\pm$ 1.5	137 $\pm$ 1.6	139 $\pm$ 1.7	141 $\pm$ 1.8
WI $\times$ F ₁	(BC ₁) (27)	107 $\pm$ 1.3	118 $\pm$ 1.3	123 $\pm$ 1.4	127 $\pm$ 1.4	128 $\pm$ 1.6	129 $\pm$ 1.7	130 $\pm$ 1.7	133 $\pm$ 1.9
F ₁ $\times$ SHR	(BC ₂) (28)	117 $\pm$ 1.3	130 $\pm$ 1.4	136 $\pm$ 1.4	140 $\pm$ 1.4	142 $\pm$ 1.3	145 $\pm$ 1.4	146 $\pm$ 1.5	147 $\pm$ 1.6

N: Number of cases observed SHR: Spontaneously hypertensive rats WI: Wistar-Imamichi
SD/JCL: Sprague-Dawley rats (Japan Central Laboratories for Experimental Animals) HOZ: Holtzman rats

TABLE III ESTIMATION OF THE DEGREE OF GENETIC DETERMINATION FROM THE COMPARISON OF THREE NORMOTENSIVE STRAINS

Weeks of age		7	9	11	13	15	17	19
Male								
Variance between strains	d.f. 2	3.00	160.00	207.00	420.00	721.50	888.50	843.50
Variance within strain	58	31.98	28.77	28.59	31.60	28.68	31.55	37.32
F ratio		0.09	5.56*	7.24*	13.29*	25.15*	28.16*	22.60*
Genetic determination		—	0.100 ±0.112	0.133 ±0.135	0.232 ±0.195	0.372 ±0.246	0.400 ±0.252	0.347 ±0.240
Female								
Variance between strains	d.f. 2	49.00	47.50	61.00	395.00	411.50	443.00	571.50
Variance within strain	68	26.75	26.45	24.44	25.64	23.39	22.94	26.75
F ratio		1.83	1.79	2.49	15.40*	17.59*	19.31*	21.36*
Genetic determination		—	—	—	0.233 ±0.193	0.259 ±0.260	0.279 ±0.214	0.300 ±0.223

d.f.: degree of freedom

F ratio: variance ratio

*: statistically significant ($P < 0.01$)

ences were noticed at 13 weeks of age in females and at 9 weeks in males and thereafter. The ratio of genetic variance to total one, which gave an estimate of the degree of genetic determination, was relatively high in both sexes. However, these values were not significant because of great standard errors.

The average of blood pressure in F_1 hybrids was intermediate between the two parent strains, SHR and WI, and did not significantly differ from the mid-parent value. The means of the backcross generations were also intermediate

between F_1 hybrids and the respective parent strains. The F_2 hybrids also showed an intermediate blood pressure level between the parent strains. However, the means of the F_2 and backcross generations were lower than the expected values obtained on an assumption of completely additive inheritance. As shown in Fig. 1, there was neither any evidence for pronounced bimodality in backcross generations nor was the expected 1:2:1 ratio in the F_2 generation noticed. The variance in the F_1 hybrids did not differ from WI, but SHR had a significantly

Fig. 1. The distribution of blood pressure at 19 weeks after birth in all generations used for cross analysis between SHR (F_{14}) and Wistar-Imamichi () : Number of cases observed

TABLE IV ESTIMATION OF THE DEGREE OF GENETIC DETERMINATION FROM VARIANCES OF F_1 AND F_2 OBTAINED FROM THE MATINGS BETWEEN SHR (F_{14}) AND WISTAR-IMAMICHI

Weeks of age	5	7	9	11	13	15	17	19
Male	0.512 ± 0.171	0.545 ± 0.159	0.557 ± 0.155	0.597 ± 0.141	0.605 ± 0.138	0.612 ± 0.136	0.633 ± 0.128	0.690 ± 0.109
Female	0.426 ± 0.207	0.469 ± 0.192	0.492 ± 0.183	0.548 ± 0.163	0.606 ± 0.140	0.684 ± 0.114	0.728 ± 0.098	0.712 ± 0.104

SHR: Spontaneously hypertensive rats

TABLE V ESTIMATION OF THE GENETIC PARAMETERS FROM VARIANCES OF BLOOD PRESSURE IN SHR (F_{14}), WISTAR-IMAMICHI, THEIR F_1 , F_2 AND BACKCROSS GENERATIONS

Weeks of age		5	7	9	11	13	15	17	19
Male data									
F_2 variance	$\frac{1}{2}D + \frac{1}{4}H + E_1$	1538	1237	1129	1036	1063	1077	1137	1245
$BC_1 + BC_2$ variance	$\frac{1}{2}D + \frac{1}{2}H + 2E_1$	1576	1470	1546	1449	1535	1619	1731	1849
Non-heritable component	E_1	848	561	416	386	445	438	502	497
Additive component	D	2800	2008	1424	1246	1162	1070	1086	1282
Dominant component	H	-3240	-1212	4	108	148	416	368	428
Dominance ratio	$\sqrt{H/D}$	-	-	0.052	0.294	0.356	0.623	0.582	0.577
Female data									
F_2 variance	$\frac{1}{2}D + \frac{1}{4}H + E_1$	1075	971	748	818	800	881	944	1026
$BC_1 + BC_2$ variance	$\frac{1}{2}D + \frac{1}{2}H + 2E_1$	1383	1251	1155	1195	1274	1366	1409	1549
Non-heritable component	E_1	817	514	411	372	400	351	314	321
Additive component	D	1534	1418	826	882	750	792	958	1006
Dominant component	H	-2036	-936	-160	20	300	536	604	808
Dominance ratio	$\sqrt{H/D}$	-	-	-	0.150	0.632	0.822	0.793	0.896

SHR: Spontaneously hypertensive rats

larger variance than WI. The variances of the segregations, F_2 hybrids and backcross generations, were greater than those in non-segregating F_1 and parent generations as theoretically expected.

After the data of blood pressure was logarithmically transformed for further analysis, the degrees of genetic determinations were calculated from the variances of F_1 and F_2 generations and are shown in Table IV. These results showed that this trait was of a heritable character. At the age of 19 weeks, when hypertension was nearly established and genetic factors were supposed to have fully developed, the genetic determination was approximately 70 per cent.

Table V shows the estimates of the genetic parameters calculated from the variances of their crosses. The summated additive effect (D) was great in both sexes, while the dominance effect (H) appeared from 11 weeks of age in females

and 9 weeks in males, respectively. The value of dominance ratio (average degree of dominance), which was obtained as $\sqrt{H/D}$, showed that the dominance likely existed but was incomplete.

On several assumptions of defined polygene theory, the minimum number of loci affecting the blood pressure was estimated from WRIGHT's equation, $n = R^2/4D$. There was no concrete evidence that this assumption could be completely applied to the inheritance of this hypertension, but if the inheritance is in conformity with these assumption, the minimum number of the genes would be hypothetically given as shown in Table VI. This table shows that the minimum number of the genes increased with age in both sexes in accordance with the development of hypertension.

2. Cross analysis between SHR (F_{18-20}) and Wistar-Kyoto.

TABLE VI ESTIMATION OF THE MINIMUM NUMBER OF LOCI AFFECTING BLOOD PRESSURE FROM THE DATA OBTAINED BY CROSS ANALYSIS BETWEEN SHR (F_{14}) AND WISTAR-IMAMICHI

Weeks of age	5	7	9	11	13	15	17	19
Male	0.172	1.561	3.085	3.988	4.216	5.684	6.343	5.430
Female	0.211	1.244	3.864	3.429	4.800	4.913	4.012	4.071

SHR: Spontaneously hypertensive rats

TABLE VII BLOOD PRESSURE IN MALES OF SHR (F_{18-20}), WISTAR-KYOTO, THEIR F_1 , F_2 AND BACKCROSS GENERATIONS

Weeks of age	15	20	25	30
Generations	Blood pressure (mmHg)		Mean $\pm$ SE	
WK (P_1)	120 $\pm$ 1.2 (16)	123 $\pm$ 1.2 (16)	124 $\pm$ 1.2 (16)	125 $\pm$ 1.3 (16)
SHR (P_2)	179 $\pm$ 1.3 (22)	184 $\pm$ 1.9 (20)	186 $\pm$ 2.3 (17)	191 $\pm$ 2.9 (16)
WK $\times$ SHR (F_1)	152 $\pm$ 0.9 (24)	151 $\pm$ 0.8 (32)	152 $\pm$ 0.9 (24)	152 $\pm$ 1.0 (24)
$F_1 \times F_1$ (F_2)	138 $\pm$ 2.5 (36)	139 $\pm$ 2.7 (36)	146 $\pm$ 3.0 (36)	146 $\pm$ 2.8 (35)
WK $\times F_1$ (BC_1)	131 $\pm$ 1.4 (62)	132 $\pm$ 1.5 (62)	134 $\pm$ 1.8 (62)	133 $\pm$ 1.5 (58)
$F_1 \times$ SHR (BC_2)	155 $\pm$ 2.0 (49)	165 $\pm$ 2.0 (53)	167 $\pm$ 2.1 (52)	173 $\pm$ 2.2 (50)

(): Number of cases observed

SHR: Spontaneously hypertensive rats

WK: Wistar-Kyoto

TABLE VIII BLOOD PRESSURE IN FEMALES OF SHR (F_{18-20}), WISTAR-KYOTO, THEIR F_1 , F_2 AND BACKCROSS GENERATIONS

Weeks of age	15	20	25	30
Generations	Blood pressure (mmHg)		Mean $\pm$ SE	
WK (P_1)	119 $\pm$ 1.4 (16)	123 $\pm$ 1.0 (21)	121 $\pm$ 0.7 (16)	123 $\pm$ 0.8 (19)
SHR (P_2)	174 $\pm$ 1.5 (23)	176 $\pm$ 1.2 (17)	180 $\pm$ 1.3 (16)	185 $\pm$ 1.3 (15)
WK $\times$ SHR (F_1)	148 $\pm$ 0.8 (27)	147 $\pm$ 0.7 (37)	147 $\pm$ 0.7 (37)	149 $\pm$ 0.9 (34)
$F_1 \times F_1$ (F_2)	128 $\pm$ 1.9 (36)	132 $\pm$ 1.8 (37)	134 $\pm$ 2.0 (37)	135 $\pm$ 2.0 (34)
WK $\times F_1$ (BC_1)	121 $\pm$ 1.2 (54)	123 $\pm$ 1.1 (52)	125 $\pm$ 1.3 (50)	128 $\pm$ 1.1 (48)
$F_1 \times$ SHR (BC_2)	142 $\pm$ 1.2 (65)	146 $\pm$ 1.2 (71)	150 $\pm$ 1.3 (70)	154 $\pm$ 1.4 (70)

(): Number of cases observed

SHR: Spontaneously hypertensive rats

WK: Wistar-Kyoto

The F_{18-20} generations of SHR, which had nearly homogenous genetic background, were used for the genetic analysis with Wistar-Kyoto whose genetic background was supposedly close to SHR. The blood pressure of these rats, their F_1 and F_2 hybrids and backcross generations was obtained up to 30 weeks of age when hypertension had completely developed. As shown in Tables VII and VIII, the blood pressure was slightly higher in males than in females, and this sex difference was especially marked in SHR. The aging effect was observed in both parent

strains and all the offspring obtained from them, although the effect was prominent in SHR than in WK. The aging effect, the increase in blood pressure from 15 to 30 weeks of age in males, was the greatest in SHR and in backcross generation between F_1 hybrids and SHR, while it was relatively great in F_2 generation and small in WK, F_1 hybrids and backcross generations between F_1 hybrids and WK. A similar tendency was also observed in females.

The F_1 hybrids showed an intermediate blood pressure between SHR and WK. Their average

TABLE IX BLOOD PRESSURE IN MALE AND FEMALE F₁-HYBRIDS OBTAINED BY RECIPROCAL CROSSES BETWEEN SHR (F₁₈₋₂₀) AND WISTAR-KYOTO

Weeks of age		15	20	25	30
Mating	Sex	Blood pressure (mmHg)		Mean $\pm$ SE	
SHR δ $\times$ WK ϕ	δ	154 $\pm$ 1.4 (10)	151 $\pm$ 1.2 (18)	155 $\pm$ 0.8** (10)	155 $\pm$ 1.2* (10)
	ϕ	148 $\pm$ 1.0 (17)	148 $\pm$ 0.5 (17)	148 $\pm$ 0.4 (17)	149 $\pm$ 1.0 (17)
WK δ $\times$ SHR ϕ	δ	151 $\pm$ 1.1 (14)	151 $\pm$ 1.1 (14)	150 $\pm$ 1.1** (14)	150 $\pm$ 1.3* (14)
	ϕ	148 $\pm$ 1.2 (10)	147 $\pm$ 1.2 (20)	147 $\pm$ 1.2 (20)	149 $\pm$ 1.9 (10)

(): Number of cases observed SHR: Spontaneously hypertensive rats

WK: Wistar-Kyoto **, *: statistically significant (**: $p < 0.01$, *: $0.05 > p > 0.01$)

blood pressure was approximately mid-parent blood pressure but slightly lower than that except for the blood pressure at 15 weeks of age. The average blood pressure in F₂ generation was intermediate between that of SHR and of WK and lower than either the average of F₁ hybrids or the mid-parent blood pressure between SHR and WK. This lowering of the average blood pressure in F₂ generation was rather marked in females. Both backcross generations in males showed also an intermediate blood pressure between F₁ hybrids and respective parent strains, but the blood pressure in female backcross generations, especially BC₁ obtained by the mating between F₁ hybrids and WK, was lower than the value expected from completely additive

inheritance.

Two groups of offspring obtained by the crosses between male SHR and female WK, and by their reciprocals showed a slightly but significantly different blood pressure level especially in males at 25 and 30 weeks of age. The blood pressure in the male F₁ hybrids obtained by the matings between male SHR and female WK was higher than that in the male F₁ obtained by their reciprocals as shown in Table IX and the data was suggestive of a maternal or paternal influence of blood pressure on the offspring.

The distribution of the individual blood pressure in non-segregating and segregating generations is shown in Fig. 2. Although the number of animals was not sufficient, the distribution

Fig. 2. The distribution of blood pressure at 20 weeks after birth in all generations used for cross analysis between SHR (F₁₈₋₂₀) and Wistar-Kyoto

(): Number of cases observed

TABLE X ESTIMATION OF THE DEGREE OF GENETIC DETERMINATION FROM VARIANCES OF F_1 AND F_2 OBTAINED FROM THE MATINGS BETWEEN SHR (F_{18-20}) AND WISTAR-KYOTO

Weeks of age	15	20	25	30
Male	0.877 ± 0.047	0.873 ± 0.044	0.882 ± 0.045	0.824 ± 0.067
Female	0.790 ± 0.090	0.858 ± 0.048	0.873 ± 0.043	0.882 ± 0.051

SHR: Spontaneously hypertensive rats

TABLE XI ESTIMATION OF THE GENETIC PARAMETERS FROM VARIANCES OF BLOOD PRESSURE IN SHR (F_{18-20}), WISTAR-KYOTO, THEIR F_1 , F_2 AND BACKCROSS GENERATIONS

Weeks of age		15	20	25	30
<i>Male data</i>					
F_2 variance	$\frac{1}{2}D + \frac{1}{4}H + E_1$	2205	2286	2608	2350
$BC_1 + BC_2$ variance	$\frac{1}{2}D + \frac{1}{2}H + 2E_1$	2900	3085	3454	3188
Non-heritable component	E_1	172	290	309	413
Additive component	D	3020	2972	3524	3024
Dominant component	H	2092	2036	2148	1700
Dominance ratio	$\sqrt{H/D}$	0.832	0.828	0.781	0.750
<i>Female data</i>					
F_2 variance	$\frac{1}{2}D + \frac{1}{4}H + E_1$	1360	1410	1383	1396
$BC_1 + BC_2$ variance	$\frac{1}{2}D + \frac{1}{2}H + 2E_1$	1906	1872	1903	1806
Non-heritable component	E_1	285	173	176	165
Additive component	D	1628	1896	1724	1972
Dominant component	H	1044	1156	1276	931
Dominance ratio	$\sqrt{H/D}$	0.801	0.781	0.860	0.689

SHR: Spontaneously hypertensive rats

was continuous and was neither likely to be bimodal in backcross generations nor to fit in 1 : 2 : 1 segregation in F_2 generation.

Among the variances in non-segregating generations SHR showed the greatest variance, while F_2 generation showed the greatest variance in segregating generations. This difference in the variances among the non-segregating generations was corrected after logarithmic transformation of blood pressure and these corrected data were further analyzed.

The degree of genetic determinations derived from the variances of F_1 and F_2 data was high and approximately from 0.8 to 0.9 as shown in Table X. These data clearly indicated that hypertension was highly heritable, that is, the blood pressure was determined mostly by the genetic factors in SHR.

The genetic parameters were calculated and dominant ratios were obtained as shown in Table XI. The dominant effect was obvious at

15 weeks of age and the dominant ratio was higher in males than females. The ratio in males was higher than 0.9. The possibility of a dominant effect was indicated by these data.

According to the assumptions of the defined polygene theory, the minimum number of genes was estimated as shown in Table XII. These data showed assumingly that the male had approximately 3 while the female had 4 genes at least which were involved in the determination of blood pressure.

3. Cross analysis between both inbred strains, SHR (F_{21}) and Wistar-Mishima (F_{58}).

Blood pressure in non-segregating and segregating generations at 15, 20, 25 and 30 weeks of age are shown in Tables XIII and XIV. The results were similar to previous experiments, but the variance in F_1 hybrids was lesser than that in F_1 hybrids of the previous experiment as might be expected because both inbred strains were used

TABLE XII ESTIMATION OF THE MINIMUM NUMBER OF LOCI AFFECTING BLOOD PRESSURE FROM THE DATA OBTAINED BY CROSS ANALYSIS BETWEEN SHR (F_{18-20}) AND WISTAR-KYOTO

Weeks of age	15	20	25	30
Male	2.506	2.576	2.222	2.799
Female	4.181	3.209	4.290	3.972

SHR: Spontaneously hypertensive rats

as the parent strains in this experiment. The blood pressure in male F_1 was intermediate between those of both parent strains as well as that in male F_2 . The two backcross generations in males had blood pressure intermediate between that of F_1 hybrids and of the respective parent generations. However, in females, the average blood pressure in F_1 , F_2 and backcross genera-

tions was lower than that expected from completely additive inheritance.

The blood pressure in male F_1 hybrids obtained by the crosses between male SHR and female WM was slightly but significantly higher than that in male F_1 hybrids obtained by their reciprocal matings at 20 to 30 weeks of age as shown in Table XV. Although the data in female F_1 hybrids was not available because of the separation for breeding and nursing, the results indicated a possibility of maternal or paternal influence on the blood pressure in male F_1 hybrids as observed in previous experiments.

As shown in Fig. 3, the distribution of blood pressure was seemingly continuous and showed neither clear bimodal segregation in backcross generations nor 1 : 2 : 1 segregation in F_2 generations.

After the blood pressure was logarithmically transformed, the degree of genetic determination

TABLE XIII BLOOD PRESSURE IN MALES OF SHR (F_{21}), WISTAR-MISHIMA (F_{58}), THEIR F_1 , F_2 AND BACKCROSS GENERATIONS

Weeks of age	15	20	25	30
Generations	Blood pressure (mmHg)		Mean $\pm$ SE	
WM (P_1)	121 $\pm$ 0.4 (26)	122 $\pm$ 0.4 (26)	123 $\pm$ 0.4 (24)	123 $\pm$ 0.4 (22)
SHR (P_2)	181 $\pm$ 1.2 (20)	185 $\pm$ 1.0 (20)	187 $\pm$ 1.0 (19)	190 $\pm$ 1.3 (18)
WM $\times$ SHR (F_1)	151 $\pm$ 0.5 (24)	152 $\pm$ 0.6 (24)	151 $\pm$ 0.6 (24)	152 $\pm$ 0.4 (24)
$F_1 \times F_1$ (F_2)	146 $\pm$ 1.9 (54)	150 $\pm$ 2.2 (53)	150 $\pm$ 2.0 (52)	149 $\pm$ 2.1 (52)
WM $\times$ F_1 (BC_1)	128 $\pm$ 1.1 (43)	131 $\pm$ 1.2 (41)	130 $\pm$ 1.0 (40)	128 $\pm$ 1.1 (40)
$F_1 \times$ SHR (BC_2)	158 $\pm$ 1.5 (33)	165 $\pm$ 2.0 (33)	167 $\pm$ 1.9 (32)	167 $\pm$ 1.7 (32)

(): Number of cases observed
WM: Wistar-Mishima

SHR: Spontaneously hypertensive rats

TABLE XIV BLOOD PRESSURE IN FEMALES OF SHR (F_{21}), WISTAR-MISHIMA (F_{58}), THEIR F_1 , F_2 AND BACKCROSS GENERATIONS

Weeks of age	15	20	25	30
Generations	Blood pressure (mmHg)		Mean $\pm$ SE	
WM (P_1)	119 $\pm$ 0.7 (20)	121 $\pm$ 0.6 (20)	/	/
SHR (P_2)	176 $\pm$ 1.1 (21)	178 $\pm$ 1.3 (21)		
WM $\times$ SHR (F_1)	147 $\pm$ 0.7 (17)	149 $\pm$ 0.6 (17)		
$F_1 \times F_1$ (F_2)	133 $\pm$ 1.4 (40)	137 $\pm$ 1.5 (40)		
WM $\times$ F_1 (BC_1)	125 $\pm$ 0.7 (28)	129 $\pm$ 1.1 (28)		
$F_1 \times$ SHR (BC_2)	149 $\pm$ 0.9 (34)	152 $\pm$ 1.2 (34)		

(): Number of cases observed
WM: Wistar-Mishima

SHR: Spontaneously hypertensive rats

TABLE XV BLOOD PRESSURE IN MALE AND FEMALE F₁-HYBRIDS OBTAINED BY RECIPROCAL CROSSES BETWEEN SHR (F₂₁) AND WISTAR-MISHIMA (F₅₈)

Weeks of age		15	20	25	30
Mating	Sex	Blood pressure (mmHg) Mean $\pm$ SE			
SHR δ $\times$ WM η	δ	152 $\pm$ 0.7 (8)	154 $\pm$ 0.6** (8)	153 $\pm$ 0.7** (8)	153 $\pm$ 0.6* (8)
	η	148 $\pm$ 0.7 (12)	149 $\pm$ 0.6 (12)	/	/
WM δ $\times$ SHR η	δ	151 $\pm$ 0.6 (16)	150 $\pm$ 0.7** (16)	150 $\pm$ 0.7** (16)	151 $\pm$ 0.5* (16)
	η	146 $\pm$ 1.6 (5)	150 $\pm$ 1.4 (5)	/	/

(): Number of cases observed SHR: Spontaneously hypertensive rats
WM: Wistar-Mishima **, *: statistically significant (**: $p < 0.01$, *: $0.05 > p > 0.01$)

TABLE XVI ESTIMATION OF THE DEGREE OF GENETIC DETERMINATION FROM VARIANCES OF F₁ AND F₂ OBTAINED FROM THE MATINGS BETWEEN SHR (F₂₁) AND WISTAR-MISHIMA (F₅₈)

Weeks of age	15	20	25	30
Male	0.952 $\pm$ 0.017	0.960 $\pm$ 0.014	0.950 $\pm$ 0.018	0.949 $\pm$ 0.018
Female	0.860 $\pm$ 0.059	0.879 $\pm$ 0.051	—	—

SHR: Spontaneously hypertensive rats

Fig.3. The distribution of blood pressure at 20 weeks after birth in all generations used for cross analysis between SHR (F₂₁) and Wistar-Mishima (F₅₈)
(): Number of cases observed

was estimated. The results in Table XVI showed that approximately 90 per cent of the phenotypic variance consisted of genetic variance while the residual 10 per cent was ascribed to the

environmental variance. These data were again consistent with the previous results that the trait of blood pressure was highly heritable.

The additivity and dominance were estimated

TABLE XVII ESTIMATION OF THE GENETIC PARAMETERS FROM VARIANCES OF BLOOD PRESSURE IN SHR (F_{21}), WISTAR-MISHIMA (F_{58}), THEIR F_1 , F_2 AND BACKCROSS GENERATIONS

Weeks of age		15	20	25	30
<i>Male data</i>					
F_2 variance	$\frac{1}{2}D + \frac{1}{4}H + E_1$	1750	2175	1393	1515
$BC_1 + BC_2$ variance	$\frac{1}{2}D + \frac{1}{2}H + 2E_1$	1080	1457	1152	1155
Non-heritable component	E_1	84	87	70	78
Additive component	D	4840	5784	3268	3748
Dominant component	H	-3016	-3220	-1244	-1752
Dominance ratio	$\sqrt{H/D}$	—	—	—	—
<i>Female data</i>					
F_2 variance	$\frac{1}{2}D + \frac{1}{4}H + E_1$	851	942		
$BC_1 + BC_2$ variance	$\frac{1}{2}D + \frac{1}{2}H + 2E_1$	392	760		
Non-heritable component	E_1	119	114		
Additive component	D	2620	2248		
Dominant component	H	-2312	-1184		
Dominance ratio	$\sqrt{H/D}$	—	—		

SHR: Spontaneously hypertensive rats

TABLE XVIII ESTIMATION OF THE MINIMUM NUMBER OF LOCI AFFECTING BLOOD PRESSURE FROM THE DATA OBTAINED BY CROSS ANALYSIS BETWEEN SHR (F_{21}) AND WISTAR-MISHIMA (F_{58})

Weeks of age	15	20	25	30
Male	1.600	1.400	2.479	2.408
Female	2.725	3.139		

SHR: Spontaneously hypertensive rats

also in this study as shown in Table XVII. The additive effect was clear but dominance was not proved in this experiment.

An assumptive estimation of the minimum number of genes was calculated according to WRIGHT's equation. Table XVIII shows the results suggestive of at least 2 genes involved in the genetic determination of blood pressure.

DISCUSSION

The degree of genetic determination derived from the analysis of the variances of three normotensive strains was rather high in comparison with that in inbred strains of mice calculated by SCHLAGER.¹⁸ However, these estimates were not significant in both sexes because of great standard errors, probably due to a small number of samples and strains. Although further genetic analysis was not available, it was presumed that the

blood pressure level in normotensive rats was determined by several genes or more with minor effect, for the distribution of blood pressure of these strains and the other strains reported by several workers seemed to be continuous. On the other hand, the distribution of the blood pressure in SHR was greatly different from that of these normotensive strains and discontinuous with abrupt change. This fact might be suggestive of the possibility of the existence of a single major genetic factor in the etiology of hypertension.

The degree of genetic determination of blood pressure in SHR, analyzed from the variances in F_1 and F_2 data, was considerably high (0.61–0.73 or 61–73%), as described in a preliminary experiment,²⁸ and it was especially high (0.79–0.88 or 79–88% and 0.86–0.96 or 86–96% in experiments 2 and 3, respectively) in the experiments using the more homogenous strains as parent strains. It was probably due to relatively lesser variance in F_1 hybrids obtained between inbred parent strains. From the results of these experiments it could be concluded that the hypertension in SHR was genetically determined to a large extent. However, the interaction of environmental influence was not disregarded as a matter of course. Genetic determination means the portion of the total phenotypic variance attributable to any genetic causes, while heritability means that portion of the total phenotypic variance attributable to additive genetic effect.

SCHLAGER²⁰ calculated realized heritability from the data on SHR reported by OKAMOTO and AOKI¹⁴ and obtained estimates of heritability of $20 \pm 2\%$ for the males and $28 \pm 3\%$ for the females. These values, as SCHLAGER suggested, may be underestimates of the true heritabilities since the foundation stock was initially propagated from a single mating from the rats of the WISTAR strain from which genetic variability had been considerably eliminated. PHELAN estimated the heritability of the blood pressure conservatively as 15 per cent for males and 10 per cent for females in the New Zealand strain of rats with genetic hypertension.¹² On the other hand, MIALI and OLDHAM suggested that 33 to 45% of the variation in systolic blood pressure in human population could be explained by genetic factors.⁸

The interaction of environmental factors in SHR was already reported on the blood pressure effect of chronic stress or salt loading. Intensive chronic stress loadings accelerated or augmented the spontaneous hypertension,²⁹ but chronic salt loading showed no remarkable effect on the blood pressure in SHR.³⁰ Therefore, the role of environmental factors in SHR seemed to be far less than that in DAHL's sensitive strain,¹³ in which the interaction of a nongenetic factor (NaCl) with appropriate genetic substrate appeared to be necessary for the development of hypertension. Environmental effect on blood pressure was observed also by WEISS et al. who suggested seasonal effect in blood pressure of chickens.³¹

The sex difference in blood pressure in control normotensive strains as well as in SHR might be interpreted as a sort of internal environmental influence. The average of the blood pressure in males was significantly higher than that in females in all strains and generations in this experiment. The lower female mean was particularly noticeable in the generations showing the higher blood pressure. Lower female average blood pressure was already reported in SHR as well as normotensive Wistar,¹⁴ in mice²⁰ and in chickens.²⁴ Progesterone administration in rats and dogs with experimental hypertension³² and humans with arterial hypertension³² as well as in SHR³³ resulted in a decrease in blood pressure level. Experimental induction of deciduomata after progesterone administration decreased the blood pressure in rats with DCA hypertension.³⁴ These findings suggest that progesterone itself may influence the blood pressure level in females. On the other hand, no effect on blood pressure

was observed after castration in SHR in both sexes,³⁵ and no relationship was found between estrous cycle and blood pressure level in mice.³⁶ Consequently, a more complex effect of endocrine systems on female blood pressure can not be eliminated.

Among the F_1 hybrids obtained by the reciprocal mating between SHR and normotensive Wistar, F_1 hybrids from a male SHR and a female Wistar showed a slightly but significantly higher blood pressure than those from a female SHR and a male Wistar. SCHLAGER et al. observed that the influence of the male parent on blood pressure level of the offspring appeared to be somewhat greater than that of the female parent in mice.²⁰ A greater paternal effect on hypertension was suggested for human populations from a study of male medical students.³⁷ However, the controversy, a greater influence of the mother on hypertension was also suggested.³⁸ The mechanism of the difference in the influence of paternal and maternal influence in the hypertension in offspring is left open to the further study, since a biochemical study on the brainstem aromatic L amino acid decarboxylase activity showed also a similar greater paternal effect in F_1 hybrids between SHR and Wistar.³⁹

All three series of cross analyses showed that the mode of inheritance in blood pressure level of the offspring obtained between SHR and normotensive strains was additive with some dominance. However, the dominance was not detected in the experiments using both inbred strains as the parent generations. The difference in the data about dominance among 3 experiments might be mainly due to the difference in the genetic background of the normotensive rats used. There was no clear evidence of pronounced bimodality in backcross generations nor was there the expected 1 : 2 : 1 ratio in F_2 hybrids. Consequently, the blood pressure in SHR seemed to be determined by several genes acting additively, but it does not mean that we could confirm the so-called polygene theory in the inheritance of hypertension. Supposing that genetic factors of hypertension should be controlled by a number of independent genes of equivalency, that is, on the assumption of defined polygene theory, the minimum number of genes could be estimated, although such assumption is rarely the case. According to the estimates based on this assumption, the minimum number of the genes was about 5 at the age when hypertension was established. But when the inbred strains were used

for genetic analysis, this number became less than 3 or 2 in females or males, respectively. Preliminary studies of LOUIS et al.²¹ reported the blood pressure in F₁ hybrids obtained by reciprocal crosses between SHR and Wistar rats. They observed an intermediate blood pressure level with a wide variance in the F₁ hybrids, and speculated a "polygenic mechanism". (It would be preferable to use the word multifactorial inheritance here.) Their data appeared to be consistent with ours but hardly enough for the speculation, for the intermediate blood pressure can be expected if the blood pressure is controlled by a single additive gene. A wide variance in F₁ hybrids also means no more than that the parent strains are still inhomogeneous, for the variance in F₁, i.e., non-segregating generation, should be theoretically nearly the same as that in the parent strains, if they are inbred.

When we consider that almost 100 per cent occurrence of spontaneous hypertension was observed even at the third generation of selective inbreeding and that this trait could be readily fixed in comparison with the New Zealand strain of genetic hypertension which needed more than 10 generations for the fixation,¹² we have to presume that the number of the genes involved in hypertension in SHR should be relatively few and we cannot eliminate even the possibility of the existence of a single major genetic factor in the etiology of this hypertension. However, we failed to observe a clear bimodality in backcross generations and 1 : 2 : 1 segregation in the F₂. A reasonable explanation for the latter possibility could be that several genes or more with minor effect suggested in normotensive strains segregate in backcrosses and F₂ generations besides the segregation of a major gene. In addition, the physiological traits, such as blood pressure in which many physiological factors are involved, are susceptible to the influence of various environmental factors and other genetic factors.

If the hypertension in this strain is determined by a relatively few genes or by a single major genetic factor, one can search for the primary biochemical abnormalities in hypertension or a unitary genetically determined biochemical defect, although its expression might be modified by environmental and other genetic factors. There have been collected some evidences suggestive of genetical-biochemical abnormality in SHR. YAMORI and OKAMOTO detected strain specific arylesterase isozymes in the kidney of SHR and proved that this specificity was trans-

mitted to the offspring in accordance with a codominant law.⁴⁰ The recent observations of YAMORI et al. revealed a low norepinephrine level and concomitant decrease in the activity of aromatic L amino acid decarboxylase.⁴¹ According to their experiments, F₁ hybrids showed an intermediate level of the enzyme activity between SHR and normotensive rats and the compensation of this biochemical defect by various pharmacological procedures cured hypertension and even prevented the development of hypertension.³⁹ Although the definite relationship between these biochemical abnormalities and blood pressure level remains to be clarified by further genetical-biochemical analyses, it is hoped that genetic mechanism of hypertension will be solved as biochemical defects in SHR as well as in the patient with essential hypertension. This seems to be the short cut to the establishment of the causative therapy or the prevention of essential hypertension.

SUMMARY

Inheritance of hypertension was studied on spontaneously hypertensive rats (SHR), which are now available as an inbred strain after selective sib-breeding for 20 generations. Three series of cross analyses were performed between SHR F₁₄ and a closed colony Wistar-Imamichi, between both inbred strains, SHR F₂₁ and Wistar-Mishima F₅₈. These three experiments, one of which was independently done, gave similar results described as follows.

1. The average blood pressure in F₁ hybrids showed an intermediate blood pressure level between both parent strains. The blood pressure of two kinds of backcross generations was also between that of F₁ hybrids and of the respective parent generation, SHR or normotensive Wistar. Males showed a higher blood pressure than females in all generations.
2. The variances of the blood pressure in segregating generations, i.e., F₂ and both backcross generations, were greater than those in non-segregating generations, i.e., both parent strains and F₁ hybrids, as theoretically expected. The degree of genetic determinations calculated from these variances of F₁ and F₂ data was 0.7 to 0.9. This value became high (0.96) when inbred strains were used as parent strains for cross analysis. On the other hand, the degree of genetic determination of blood pressure level analyzed in 3 normotensive strains was about 0.3.
3. The analysis of genetic parameters using the

variances of logarithmically transformed blood pressure data in all generations for cross analysis, proved to have some dominant effect as well as additive effect on blood pressure. But the dominant effect was not clearly detected when inbred strains were used for analysis.

4. The distribution of the blood pressure was continuous in each generation and showed no clear bimodal or 1:2:1 segregation in back-cross generations or in F_2 generations, respectively.

5. The minimum number of genes was estimated on the assumption of defined polygene theory that the high blood pressure level in SHR was controlled by a number of independent genes of equivalency. The estimate was 2 or 3 when inbred strains were used for analysis.

6. These experiments showed that the blood pressure level in SHR was regulated by genetic factors to a large extent, and that the mode of inheritance was additive. The blood pressure level appeared to be regulated by a relatively small number of genes acting additively.

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