EFFECTS OF CHRONIC EXCESS SALT INGESTION

Genetic Influence on the Development of Salt Hypertension in Parabiotic Rats: Evidence for a Humoral Factor*

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By selective inbreeding, two strains of rats were evolved with opposite genetic propensities for hypertension from a high NaCl (salt) diet (1, 2). Subsequently it was found that the two strains also showed opposite innate predispositions for developing experimental hypertension from DOCA-salt, unilateral renal artery compression without salt, cortisone, or adrenal regeneration (3, 4). These observations suggest that the basic mechanism of these several "varieties" of hypertension may be the same although the etiological agents differ.

In the present study the technique of parabiosis has been used to explore the hypothesis that a humoral agent was instrumental in the pathogenesis of "salt" hypertension and, by inference, in other "varieties" of experimental hypertension as well. The chronicity of the parabiotic union, with its exchange of extracellular fluids between two animals, could allow subtle humoral influences to modify the blood pressure in a manner that might be inapparent from acute studies. This seemed to be the case, for when two rats, one from each strain, were united in parabiosis, the animal from the strain that normally fails to develop salt hypertensoin rapidly developed chronic hypertension provided that a high NaCl diet was consumed by the pair. This response has been interpreted as being compatible with the transfer of a humoral influence from one parabiotic animal to the other under these conditions. If this is true, such an agent could play a role in evoking the fulminating hypertension characteristically observed in nonparabiotic S animals consuming the same high NaCl diet.

Materials and Methods

The rats used in these studies were derived originally from a Sprague-Dawley strain (1, 2). All animals came from the ninth, or subsequent, generations of selectively inbred animals. The

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strain with the genetic propensity for developing hypertension is called the Sensitive (or S) strain, the other Resistant (or R) strain. Details on the care, feeding, and technique of measuring blood pressure were presented earlier (5–7) and only those pertinent to the current work are included here. All rats had free access to tap water (<1 meq Na/liter) and chows which contained either 0.38% NaCl ("low NaCl") or 8% NaCl ("high NaCl"), but were otherwise identical. Blood pressures (B.P.) and weights were measured under standard conditions at intervals ranging from twice a week to once a month, depending on the observed rate of progression of the hypertension. In instances of hypertension known to be evolving rapidly, B.P. was measured 1–2 times per week but statistical calculations were based on the last measurement made when the animal appeared still in good health; in our experience the most sensitive index of ill health in these rats has been weight loss and we have regarded a weight loss of 10 g as such evidence. Accordingly, we have not included blood pressures associated with a weight change of this magnitude. If the intervals between readings were several weeks or more, we may have missed the peak of the B.P. elevation in S rats on high NaCl since B.P. usually declines during their terminal illness: in such circumstances the reported values are likely to have underestimated the degree of hypertension. We have considered a B.P. of 140 mm Hg or more as indicative of "hypertension" (5–7). Statistical significance for difference between the average blood pressures of groups was assessed by the technique of analysis of variance[1] and P values of <0.05 were accepted as significant. Parabiosis was performed under Pentothal anesthesia according to the technique of Bunster and Meyer (8) on 3-wk-old weanling animals and zero time was considered to begin with this operation. Only female weanling rats from the Sensitive (S) and Resistant (R) strains were used. Females were used arbitrarily because of their availability when this study began, but numerous pairs of males in parabiosis have now been observed to respond like the females reported here. During the 7 days following surgery, all animals were maintained on the low NaCl (0.38%) chow, after which some were changed permanently to the high NaCl (8%) chow. The animals united in parabiosis were identified according to the following combinations: R+R, S+S, and R+S. Some groups were further identified by indicating their NaCl intake, e.g., R+S (8%), or S (0.38%). Rats united in parabiosis were called *parabionts*. In pairs from the same strain, the members were identified as *left*, or as *right*, viewed from above with heads away from observer. A total of 80 pairs of animals in the several combinations shown below were united in parabiosis but death during the first 3 wk after operation left 53 pairs for analysis in this study. Animals not in parabiosis have been called *single*. Four groups of 10 single animals were studied as controls; one animal in the R (8%) group died shortly after the experiment began and has not been included in the final analysis. There were 10 groups of animals divided as follows:

Group No.		*No. in Group*
(1)	Single R on 0.38% NaCl chow	10
(2)	" " " 8% " "	9
(3)	" S " 0.38% " "	10
(4)	" " " 8% " "	10
(5)	R + R (i.e., in parabiosis) on 0.38% NaCl chow	8 pairs
(6)	" " " " " 8% " "	9 "
(7)	S + S " " " " 0.38% " "	9 "
(8)	" " " " " 8% " "	9 "
(9)	R + S " " " " 0.38% " "	9 "
(10)	" " " " " 8% " "	9 "

[1] We wish to thank Keith Thompson for his continued assistance with the statistical analysis in this study.

OBSERVATIONS

Single Animals (Table I)

The responses were like those we have observed repeatedly, and reported earlier (9) for animals from these two strains on chronic low and high NaCl

TABLE I

*Single Animals**

Strain	R		S		
Diet (% NaCl)	0.38	8	0.38	8	
					Died, *Month*‡
Systolic B.P. of individual animals (mm Hg)	118	104	114	182	2
	120	122	100	202	2
	116	100	122	242	4
	100	146	128	186	3
	118	120	128	194	2
	118	114	120	190	—
	102	120	172	212	2
	98	120	162	164	1
	132	132	150	189	—
	111		149	185	2
No. rats in group	10	9	10	10	
Mean B.P. of group (±S.E.)	113.3 (3.35)	119.8 (4.59)	134.5 (7.21)	194.6 (6.60)	
Median B.P.	117	120	128	190	

Analysis of variance of mean B.P.: S (8%) >** all others; S (0.38%) >** R (0.38%).

* Blood pressures of single female rats at end of study (6 months) or last B.P. before death (see Materials and Methods).

‡ Animal died during month after weaning.

** $P \leq 0.01$, here and in Tables II and III.

diets. Among rats from the R strain, 8% NaCl chow was almost without influence on either B.P. or mortality: at the end of the study all 19 rats were in good health and the mean blood pressures of 113.3 and 119.8 mm Hg for the groups on 0.38 and 8% NaCl, respectively, were not significantly different ($P > 0.05$). However, one R animal on 8% NaCl had a mild elevation in blood pressure on the final measurement, 146 mm Hg. On comparable NaCl intakes, the S rats had significantly higher average B.P. than the R animals ($P < 0.01$). In animals from the S strain on low NaCl chow, 4 of the 10 developed mild hypertension (149–172 mm Hg) but all remained in good health at the end of

the experiment. On high NaCl by contrast, all animals from the S strain rapidly developed severe hypertension and 8 of the 10 were dead before the end of the 4th month. Table I shows that one of these S animals died during the first month with a measured pressure of only 164 mm Hg. We have recorded such blood pressures before in animals with fulminating hypertension that was not recognized in time to institute frequent B.P. measurements: among many similar

TABLE II

*Parabionts from Same Strain**

Strain.....	R + R				S + S				
Diet (% NaCl)...	0.38		8		0.38		8		
	Left	Right	Left	Right	Left	Right	Left	Right	Died‡
									(*months*)
Systolic B.P. of individual parabionts (mm Hg)	122	110	108	122	124	150	198	220	3
	120	110	116	106	140	146	202	210	3
	118	98	112	120	128	144	221	218	3
	124	130§	100	114	124	140	172	211	2
	104	128	122	123	120	132	172	210	2
	120	112	122	106	124	122	184	212	2
	122	124	114	106	150	120	184	170	2
	118	111	102	100	124	120	198	193	3
			110	120	114	120	224	162	3
No. rats in group	8	8	9	9	9	9	9	9	
Mean B.P. of group (±S.E.)	118.5 (2.20)	115.4 (3.87)	111.8 (2.59)	113.0 (2.88)	127.6 (3.63)	132.7 (4.18)	195.0 (6.33	200.7 (7.05)	
Median B.P.	120	112	112	114	124	132	198	210	

Analysis of variance of mean B.P.: In all four parabiont groups, left = right ($P > 0.05$) and S (8%) >** all others.

* Blood pressures of female rats from same strain united in parabiosis.

Results at end of study (6 months) or last B.P. before death (see Materials and Methods).

‡ Pair died during month indicated.

§ Animal died during 3rd month, B.P. of both parabionts at 2½ months.

animals in which B.P. was measured every few days, marked elevations invariably have been found before death.

Animals in Parabiosis

(1) R + R (Table II)

Parabionts in which both members were from the R strain resembled single animals from this same strain in that dietary NaCl appeared to be without significant influence on blood pressure: among these 17 pairs, final pressures among individuals ranged between 98 and 130 mm Hg and blood pressures averaged about 115 mm Hg for the R + R parabiont groups, a figure almost

identical with that for single R animals (Table I). One parabiont on low NaCl died during the 3rd month with normal B.P., 130 mm Hg. (In this instance only, the living member of this pair was separated and was followed to the end of the experiment at which time it was in good health with a B.P. of 114 mm Hg). All other parabionts in these groups appeared healthy after 6 months.

TABLE III
*Parabionts from Opposite Strains**

Strain	R + S			
Diet (% NaCl)	0.38		8	
	R	S	R	S
Systolic B.P. of individual parabionts (mm Hg)	108	122	154	128
	112	118	169	132
	134	130	204	212‡
	110	112	174	170
	124	122	172	184
	102	130	144	157
	122	116	174	128
	110	128	192	150
	110	134	164	204
No. rats in group	9	9	9	9
Mean B.P. of group (±S.E.)	114.7 (3.32)	123.6 (2.47)	171.8 (6.02)	162.8 (10.7)
Median B.P.	110	122	172	157

Analysis of variance of mean B.P.: In both paraboint groups, R = S, but R (8%) or S (8%) >** R (0.38%) or S (0.38%).

* Blood pressures of female rats from both strains united in parabiosis. Results at end of study (6 months).

‡ Died during final week of experiment.

(2) S + S (*Table II*)

Again the results were like those obtained with single animals from this strain on the same NaCl intakes: on low NaCl chow, the average pressures of 127.6 and 132.7 mm Hg in the left and right groups of parabionts were close to the average of 134.5 mm Hg for the single S group: 6 of the 18 *individual* parabionts —there was no pattern by pairs—developed mild hypertension ranging from 140 to 150 mm Hg. All animals seemed in good health when the experiment was terminated. On 8% NaCl chow all of the S parabionts developed hypertension rapidly and none was alive by the end of the 3rd month. The average pressures

of 195 and 200.7 mm Hg for the left and right groups of parabionts were nearly identical with the average of 194.6 mm Hg for the "single S" group on high NaCl; the individual blood pressures of the members in S + S parabiosis rose together, but the values were rarely identical.

(*3*) *R + S* (*Table III and Fig. 1*)

On Low NaCl.—

All the individuals in such pairs remained normotensive and in good health when on low NaCl. The average B.P. of the R parabionts was 114.7 mm Hg, a figure very close to that of the other R groups described thus far in this study. The average B.P. of the S parabionts was 123.6 mm Hg, not significantly ($P > 0.05$) different from the other S groups studied here on low NaCl chow. However, the blood pressure response may have differed slightly from that of similarly fed single animals in that none of these S rats developed even mild hypertension (>140 mm Hg). This may be related to the observations now to be described with R + S parabionts on 8% NaCl.

On High NaCl.—

Since the response of the R + S parabionts on high NaCl differed in three significant respects from all previous experience with these animals, it is reported in some detail.

(*A*) *Development of hypertension in R animals* (Table III, Fig. 1): The R animals rapidly developed a rise in blood pressure which generally appeared sooner and reached higher levels than in the S parabionts with which they were united. By the end of the 4th wk, for instance, all but one of the nine R animals had elevated B.P. ranging from 144 to 192 mm Hg (the ninth had 112 mm Hg); in contrast, at this time among their nine S partners, only two had B.P. as high as 142 mm Hg. At the end of the 8th wk, when only one of the R rats had a pressure *below* 150 mm Hg (range 142–212, average 174.3 mm Hg) only two of the S rats were *above* 150 mm Hg (range 82–162, average 136.8 mm Hg). In the period from 10 to 13 wk the average B.P. of the R animals reached a peak of 178 mm Hg, a mean level that their S partners never equalled. Indeed, during the whole period from the 2nd through the 12th wk, the average B.P. of the R parabionts was significantly higher ($P < 0.05$–0.01) than that of their S partners at comparable times. After the 12th wk, the average B.P. among R animals appeared to decline slightly, reaching a low of 154.9 mm Hg about the 16th wk, after which it rose to 171.9 mm Hg in the final week. This is shown in Fig. 1. Caution must be used in interpreting the precise character of the curve for the R animals after the 12th wk, however, since except for the mean B.P. at 16 wk ($P < 0.05$) none of the other means differed significantly from that at 12 wk. In summary, parabiosis of S and R rats on 8% NaCl commonly led to the development of chronic elevations in blood pressure in the R parabionts such as we have

almost never observed in single animals from this strain even after ingesting 8% NaCl for much longer periods.

(*B*) *Amelioration of hypertension in S animals* (Table III, Fig. 1): The rapidly evolving hypertension so characteristic of single S or S + S parabiont animals,

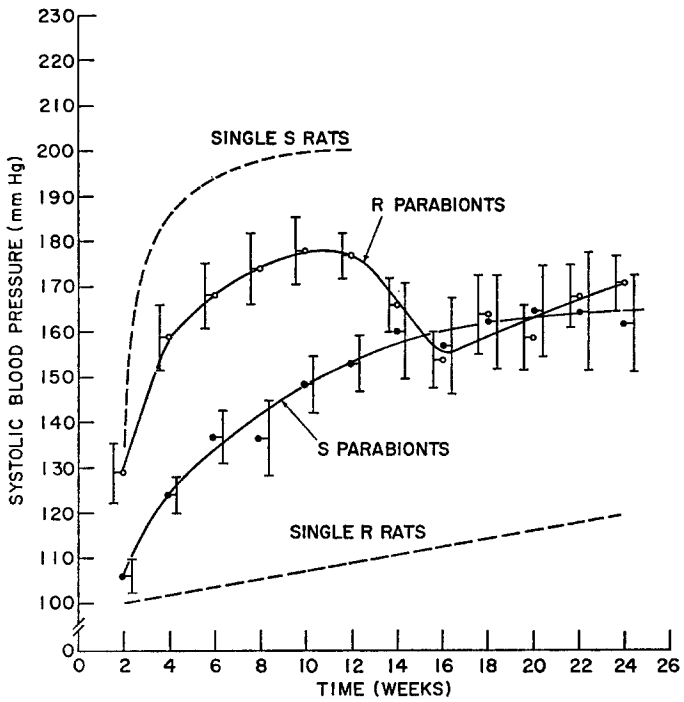

FIG. 1. The symbols with open and closed circles represent mean ±1 standard deviation of B.P. obtained from group 10 (R + S parabionts on 8% NaCl) measured every 2nd wk during the study, and demonstrate the anomalous development of B.P. in this group. The broken lines represent idealized average blood pressures of large numbers of single S and R rats on 8% NaCl chow from both published and unpublished studies in our laboratory. The change in response to NaCl effected by parabiosis between rats, one from each strain, is apparent. From the 2nd through the 12th wk, the average B.P. of the R parabionts was higher ($P < 0.05$) than that of their S partners at corresponding times. After the 12th wk, average B.P. in the two groups was not significantly different ($P > 0.05$). Furthermore, only the average of the R parabionts at 16 wk was significantly different from the average of this R group at 12 wk; for this reason, the curve shown for the R parabionts should be accepted with caution after the 12th wk.

on 8% NaCl chow (Tables I and II) was clearly modified by parabiosis with R animals: both the *rate* of development and the average *level* of hypertension were decreased. The general course of the development of hypertension is shown in Fig. 1. This graph indicates that during the initial 2 months when the R

TABLE IV

*Summary of Final Blood Pressures by Group and Strain**

Group	No. Rats in Group	Mean Systolic B.P. of Group (± S.E.) (*mmHg*)
R animals only		
R, Single, 0.38% NaCl	10	113.3 (3.35)
R, " 8% "	9	119.8 (4.59)
R + R 0.38% "		
Left	8	118.5 (2.20)
Right	8	115.4 (3.87)
R + R 8% "		
Left	9	111.8 (2.59)
Right	9	113.0 (2.88)
R [+ S]‡ 0.38% "	9	114.7 (3.32)
R [+ S]‡ 8% "	9	171.8 (6.02)
S animals only		
S, Single 0.38% NaCl	10	134.5 (7.21)
S, " 8% "	10	194.6 (6.60)
S + S 0.38% "		
Left	9	127.6 (3.63)
Right	9	132.7 (4.18)
S + S 8% "		
Left	9	195.0 (6.33)
Right	9	200.7 (7.05)
[R +]S§ 0.38% "	9	123.6 (2.47)
[R +]S§ 8% "	9	162.8 (10.7)

Statistical Significance of Difference in Mean B.P. among Groups‖

Among all parabionts: right = left.

Among R animals only: All R groups are equal *except* in R + S (8%) where R >** all other R groups.

Among S animals only: All S on 0.38% NaCl are equal; S (8%) = S + S (8%) >** S in R + S (8%) >** all S on 0.38% NaCl.

Among both R and S animals:

S, Single (0.38%)
- ** > R, Single (0.38%); R + R (8%)
- ¶ > R + R (0.38%); R + S (0.38%)

All S on 8% >** all R, *except* in R + S (8%) where R = S; R + S (8%) >** R + S (0.38%)

The most important items to be derived from this summary are (*a*) parabiosis between rats from the same strain (i.e., R *or* S) does not affect B.P. differently from comparable single animals on the same regimen; (*b*) parabiosis between rats from both strains (i.e., R + S) affects B.P. significantly if the animals are on 8% NaCl: those from the Resistant strain have significantly higher ($p < 0.01$) and those from the Sensitive strain significantly lower ($P < 0.01$) B.P. than comparable single rats on 8% NaCl.

* See Tables I–III for primary data.

‖ Definitions: equal or =, $P > 0.05$; **, $P \leq 0.01$; ¶, $P \leq 0.05$.

‡ See data for S animals under "S animals only."

§ See data for R animals under "R animals only."

animals rapidly developed hypertension, their corresponding S parabionts did so only slowly; not until after the 12th wk did the mean blood pressures of the two strains attain roughly equivalent levels ($P < 0.05$) when, between the 14th and 24th wk, S parabionts seemed to reach a plateau at about 160–165 mm Hg. At no time did the average pressure of the group of S parabionts exceed that of their partners significantly although in one pair the S parabiont ended up significantly higher than its R mate (204 vs. 164 mm Hg, respectively). Whereas the final pressures of both the S and S + S groups on 8% NaCl had been found to average about 195–200 mm Hg (Tables I and II), that of the S parabionts in the R + S group was only 162.8 mm Hg ($P < 0.01$). One of the most striking observations was that after 6 months on 8% NaCl three S parabionts remained normotensive with pressures of 128, 132, and 128 mm Hg, respectively: we had not previously observed S rats from this generation of inbred animals that failed to develop significant hypertension after 6 months on 8% NaCl chow.

In summary, parabiotic union with an R animal effected a significant decrease in the average level of hypertension characteristically observed in S rats on 8% NaCl.

(*C*) *Decreased mortality of S rats on 8% NaCl:* Only one of the nine S rats in the R + S group on 8% NaCl died and this was not until the last week of the study. This is in sharp contrast to the high mortality observed among animals in the single S (Table I) and S + S (Table II) groups, on 8% NaCl: in the former, only 2 out of 10 rats survived 6 months and in the latter, none survived 3 months. In another recent unpublished series, among *40* single S animals maintained after weaning on 8% NaCl, only one sickly animal was alive at the end of the 6th month. Indeed, in our studies involving several thousand weanling S animals on 8% NaCl during the last 3 years, healthy survivors were so uncommon after 3 months that experiments ordinarily were not continued longer except to obtain absolute mortality figures. Therefore, we have considered the increased survival of these S rats in the current studies as markedly divergent from our past experience.

In Table IV, we have summarized the blood pressure responses of the several groups of animals and the statistical comparisons among them.

DISCUSSION

In this study, the influence of parabiosis on experimental hypertension has been explored and, in line with our earlier experience, the genetic substrate has been found to strongly modify the influence of NaCl on the development of hypertension. By appropriate attention to salt intake and to genetic origins of the animals, we could produce pairs both members of which had fulminating hypertension or pairs in which both members had normal blood pressure. These results would have been predicted from our previous experiments: i.e., rats from the Sensitive (S) strain prone to experimental hypertension would develop

severe hypertension on NaCl whereas rats from the Resistant (R) would not. However, when rats, one from each strain, were united in parabiosis and maintained on a high NaCl intake, the genetic influence seemed to be anomalous: hypertension then appeared rapidly in the parabionts from the Resistant strain while their mates from the Sensitive strain had significantly less hypertension than expected.

Hypertension in these R animals was not dependent upon parabiosis *per se* since it was not observed among other groups of R parabionts studied. Neither was this hypertension dependent solely on parabiosis with a member of the S strain, since it was not present among members of the control R + S group maintained on low NaCl chow. Furthermore, hypertension in the R parabiont was not dependent upon the presence of *overt* hypertension in the S partner: elevated pressure usually developed in the R parabiont before becoming manifest in the S partner and in three of these S parabionts, hypertension never appeared. Finally, hypertension in R parabionts was not solely related to dietary NaCl since R + R parabionts on a high NaCl diet manifested no hypertension. Only when an R animal was in parabiosis with a member from the S strain *and* the pair was on a high NaCl intake did hypertension develop in the R partner.

Our observations seem related to those reported by Hall and Hall in 1951 (10) in which DOCA-NaCl was used to induce hypertension in parabionts. In that study, one member, only, of each pair received DOCA implants while both were on added NaCl. Instead of the expected hypertensive disease in DOCA-treated animals, they found that in 15 out of 20 pairs the *untreated* partner suffered while the animals with DOCA implants seemed to be unaffected. Only five pairs showed the expected response: hypertensive disease in the DOCA-treated animal, no disease in the partner. And at autopsy, the parabiosis junction in these five pairs was found to be poor, suggesting the possibility that vascular exchange was less than among the remaining 15 pairs. Subsequently, Hall and Hall (11) reported that without the use of DOCA in about 40% of pairs "spontaneous" hypertension developed in one animal but never in the other. From later studies (12, 13) they concluded that an "unusually" high NaCl intake was not, but that adrenal function was necessary for the development of this hypertension. Since the experimental design of the studies by our two laboratories was different, the results are not wholly comparable; yet the similarities are considerable. In particular, there is a parallelism between their findings with DOCA-NaCl using unselected rats and ours using NaCl and two genetically different strains of rats. In their experiments one has to assume that the hypertensive process started in the animal receiving DOCA. The similarity between the experimental hypertension induced by DOCA-NaCl or NaCl alone (3) allows the inference that in our experiments the hypertension was initiated in the S animals by an interaction with NaCl. Although possible, it is improbable that R animals, genetically resistant to the induction of hypertension by either NaCl or DOCA-NaCl (1–3, 9) would undergo a fundamental reversal by parabiosis: if so, hypertension might have been expected to develop in the R + R

pairs or in the R + S parabionts on low NaCl. This did not occur. It seems more logical to assume that the S animal with the genetic predilection for hypertension was basically responsible for *initiating* the hypertension that developed in the R partners when both were on high NaCl.

It seems clear that some humoral influence can pass the parabiosis junction, thereby modifying the blood pressure of one or both animals. However, except for suggesting that both a high NaCl diet and a genetic propensity for hypertension are required, this humoral influence cannot presently be characterized as to nature, site of origin, or mode of action. Furthermore, if the S rat is assumed to initiate the hypertension that develops in its R partner, it also requires an explanation as to why this should moderate, or even prevent, hypertension in the S rat.

Estimates of the exchange rate between parabiont rats suggest that about 0.5 to 1% of blood volume of each rat is exchanged per minute (14, 15). In unpublished studies from our laboratory, the exchange rate between parabionts similar to those used in these studies was measured with ^{24}Na and was found to support these estimates, namely, 0.1 to 1% of extracellular fluid per minute. The short biological half-lives of the common steriods and vasopressor agents combined with this limited exchange make it difficult to postulate that such agents in concentrations sufficient to induce hypertension would be transferred from the S animals to their R partners. In earlier studies we found that animals from the Resistant strain were less responsive to DOCA (3), cortisone (4), norepinephrine, angiotensin, and possibly vasopressin (16), than were comparable animals from the Sensitive strain. Therefore, it is unlikely that lesser quantities of steroids and vasopressors could be more effective in the R rats than in their S partners. Finally, no vasopressor activity was demonstrable in the blood from rats with either acute or chronic salt hypertension (17). However, for this latter kind of bioassay, pharmacological quantities of pressor agent must exist in the blood and, therefore, one might fail to detect low concentrations that could be effective acting over periods of weeks.

Floyer and Richardson (15) and Floyer (18, as well as by personal communication) have suggested that a higher mean capillary pressure may exist in hypertension. This might be the genetic defect in our S strain of rats, present even before manifest hypertension. Following establishment of joint circulation between parabionts from the two strains, the higher capillary pressure in the S animal could tend to increase the blood volume of the R animal at the expense of the S rat. Venous return and cardiac output would be expected to increase at least transiently, leading to elevation in blood pressure until appropriate homeostatic mechanisms had come into play resulting in return of cardiac output and venous return to normal levels. Potentially, a new "setting" of baroceptors could maintain the pressure at a slightly elevated level and, if the stimulus leading to the initial insult were continuous or repetitive, a chronic and increasing elevation might follow. On the basis of experimental work, Ledingham has proposed a similar mechanism for the inception of hypertension (19, 20).

At this juncture, it is unwarranted to pursue these speculations further. The evidence indicates the existence of a transmittable humoral influence but does not identify it. Studies now under way may aid in characterizing it. While these studies have dealt only with NaCl-induced experimental hypertension, we

suspect this phenomenon has more general implications for the pathogenesis of hypertension.

SUMMARY AND CONCLUSIONS

Parabiosis has been found to modify the expected blood pressure response of rats from two strains with opposite genetic propensities for experimental hypertension. When a member from one strain was united in parabiosis with a member from the other *and* both were maintained on high NaCl diet, the rat from the strain ordinarily resistant to it rapidly developed hypertension, in contrast to appropriate controls from this strain. The development of hypertension in this resistant animal preceded that in its mate from the strain highly sensitive to hypertension. In the latter, both the level of hypertension and mortality were significantly less than in its control. It seems likely that the hypertension observed is the resistant parabiont was *initiated* in its partner from the sensitive strain. This modification in blood pressures was not observed in the absence of a high NaCl diet.

Parabiosis between animals from the same strain did not alter their response. Thus, as in earlier experiences (1–4) the interaction of a nongenetic factor (NaCl) with the appropriate genetic substrate appeared to be necessary for the development of hypertension.

The findings are interpreted as evidence that a transmittable humoral influence plays an important role in the pathogenesis of rat hypertension. The presence of this agent is genetically determined but, under the conditions of these experiments, it took the added stimulus of dietary NaCl to demonstrate its existence.

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