

EFFECTS OF CHRONIC EXCESS SALT INGESTION
ROLE OF GENETIC FACTORS IN BOTH DOCA-SALT AND RENAL HYPERTENSION*

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In an earlier study (1, 2) we reported that by using the technique of selective inbreeding, two strains of rats were evolved which differed markedly in their tendency to develop hypertension from chronic excess salt ingestion: one population was predisposed to develop hypertension (the *sensitive* or S strain) from the same high salt intake that proved ineffective in producing hypertension in the other population (the *resistant* or R strain). It was concluded that genetic factors played an important role in determining susceptibility to that form of experimental hypertension.

Prior to working with these two strains of selectively inbred rats, over a period of about 15 years we had observed the response of hundreds of stock animals to a chronically high sodium intake and had found that only about three-fourths of such animals would develop varying degrees of hypertension. Our experience with a combination of desoxycorticosterone acetate and a high sodium chloride intake (DOCA-salt) was similar. We were intrigued to learn that other investigators had found unilateral renal artery compression in the rat gave roughly similar results, namely only about half to two-thirds of animals so treated developed hypertension (3, 4). These several experiences suggested that variations in genetic susceptibility were operating in experimental hypertension induced by either renal artery compression or DOCA-salt, just as we had observed in that from salt alone.

The present paper is a report of experiments which demonstrate that this is true. Depending upon whether animals were derived from the sensitive or resistant strain of rats, susceptibility to experimental hypertension induced by either unilateral renal artery compression or DOCA-salt was found to be significantly different. Thus, variations in genetic substrate clearly influence the development of at least 3 "varieties" of experimental hypertension. It is postulated that this may hold true for other, and conceivably all, means of producing experimental hypertension. If so, it may be possible to develop a general hypothesis that will unify these presently disparate entities.

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Materials and Methods

All of the animals used in these studies were Sprague-Dawley rats derived from lines developed in our laboratory by selective inbreeding to manifest increased resistance or sensitivity, respectively, to the hypertensogenic effect of a high sodium diet (1, 2). The care, feeding, and technique of blood pressure measurements have been reported in earlier papers (5-7) and only the items pertinent to the present studies will be noted here.

Experiment 1.—DOCA-Salt Hypertension.

This experiment was set up to test whether or not the blood pressure responses of the two strains of rats would differ significantly following the administration of desoxycorticosterone and salt.

To this end, in intact male weanling rats 21 to 23 days of age and weighing about 40 to 50 gm each, a single 25 mg pellet of desoxycorticosterone acetate¹ (DOCA) was implanted subcutaneously between the shoulder blades.

Implantation of the pellet was done on the day of weaning and simultaneously the animals were started on special Ralston Purina fox chow containing sea salt, in a concentration of 11.6 per cent, found by repeated analysis to contain the equivalent of about 7.3 per cent NaCl (6). Tap water, containing only 0.5 to 0.7 mEq of sodium per liter, was allowed *ad lib*. Food consumptions were measured periodically and indicated no significant differences between the two groups.

12 rats from each of the two lines were studied. All animals were from the 5th inbred generation; by our nomenclature, such animals selectively inbred for their *resistance* to hypertension from a high sodium intake are designated R_5 animals, whereas animals in the 5th generation inbred for their *sensitivity* to salt are called S_5 .

Systolic blood pressures were measured under standard conditions (5, 6) at weekly intervals until the experiment was terminated 12 weeks after DOCA implantation. As noted previously (5, 6), systolic pressures of 140 mm Hg, or more, are regarded as being indicative of "hypertension" since 140 mm exceeds by nearly 3 standard deviations the mean pressure on our control animals. Similarly, pressures of approximately 180 mm Hg or more are associated with markedly shortened life expectancy in our salt-fed animals, and therefore such pressures are regarded as evidence of "severe" hypertension. Because the severity and rapidity of development of hypertension was found to be very different in the two strains, the pressures recorded each week have been shown for the S_5 animals whereas only the pressures at the end of 4, 8, and 12 weeks are shown for animals in the R_5 group.

Results.—The response of the S_5 and the R_5 group to the DOCA-salt regimen differed sharply in two major respects, namely, in the character of the blood pressure response and in mortality.

S_5 animals: (Table I, Fig. 1).

Severe hypertension became manifest in the S_5 animals very early (Table I). Only 2 of the 12 animals were still normotensive by the end of the 3rd week and 1 week later, with almost explosive swiftness, the entire group was

¹We are indebted to Drs. Robert Gaunt and Albert J. Plummer of Ciba Pharmaceutical Products, Inc., Summit, New Jersey, for all of the desoxycorticosterone acetate (DOCA) used in these studies.

seriously affected: 2 animals had died of fulminating disease and severe hypertension was present in all 10 survivors among which the mean and median systolic pressures were 212 and 214 mm Hg, respectively. 4 more animals

TABLE I
S₅ Males
Experiment 1. DOCA-Salt Hypertension

Rat No.	Systolic B. P.							
	1 wk.	2 wks.	3 wks.	4 wks.	5 wks.	6 wks.	7 wks.	8 wks.
†	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg	mm Hg
2054	122	102	163	*				
2061	114	110	162	208	‡	239	238	*
2062	94	100	154	*				
2069	110	66	150	222	260	*		
2070	64	60	128	190	*			
2074	102	144	170	232	*			
2075	110	84	110	192	*			
2078	94	130	152	214	230	*		
2086	70	119	164	214	208	*		
2087	106	132	170	248	*			
2091	92	134	158	216	204	*		
2092	71	114	140	182	184	192	*	
n.....	12 *	12	12	10	5	2	1	0
Mean.....	95.8	107.9	151.8	211.8	217.2	NC	NC	
SD.....	±18.8	±26.9	±18.0	±20.0	±29.0	"	"	
Median.....	98	112	160	214	208			

Effect of DOCA-salt regimen on systolic blood pressure of male rats, selectively inbred for 5 generations to develop a line sensitive to the hypertensogenic effect of a high salt diet. Rats were 21 to 23-day weanlings at onset of experiment; B.P.'s at weekly intervals thereafter.

By Student's *t* test, the mean B.P. of the S₅ animals increased significantly as follows: 4 weeks > 3 weeks ($t = 9.94, p < 0.01$) > 2 weeks ($t = 8.72, p < 0.01$) > 1 week ($t = 2.40, p 0.05 > 0.01$). B.P.'s at 4 and 5 weeks were not significantly different ($p > 0.1$). Comparison of mean B.P.'s of S₅ and R₅ animals indicated that the S₅ group at 4 weeks had significantly higher pressures than the R₅ group at 4 weeks ($t = 18.68, p < 0.01$), 8 weeks ($t = 3.136, p < 0.01$), or 12 weeks ($t = 5.267, p < 0.01$).

* Animal died during the week following last B.P.

‡ Animal sick at 5th week, no B.P.

died during the 5th week and before the end of the 8th week, no survivors remained.

R₅ animals: (Table II, Fig. 1).

The response of the R₅ animals contrasted sharply with the foregoing: after 4 weeks, 8 of the 12 animals remained normotensive and among the 4

hypertensive animals pressure elevations were moderate at most, with the highest pressure being 172 mm Hg (No. 1085). After 8 weeks, at a time when all S_5 animals were dead, all R_5 animals were alive. However, a significant degree of hypertension was now manifest in all but 3 of the R_5 animals as evidenced by mean and median pressures for the group of 178 and 187 mm Hg, respectively. By the 12th week, the pressure of a few R_5 individuals had risen

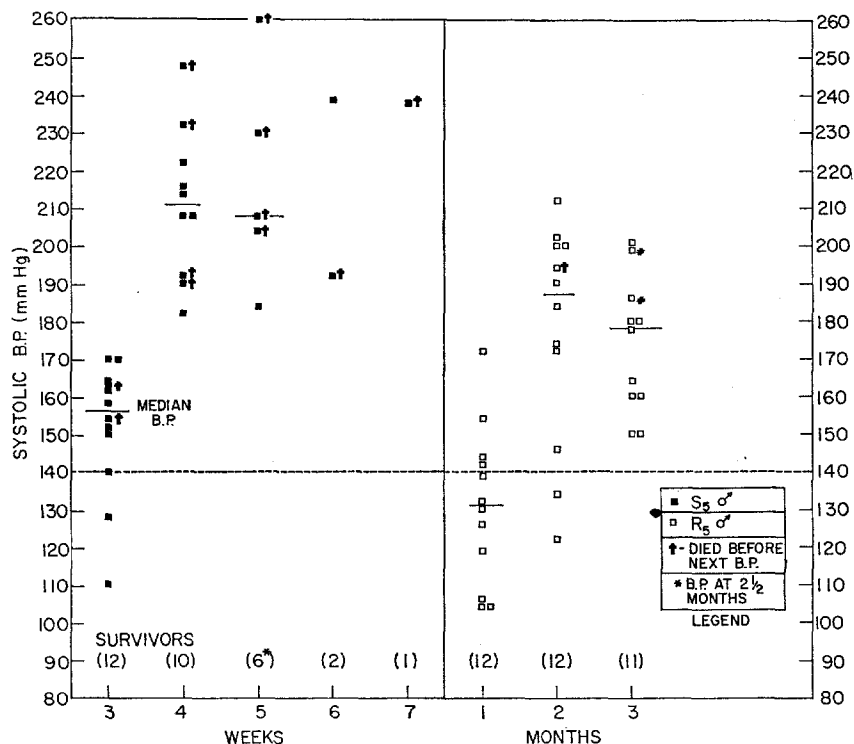


FIG. 1. Effect of genetic factors on development of DOCA-salt hypertension in rats. See legends for Tables I and II.

further, but this was not true for the group as a whole, since the mean and median pressures at this time were 174 and 178 mm Hg, respectively, pressures which were not significantly different from those found at the 8th week ($p > 0.5$). Despite these undeniable elevations among the R_5 animals at 8 and 12 weeks, the mean pressure of the S_5 animals at 4 (or 5) weeks was always significantly ($p < 0.01$) higher than that of the R_5 group at any time. Finally, as manifested by mortality rates the response to hypertension differed strikingly in the two groups: the only R_5 animal (No. 1069) that died during the study did so during the 9th week, when every S_5 animal was already dead. Although

2 other R_5 rats (Nos. 1084 and 1085) clearly would have died had the experiment been continued longer, the remaining 9 R_5 animals appeared in excellent health when the experiment was terminated.

In summary, from the same DOCA-salt regimen S_6 animals developed a

TABLE II
R₅ Males
Experiment 1. DOCA-Salt Hypertension

Rat No.	Systolic B.P.		
	4 wks.	8 wks.	12 wks.
	<i>mm Hg</i>	<i>mm Hg</i>	<i>mm Hg</i>
1068	130	174	160
1069	139	194	*
1070	154	184	201
1072	106	122	150
1073	104	134	164
1074	104	173	150
1078	119	190	180
1079	126	202	180
1080	144	200	178
1083	132	146	160
1084	142	200	199‡
1085	172	212	186‡
<i>n</i>	12	12	11
Mean.....	131.0	177.6	173.5
SD.....	±20.9	±29.0	±18.0
Median.....	131	187	178

Effect of DOCA-salt regimen on systolic blood pressure of male rats, selectively inbred for 5 generations to develop a line resistant to the hypertensogenic effect of a high salt diet. Rats were 21-23 day weanlings at onset of experiment; blood pressures are shown 4, 8, and 12 weeks later.

By Student's test the mean B.P. was significantly higher at 8 weeks ($t = 4.529$, $p < 0.01$) and 12 weeks ($t = 9.819$, $p < 0.01$) than at 4 weeks.

* Animal died between 8 and 9 weeks.

‡ B.P. at 10 weeks; animal sick thereafter.

fulminating, rapidly fatal hypertension whereas R_5 animals although they also developed hypertension, did so at a slower rate, to a significantly lesser degree, and of markedly lesser gravity.

It was concluded that a significant difference in response to DOCA-salt had been observed in the two strains of rats.

Experiment 2.—Renal Hypertension.

This study was undertaken to determine whether the response of the sensitive and resistant strains of rats differed in respect to the development of experimental renal hypertension.

The technique of Wilson and Byrom (3) was used: in young adult animals of both sexes, weighing approximately 150 to 200 gm, a left lumbar incision was made under ether anesthesia; the kidney and renal artery were then clearly exposed, and an annealed silver ribbon clip was applied to compress the renal artery, thereby partially occluding the blood flow to that kidney, with the right kidney being left untouched.² From the time of weaning all animals had been maintained on a special low sodium chow containing, by analysis, only 0.15 per cent sodium (equivalent to approximately 0.4 per cent NaCl); this same diet was continued *ad lib* throughout the experiment. By the same technique used in Experiment 1, blood pressures were measured every 2 weeks, of which the data obtained at 4, 8, and 12 weeks were representative and therefore only these are used in this paper. Tap water was allowed *ad lib* as before. The animals for Experiment 2 were derived from the 6th generations inbred for either sensitivity or resistance to a high salt diet, and in conformity with our nomenclature (see Experiment 1), are called S_6 and R_6 , respectively. Unilateral renal artery constriction was performed on 20 S_6 and 20 R_6 rats, 14 males and 6 females in each instance. One S_6 male and 3 R_6 males died during the 1st month following operation before significant observations were made and have been discarded from further consideration. The results in this paper are based on the data from the remaining 19 S_6 (13 males, 6 females) and 17 R_6 (11 males, 6 females) animals. Observations were concluded 3 months after each animal had undergone unilateral renal artery constriction, except for S_6 female 2402, which died during the 11th week of the study; in this instance the blood pressure at 10 weeks has been used.

Results.—

S_6 group:—(Table III, Fig. 2).

Blood pressures tended to rise rapidly and progressively: the mean systolic blood pressures for the 19 animals at 4, 8, and 12 weeks were 162, 180, and 198 mm Hg, respectively. These were significantly higher than the mean values of 146 ($0.05 > p > 0.01$), 140 ($p < 0.01$), and 140 ($p < 0.01$), mm Hg at corresponding times for the R_6 animals. At the end of the experiment, none of the S_6 animals was normotensive and 15 of the 19 rats had systolic pressures in excess of 180 mm Hg, severe hypertension by our standards. Despite this degree of hypertension, the animals seemed to withstand it well: only 1 rat died (\varnothing 2402) and this was late in the 11th week of the study. The remaining 18 animals appeared to be in good health, comparable in weight, appearance, activity, and food intake with the R_6 animals.

R_6 animals: (Table IV, Fig. 2).

In contrast with the S_6 animals, the mean blood pressure response was very modest and did not change significantly after the 4th week: the average systolic pressures for the 17 animals in this group at 4, 8, and 12 weeks were 146, 140, and 140 mm Hg, respectively. When the experiment was terminated after 12 weeks, 8 of the 17 R_6 animals remained normotensive (< 140 mm Hg), 7 had

²The senior author is deeply indebted to Dr. Quentin B. Deming of the Department of Medicine, Albert Einstein Medical School, for teaching him this technique.

TABLE III
S₆ Animals
Experiment 2. Renal Hypertension

Rat No.	Sex	Systolic B.P.		
		4 wks.	8 wks.	12 wks.
		<i>mm Hg</i>	<i>mm Hg</i>	<i>mm Hg</i>
2345	♀	151	168	202
2346	♀	115	156	158
2347	♀	175	166	212
2348	♀	128	160	166
2404	♀	152	142	144
2402	♀	164	208	230*
<i>n</i>		6	6	6
<i>Mean</i>		147.5	166.7	185.3
<i>SD</i>		±22.3	±22.2	±34.1
<i>Median</i>		151.5	163	184
2381	♂	158	190	196
2382	♂	174	184	204
2383	♂	190	162	188
2384	♂	170	202	244
2386	♂	174	202	212
2387	♂	133	144	166
2388	♂	160	156	186
2391	♂	170	212	237
2392	♂	200	196	216
2393	♂	170	186	183
2395	♂	162	180	204
2396	♂	170	240	234
2397	♂	166	172	186
<i>n</i>		13	13	13
<i>Mean</i>		169.0	186.6	204.3
<i>SD</i>		±15.8	±25.3	±23.5
<i>Median</i>		170	186	204
<i>n</i>	♀ and ♂	19	19	19
<i>Mean</i>	♀ and ♂	162.2	180.3	198.3
<i>SD</i>	♀ and ♂	±20.3	±25.6	±27.8
<i>Median</i>	♀ and ♂	166	180	202

Effect of unilateral renal artery compression on systolic B.P. of rats selectively inbred for 6 generations to be sensitive to hypertensogenic effects of a high salt diet. Rats weighed 150 to 200 gm at time of operation. Animals had been on low sodium (0.15 per cent) diet from time of weaning.

By Student's *t* test the mean blood pressures differed significantly as follows:

Females: 12 > 4 weeks ($t = 2.27, p 0.05 > 0.01$)

Males: 12 > 8 ($t = 1.85, p 0.1 > 0.05$) > 4 weeks ($t = 2.12, p 0.05 > 0.01$);

12 > 4 weeks ($t = 4.43, p < 0.01$).

By the same test, comparison of mean pressures in *S₆* and *R₆* groups differed significantly as shown:

4 weeks: *S₆* ♀ + ♂ > *R₆* ♀ + ♂ ($t = 2.72, p 0.05 > 0.01$)

8 weeks: *S₆* ♀ > *R₆* ♀ ($t = 3.20, p < 0.01$); *S₆* ♂ > *R₆* ♂ ($t = 4.78, p < 0.01$);

S₆ ♀ + ♂ > *R₆* ♀ + ♂ ($t = 5.59, p < 0.01$).

12 weeks: *S₆* ♀ > *R₆* ♀ ($t = 3.94, p < 0.01$); *S₆* ♂ > *R₆* ♂ ($t = 6.656, p < 0.01$);

S₆ ♀ + ♂ > *R₆* ♀ + ♂ ($t = 7.385, p < 0.01$).

*B.P at 10 weeks; animal died during 11th week.

mild elevations ranging from 140 to 154 mm Hg, and the remaining 2 animals (Nos. 1287 and 1351) had pressures of 172 and 176 mm Hg, respectively. No deaths had occurred, and all animals appeared in good health.

It was concluded that a significant difference in response to unilateral renal artery compression had been observed in the two strains of rats.

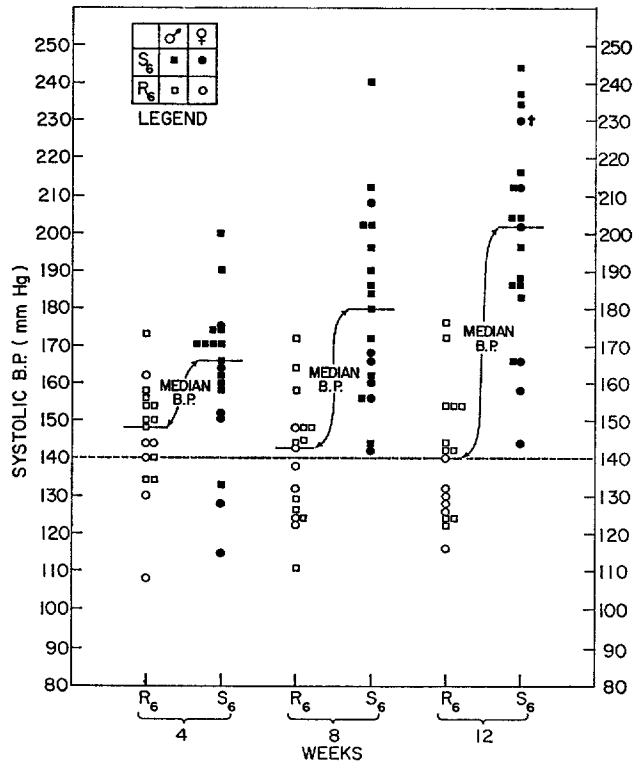


FIG. 2. Effect of genetic factors on development of renal hypertension in rats. See legends for Tables III and IV.

DISCUSSION

We have already reported (1, 2) the development, by selective inbreeding, of two strains of rats, one of which was very susceptible to the development of hypertension from chronic excess salt ingestion (the *sensitive* or S strain) whereas the other was not, (the *resistant* or R strain). The current studies, with the same strains of selectively inbred rats, have shown that genetic factors play a similar role in experimental hypertension induced by two other techniques, namely, that which results from simultaneous exposure to desoxycorticosterone acetate and a high sodium diet (DOCA-salt), and that which results from unilateral renal artery compression without additional dietary sodium.

TABLE IV
R_s Animals
Experiment 2. Renal Hypertension

Rat No.	Sex	Systolic B.P.		
		4 wks.	8 wks.	12 wks.
		<i>mm Hg</i>	<i>mm Hg</i>	<i>mm Hg</i>
1212	♀	130	138	128
1213	♀	108	123	132
1214	♀	144	143	130
1215	♀	144	132	116
1216	♀	162	148	140
1217	♀	140	124	126
<i>n</i>		6	6	6
Mean.....		138.0	134.7	128.7
SD.....		±18.0	±10.2	±7.9
Median.....		142	135	129
1282	♂	150	144	172
1283	♂	158	158	142
1284	♂	140	148	154
1286	♂	154	124	142
1287	♂	156	145	154
1288	♂	134	126	124
1289	♂	173	129	124
1293	♂	150	164	144
1294	♂	134	111	122
1295	♂	154	148	154
1351	♂	149	172	176
<i>n</i>		11	11	11
Mean.....		150.2	142.6	146.2
SD.....		±11.3	±18.5	±18.3
Median.....		150	145	144
<i>n</i>	♀ and ♂	17	17	17
Mean.....	♀ and ♂	145.9	139.8	140.0
SD.....	♀ and ♂	±14.7	±16.2	±17.4
Median.....	♀ and ♂	149	144	140

As for Table III, except animals were from 6th generation of rats selectively inbred for resistance to hypertensogenic effect of high salt diet.

By Student's *t* test, the mean systolic blood pressures of the females was not significantly different at 4, 8, or 12 weeks. This was also true for the males. Only at 12 weeks was the mean pressure of the males significantly higher than that of the females (*t* = 2.210, *p* 0.05 > 0.01).

It is perhaps not surprising to find that experimental hypertension from DOCA-salt resembles that from salt alone, in this respect; for in all probability, these two forms of hypertension are produced by very similar or even identical mechanisms, with the DOCA serving only to accelerate the process resulting ultimately in the production of hypertension. In the absence of excess salt, DOCA is quite ineffective in producing hypertension in our experience, as well as that of numerous other observers.

However, the similarity between experimental renal hypertension induced by unilateral renal artery compression and either "salt" or DOCA-salt hyper-

TABLE V
Comparison of Blood Pressure Response in Male Rats after DOCA-Salt (Experiment 1) and Induction of Renal Hypertension (Experiment 2)

Strain	Study	Systolic B.P.		
		4 wks.	8 wks.	12 wks.
		<i>mm Hg</i>	<i>mm Hg</i>	<i>mm Hg</i>
S ₅	DOCA-salt	211.8 (±20.0)	No animals	
S ₆	Renal hypertension	169.0 (±15.8)	186.6 (±25.3)	204.3 (±23.5)
R ₅	DOCA-salt	131.0 (±20.9)	177.6 (±29.0)	173.5 (±18.0)
R ₆	Renal hypertension	150.2 (±11.3)	142.6 (±18.5)	146.2 (±18.3)

By Student's *t* test the mean B.P. of S₅ DOCA-salt animals at 4 weeks > S₆ renal hypertensives at both 4 and 8 weeks ($t = 5.07$, $p < 0.01$; $t = 2.84$, $p < 0.01$, respectively); the mean pressure at 4 weeks for the DOCA-salt animals was not significantly different from that of the renal hypertensive group at 12 weeks ($p > 0.1$). By the same test the mean pressure, at 4 weeks, of R₆ renal hypertensives (R.H.T.) > R₅ DOCA-salt ($t = 2.965$, $p < 0.01$); at 8 and 12 weeks, R₅ DOCA-salt > R₆ R.H.T. ($t = 3.40$, $p < 0.01$, and $t = 3.28$, $p < 0.01$, respectively).

tension is less evident since excess dietary salt is not required to produce the former and there is no evidence of renal artery constriction in the latter. Nonetheless, the results described here suggest that the dissimilarities between "renal" hypertension and "salt" (or DOCA-salt) hypertension may be more apparent than real. If differences in genetic substrate determine which animals will or will not develop hypertension after exposure to these (seemingly) different triggering factors, it suggests that this may hold true for other, and possibly all, varieties of experimental hypertension. We are now in the process of exploring this in different groups of S and R animals with other techniques, each of which may result in hypertension under some circumstances. We suspect that the described differences in susceptibility to experimental hypertension in the S and R strains of rats, will be observed again. In our opinion, this would go a long way toward allowing the elaboration of a hypothesis that would unify

these presently disparate "varieties" of experimental hypertension and might, of course, have implications for the human counterparts.

The DOCA-salt regimen evoked more serious disease than did unilateral renal artery compression as evidenced both by the speed of evolution of hypertension as well as the mortality associated with it. The differences were most pronounced among the sensitive animals: not until the 12th week was the mean pressure of the renal hypertensive group as high as that of the DOCA-salt group at the 4th week (Table V); at the 8th week when all S_6 renal hypertensive animals were living all S_6 DOCA-salt animals were dead. To a lesser degree, the greater toxicity of the DOCA-salt regimen was manifested in the resistant groups, too. Notwithstanding that the blood pressures initially rose more rapidly in those with renal hypertension, after 8, and 12 weeks, the mean pressure of the DOCA-salt group was significantly higher ($p < 0.01$, Table V). Among the resistant males (there were no females in the DOCA-salt experiment) there were no deaths in the group with renal hypertension and while only 1 DOCA-salt male died during the 12 weeks of the study, 2 more in this group were so ill by the 12th week that they were sacrificed immediately after the experiment came to an end.

There are at least two possible explanations for these differences. Firstly, because the type of operation used in Experiment 2 to induce hypertension is technically difficult in animals less than about 150 to 200 gm in weight, the animals with renal hypertension were approximately 1 month older than the DOCA-salt animals at the time the respective experiments were begun. Younger animals are frequently more susceptible to metabolic insult than are more mature animals.

Secondly, there were great differences in NaCl intakes of the two groups: the animals with low mortality were on a low NaCl intake and the animals with high mortality were on a high NaCl intake. Although Tobian, Janecek, and Tomboulian (4) observed no significant increase in the incidence or severity of hypertension in rats with experimental renal hypertension drinking saline solution, the capacity of NaCl to induce severe vascular disease in the rat is generally well established (8-12). This toxic effect of NaCl on vascular structures may be related to Kempner's original observation that among patients with severe hypertension who were treated by the "rice diet," vascular retinopathy could improve markedly without significant change in blood pressure (13). We have confirmed this same phenomenon repeatedly over a period of 15 years, during which time hypertensive patients were cycled on diets high and low in sodium under controlled, metabolic ward conditions. Finally, since we have observed that chronic excess ingestion of salt is much more injurious to weanling rats than to animals older by only a month or 2 (14) perhaps the difference in *both* age and salt intake accounts for the more severe effect of the DOCA-salt regimen described in this paper.

CONCLUSIONS

By selective inbreeding, two strains of rats were developed previously that differed markedly in their susceptibility to the development of experimental hypertension from excess salt ingestion (1, 2). The present report indicates that with animals derived from the same strains, similar differences in response were obtained in rats subjected to either combined desoxycorticosterone-NaCl (DOCA-salt) treatment or unilateral renal artery compression without extra dietary salt. Thus, differences in genetic substrate appear to influence the development of experimental hypertension produced by these three techniques and possibly this may hold true for all "varieties" of experimental hypertension. If true, it might allow the development of a unifying hypothesis that could be relevant not only to experimental hypertension but perhaps to human hypertension as well.

The DOCA-salt regimen was more toxic to the animals than unilateral renal artery compression. Tentatively, this was ascribed to either, or both, the younger age or the higher NaCl intake of the animals in the former.

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