EFFECTS OF CHRONIC EXCESS SALT INGESTION

Further Demonstration that Genetic Factors Influence the Development of Hypertension: Evidence from Experimental Hypertension Due to Cortisone and to Adrenal Regeneration*

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Following the application of the technique of selective inbreeding, we reported that there evolved two strains of rats with opposite propensities to develop hypertension from chronic salt ingestion (1, 2). Subsequently it was observed that the two strains were similarly disparate in their responses to either desoxycorticosterone-NaCl treatment or unilateral renal compression without extra dietary NaCl (3). It was conjectured that since the genetic substrate had affected the development of experimental hypertension induced by three standard techniques, this might be true for experimental hypertension in general.

We report in the present paper that this postulate has been sustained when two additional techniques were applied to induce experimental hypertension, namely the use of cortisone (4) and of adrenal regeneration (5, 6). The sum of these experiences has led us to propose the thesis that the genetic substrate modifies significantly the effect of all non-genetic factors (*i.e. acquired* or *environmental*) that have been shown to play etiological roles in the induction of experimental hypertension. We further propose that similar interactions between genetic and non-genetic factors operate to promote or to oppose the development of hypertension in man. According to this thesis the development of hypertension could be triggered by either a single acquired factor or the algebraic sum of several, depending upon the genetic composition of an individual.

MATERIALS AND METHODS

The rats used in these studies were derived originally from a Sprague-Dawley strain. By selective inbreeding two lines were evolved in our laboratory on the basis of their capacity to manifest resistance or sensitivity, respectively, to the hypertensogenic effect of a high sodium diet (1, 2). Because of these opposite genetic tendencies, the two lines were called the *resistant* (or R) and *sensitive* (or S) strains, and this nomenclature has been continued here. All rats had been selectively inbred for at least 8 generations. Details on the care, feeding, and

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technique of blood pressure measurement have been reported in earlier papers (7–9) and only items relevant to the current report will be included.

Experiment 1: Cortisone Hypertension

It had been demonstrated by Knowlton *et al.* that hypertension could be rapidly induced in both normal and adrenalectomized rats by the administration of cortisone acetate (4). In our studies, in order to minimize the factor of variable adrenal function, cortisone was administered to adrenalectomized animals and the response compared with similarly prepared animals that did not receive cortisone. This necessitated the use of saline (0.85 per cent NaCl) as drinking fluid for all animals since the adrenalectomized controls might not have survived otherwise.

Ninety-nine 21-day-old weanling rats (50 R strain with 20 ♀ plus 30 ♂; 49 S strain with 20 ♀ and 29 ♂), were placed on tap water and our special low NaCl chow (0.38 per cent NaCl) at weaning. When they were approximately 6 weeks of age and weighed about 100 gm, all animals were operated on under ether anesthesia. Through a single skin incision over the lumbar spine, both kidneys and adrenals were exposed through separate lumbar incisions: in two-thirds of the animals bilateral adrenalectomy was performed while in the remaining one-third the adrenals were manipulated but not removed (sham adrenalectomy). Following operation, normal saline was substituted for tap water as the sole fluid source while the same low NaCl chow was continued *ad lib.* Seven days after operation by random selection half of the adrenalectomized animals were begun on injections with 5.0 mg cortisone acetate daily, subcutaneously, and this regimen was continued for 28 days. Thus there were observed the following 3 groups of animals: (*a*) sham-adrenalectomized controls, referred to hereafter as intact controls; (*b*) adrenalectomized controls; and (*c*) adrenalectomized animals that received cortisone. Immediate postoperative mortality as well as death and debility during the next few weeks left a final total of 67 animals on which this analysis was based at the end of the 4th week. Blood pressures and weights were measured at weekly intervals for 4 weeks at which time the experiment was terminated (4).

Results (Tables I to III, Fig. 1).—In any one group there were no significant differences between the values for mean systolic blood pressure at the end of the 3rd and 4th weeks. Among all 3 groups, animals from the sensitive (S) strain had significantly higher mean blood pressures than did corresponding animals from the resistant (R) strain. At 4 weeks, the results were as follows: intact controls, S, 126.6 *vs.* R, 107.9 mm Hg ($P < 0.001$); adrenalectomized controls, S, 117.4 *vs.* R, 101.7 mm Hg ($P < 0.001$); adrenalectomized animals receiving cortisone, S, 185.9 *vs.* R, 150.3 mm Hg ($P < 0.001$). Since both intact and adrenalectomized rats from the sensitive strain had significantly higher mean blood pressures without cortisone than did comparable animals from the R strain the difference in mean blood pressures between the S and R animals in the cortisone-treated group did not necessarily indicate a greater response by the S animals. However, comparison of the response of adrenalectomized animals using analysis of covariance suggested that those from the S strain responded to cortisone significantly more than did those from the R strain ($F = 7.42$, $P = 0.01$).[1] It was concluded that a difference in response to cortisone had been observed in the two strains.

[1] We are grateful to Dr. Keith Thompson for performing the analysis of covariance.

TABLE I

Experiment 1: Cortisone Hypertension
Controls (Sham Adrenalectomy)

Resistant strain				Sensitive strain			
Rat No.	Sex	Systolic blood pressure		Rat No.	Sex	Systolic blood pressure	
		3 weeks	4 weeks			3 weeks	4 weeks
1899	♂	116	102	4488	♂	128	122
1959	♂	114	103	4491	♂	138	148
1971	♂	132	110	4494	♂	No BP	140
1975	♂	124	112	4497	♂	122	118
1979	♂	114	106	4500	♂	110	142
1988	♂	94	92	4553	♂	124	130
1992	♂	122	120	4556	♂	100	118
n		7	7			6	7
Mean B.P.		116.6	106.4			120.3	131.1
± SD		119	8.8			13.5	12.3
Median B.P.		116	106			123	135
1802	♀	110	112	4110	♀	130	121
1805	♀	122	114	4113	♀	132	130
1808	♀	122	112	4116	♀	124	124
1811	♀	102	119	4119	♀	130	142
1814	♀	111	104	4122	♀	134	132
1817	♀	122	114	4125	♀	122	132
1821	♀	116	114	4128	♀	122	122
1824	♀	120	104	4131	♀	132	106
1827	♀	106	103	4134	♀	114	110
1830	♀	94	94	4148	♀	120	116
n		10	10			10	10
Mean B.P.		112.5	109.0			126.0	123.5
± SD		9.7	7.5			6.5	11.0
Median B.P.		114	113			127	
n	♀ + ♂	17	17		♀ + ♂	16	17
Mean B.P.		114.2	107.9			123.9	126.6
± SD		10.5	7.9			9.7	11.8
Median B.P.		116	110			124	124

All animals were operated when they were approximately 6 weeks old, and weighed about 100 gm. They were maintained on low NaCl (0.38 per cent) chow from weaning; normal saline replaced tap water as drinking fluid beginning the day of operation. Seven days were allowed for recovery before experiment was begun. Blood pressures (B.P.) were measured weekly but only those for the last 2 weeks are shown and statistics only for the 4th week are included. Mean B.P. did not differ significantly between 3rd and 4th weeks in any single group. By Student's t test, mean blood pressures of comparable groups in the 2 strains differed significantly ($P < 0.05$) as follows: (S ♂ 4 weeks > R ♂ 4 weeks, $t = 4.316$, $P < 0.005$; S ♀ 4 weeks > R ♀ 4 weeks, $t = 4.876$, $p < 0.001$; S ♂ + ♀ 4 weeks > R ♂ + ♀ 4 weeks, $t = 5.442$, $P < 0.001$). Weights (not shown) did not differ significantly for respective groups ($P > 0.05$).

TABLE II

Experiment 1: Cortisone Hypertension
(Adrenalectomy Only)

Resistant strain				Sensitive strain			
Rat No.	Sex	Systolic blood pressure		Rat No.	Sex	Systolic blood pressure	
		3 weeks	4 weeks			3 weeks	4 weeks
1900	♂	90	98	4492	♂	110	130
1958	♂	84	104	4495	♂	120	114
1995	♂	120	112	4555	♂	128	114
				4566	♂	114	*
n	not cal-	3	3			4	3
Mean B.P.	culated						
Median B.P.							
1750	♀	116	102	4108	♀	112	112
1803	♀	102	100	4111	♀	112	110
1806	♀	116	100	4114	♀	130	124
1809	♀	112	100	4117	♀	122	114
1812	♀	130	110	4120	♀	132	144
1815	♀	112	102	4123	♀	113	134
1818	♀	84	98	4126	♀	112	112
1822	♀	104	110	4129	♀	102	98
1825	♀	102	92	4135	♀	112	112
1828	♀	110	94	4203	♀	122	108
n		10	10			10	10
Mean B.P.		108.8	100.8			116.9	116.8
± SD		12.1	5.8			9.3	13.5
Median B.P.		111	100			113	112
n	♀ + ♂	13	13			14	13
Mean B.P.		106.3	101.7		♂ + ♀	117.2	117.4
± SD		13.9	6.1			8.7	12.3
Median B.P.		110	100			114	114

Animals bilaterally adrenalectomized at 6 weeks of age. Otherwise as per legend for Controls (Table I).

By Student's *t* test, mean blood pressures (B.P.) differed significantly as follows: S ♀ 4 weeks > R ♀ 4 weeks, $t = 3.445$, $P < 0.005$; S ♀ + ♂ 4 weeks > R ♀ + ♂ 4 weeks, $t = 4.128$, $P < 0.001$. Weights (not shown) did not differ significantly for respective groups ($P > 0.05$).

* Animal died during this week.

Experiment 2: Adrenal Regeneration

The technique described by Skelton (5, 6) was used to induce hypertension in female members of both strains of rats[2]. After weaning at 21 days they were maintained on tap

[2] The senior author is deeply indebted to Dr. Floyd Skelton for teaching him this technique.

water and our low sodium chow (0.38 per cent as NaCl). At approximately 6 weeks of age, when they weighed about 100 gm a right adrenalectomy-nephrectomy and a left adrenal enucleation were performed on all animals, under anesthesia *via* the lumbar approach. Following operation, 1 per cent NaCl solution was substituted for tap water as the sole drinking fluid and the same chow continued *ad lib.* Measurements of weight and blood pressure were begun 2 weeks postoperatively and thereafter were made at weekly intervals on the S strain animals and biweekly on the R strain rats. The need for a difference in the frequency of meas-

TABLE III

Experiment 1: Cortisone Hypertension
(Adrenalectomy plus Cortisone)

Resistant strain				Sensitive strain			
Rat No.	Sex	Systolic blood pressure		Rat No.	Sex	Systolic blood pressure	
		3 weeks	4 weeks			3 weeks	4 weeks
1974	♂	138	150	4490	♂	192	181
1976	♂	122	142	4493	♂	208	220
1987	♂	152	150	4499	♂	202	180
1991	♂	164	150	4551	♂	150	*
1994	♂	162	140	4552	♂	182	170
3051	♂	162	150	4559	♂	172	180
3057	♂	164	180	4561	♂	174	180
3059	♂	150	140	4562	♂	157	190
n		8	8			8	7
Mean B.P.		151.8	150.3			179.6	185.9
± SD		15.1	12.9			20.5	16.1
Median B.P.		157	150			178	180

Animals bilaterally adrenalectomized at 6 weeks of age. Thereafter each animal received 5 mg cortisone acetate daily subcutaneously for 28 days. Otherwise as per legend for Controls (Table I).

By Student's t test, mean blood pressures (B.P.) of the sensitive strain were higher than those of the respective resistant strain as follows: S 4 weeks > R 4 weeks, $t = 4.738$, $P < 0.001$. Weights (not shown) did not differ significantly for respective groups ($P > 0.05$).

* = Animal died during week indicated.

urement had been established in some pilot studies which showed that the postoperative course was strikingly different in the two strains. Twenty-five animals from each strain had been operated on but only those surviving at least 3 weeks have been included here. Although blood pressures were measured through the 12th week in the resistant animals, data beyond the 8th week have not been included since there were no significant ($P > 0.05$) differences between biweekly mean blood pressures from the 6th through the 12th weeks. In the sensitive rats blood pressure measurements ceased during the 6th postoperative week, because of the terminal state of all survivors ending with the death of the last animal during the 8th week.

Results (Tables IV and V, Fig. 2).—In the resistant animals when blood pressures rose at all they did so slowly and only mildly, reaching a plateau

at the 6th week with a mean systolic blood pressure of 130 mm Hg. We have regarded pressures of 140 mm Hg or more as "hypertensive" and in this resistant group at the end of the 8th week, only 8 of the 23 test animals had such pressures, ranging from 142 to 164 mm Hg. There were no deaths and all animals appeared in good health at the end of the study.

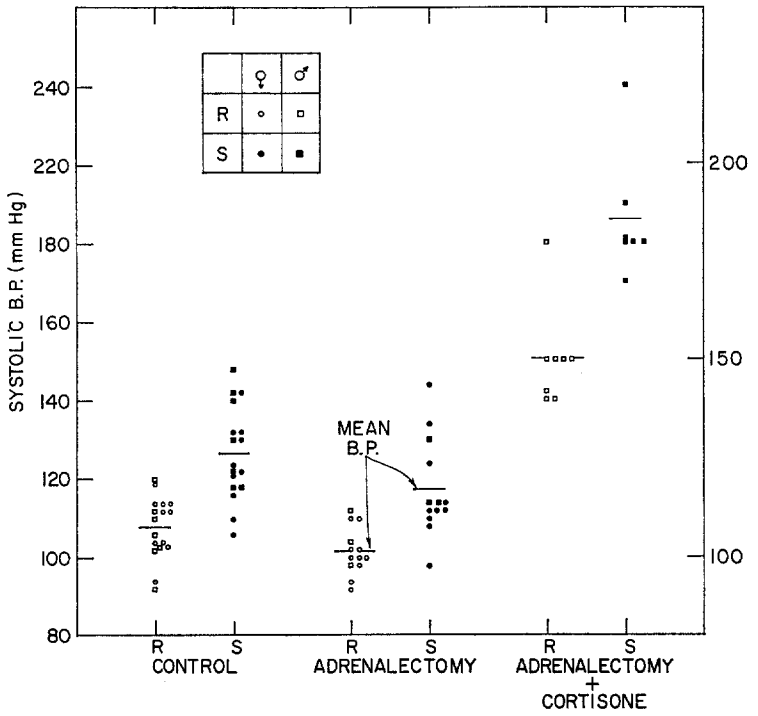

FIG. 1. Cortisone study. Effect of cortisone on blood pressure of resistant (R) and sensitive (S) strains of rats. Result at the end of the 4th week on cortisone.

By contrast, the pressures of the sensitive animals rose steeply to a mean level of about 210 mm Hg during the 4th and 5th weeks and the course of the hypertension was fulminating: by the end of the 4th week 8 of the original 16 animals were dead or dying and by the end of the 8th week, none was alive. Yet dramatic as this response was, it probably was underestimated: our experience suggests that, had blood pressures been measured more often, significantly higher pressures would have been recorded on some animals (*e.g.* Numbers 4524, 4526, and 4546) that had rapidly evolving disease but had only moderate elevations of pressure recorded prior to becoming ill, after which blood pressure measurements became either unreliable or impossible to obtain.

The marked disparity in the responses of these two strains cannot be explained by the modest difference in basal blood pressure that exists: among rats on a low salt diet in this and other studies on similar animals during the first few months after weaning, this averaged only about 10 to 20 mm Hg higher systolic blood pressures in members of the S strain. Therefore, it was

TABLE IV

Females from Resistant Strain
Experiment 2: Adrenal Regeneration Hypertension

Rat No.	Systolic blood pressure			
	2 weeks*	4 weeks	6 weeks	8 weeks
3047	94	127	120	126
3048	92	118	130	124
3049	120	122	138	150
3050	90	123	142	149
3101	108	135	160	150
3102	100	122	132	134
3103	112	110	142	130
3105	96	120	140	164
3113	97	130	124	154
3114	114	120	122	116
3116	118	120	120	122
3117	114	118	104	112
3213	120	130	132	130
3214	114	132	122	122
3226	134	148	134	150
3227	118	150	154	150
3228	130	126	130	134
3229	120	132	140	124
3230	132	122	130	142
3234	114	134	122	132
3235	94	128	114	130
3236	128	130	124	124
3237	111	120	120	124
n	23	23	23	23
Mean B.P.	111.7	126.8	130.3	134.5
± SD	13.3	9.3	12.7	13.9
Median B.P.	114	126	130	130

All animals had a right adrenalectomy-nephrectomy and a left adrenal enucleation when they were approximately 6 weeks old and weighed about 100 gm. For details see Materials and Methods. Blood pressures (B.P.) and weights measured every 2 weeks. By Student's *t* test, mean blood pressures differed significantly at biweekly intervals as follows: 4, 6, or 8 weeks > 2 weeks, $P < 0.001$; 8 weeks > 4 weeks, $P < 0.05$.

* After operation.

TABLE V

Females from Sensitive Strain
Experiment 2: Adrenal Regeneration Hypertension

Rat No.	Systolic blood pressure						
	2 weeks*	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
4518	140	170	192	212	‡	§	
4522	132	182	§				
4524	134	164	‡	§			
4525	112	190	223	215	195	§	
4526	144	168	‡	§			
4527	130	159	210	219	240	‡	§
4528	130	192	223	200	250	§	
4529	140	183	230	221	‡	§	
4541	160	182	‡	§			
4542	160	206	§				
4543	122	160	210	240	§		
4544	150	212	§				
4545	144	194	210	§			
4546	164	‡	§				
4547	154	161	‡	§			
4548	129	172	170	196	§		
n	16	15	8	7	3	0	0
Mean B.P.	140.3	179.7	208.5	214.7			
± SD	14.7	16.7	19.4	14.6	Not calculated		
Median B.P.	140	182	210	215			

See Table IV. Blood pressures (B.P.) and weights were measured at weekly intervals.

By Student's *t* test, blood pressures differed significantly at weekly intervals, as follows: 3 weeks > 2 weeks, $P < 0.001$; 4 or 5 weeks > 3 weeks, $P < 0.001$.

By the same test, comparison of the blood pressure response of the sensitive *versus* the resistant strains at comparable times was as follows: S 2 weeks, > R 2 weeks, t 6.318, $P < 0.001$. S 4 weeks, > R 4 weeks, t 15.95, $P < 0.001$. S 3, 4, or 5 weeks, > R 4, 6, or 8 weeks, $P < 0.001$.

Weights not shown, at comparable times, did not differ significantly ($P > 0.05$) between the two strains.

* = After operation.

‡ = Sick, No B.P.

§ = Died during week indicated.

concluded that a significant difference in response of the two strains to adrenal enucleation had been demonstrated.

DISCUSSION

The results of this study support those we have reported earlier using these same strains of selectively inbred rats: both the frequency and severity of

experimental hypertension are markedly influenced by the respective genetic endowment of the two strains. The sensitive strain, previously demonstrated to rapidly develop severe hypertension from chronic excess salt ingestion (1, 2) combined DOCA-NaCl (3) or unilateral renal artery constriction without NaCl (3) has been found here to respond similarly both to cortisone and to

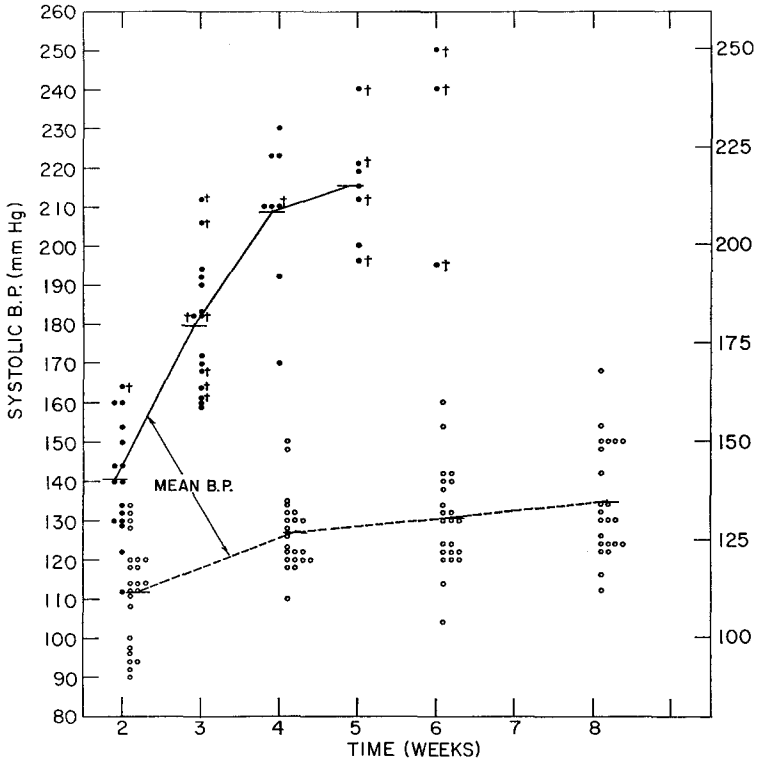

FIG. 2. Effect of adrenal regeneration on blood pressure of sensitive (•) *versus* resistant (○) female rats.

adrenal enucleation. By contrast, in members of the resistant strain exposed to the same hypertension-inducing agencies, the frequency, the degree, and the severity of hypertension were sharply less.

In both of the techniques used to induce hypertension in the present studies, the animals ingested saline solution so it is conceivable that only another form of "salt hypertension" was being induced. However, according to the report of Knowlton *et al.* (4), the administration of cortisone to adrenalectomized rats resulted in a lesser degree of hypertension if the animals received extra sodium than if they were on a restricted sodium intake. Therefore, at least in

the case of "cortisone hypertension", the ingested saline probably played no primary role in the development of hypertension other than to promote survival of the adrenalectomized animals.

Adrenal-regeneration hypertension cannot be as readily differentiated from salt hypertension. Crane (10) has suggested that hypertension develops in salt-loaded animals with regenerating adrenals because of an impaired ability to excrete the salt. Skelton (5, 6, 11) and Oelsner and Skelton (12) feel that added salt is necessary but not sufficient to explain the rapid development of hypertension: rather, the data suggest that adrenal-regeneration hypertension results from an interaction between NaCl and regenerating adrenal cortical tissue.

The present studies, combined with the earlier ones in this series (1, 2, 3), indicate that, whether experimental hypertension is induced by salt, by impairing blood flow to a kidney, or by hormonal manipulations, the development of hypertension is markedly affected by the differences in genetic background of the two strains of rats. The sum of these experiences leads us to propose the thesis that the genetic substrate will modify significantly the effect of all non-genetic factors that have been shown to play etiological roles in the induction of experimental hypertension.

If these experimental models have relevance to hypertension in man, they suggest that hypertension may result from one or more non-genetic (*acquired* or *environmental*) factors interacting with the appropriate genetic substrate. Such non-genetic factors would be expected to be modified not only by dissimilarities in genetic composition of the respective individuals but by such variables as differences in character, intensity, and duration of the non-genetic factors. If this thesis is valid, at one extreme there should exist individuals with so strong a genetic predisposition to hypertension as to require only minimal additional factors to develop high blood pressure; at the other extreme there should be persons so lacking in genetic predisposition as to develop chronic hypertension only after exposure to noxious influences of great severity and for prolonged periods. However, given the usual genetic heterogeneity of man, it is probable that the much more common individual would be one with modest genetic predilection who, after variable exposure to one or more of the effective non-genetic influences, manifests hypertension. We have summarized this thesis in schematic fashion in Fig. 3.

The above hypothesis would help to explain the rapid development of the malignant phase in some young individuals with hypertension, as well as the failure of many individuals to become hypertensive from lesions or diseases commonly associated with hypertension. For instance, while the association of hypertension and renal disease has been known since the time of Richard Bright, there is no necessary relationship between the two. Indeed, from a perusal of Strauss and Welt's recent monograph on the kidney (13), it ap-

peared that none of the numerous afflictions to which this organ is prone were uniformly associated with hypertension: generally, one-quarter to one-half of affected individuals were considered to be normotensive. Despite the recent interest in surgical correction of a wide variety of renal artery lesions that may lead to the development of hypertension, many normotensive individuals have been found among patients with equally severe lesions (14). Among

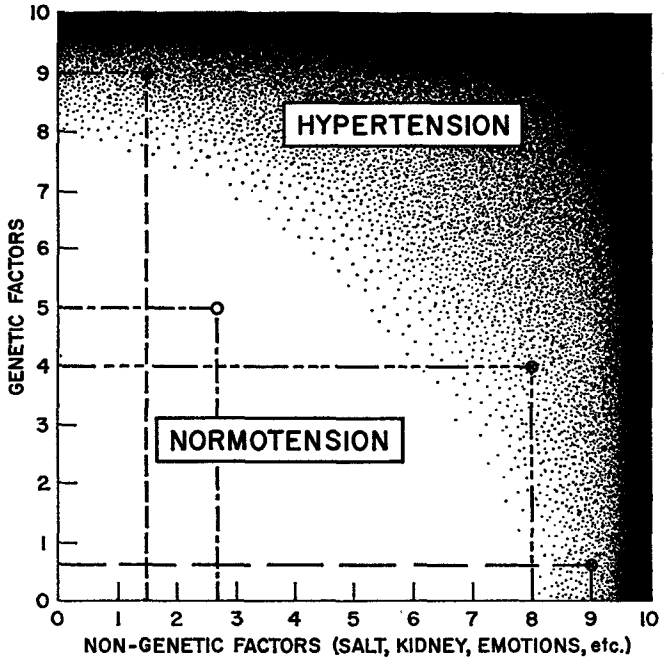

FIG. 3. Diagram to suggest possible relative roles of genetic and non-genetic factors in hypertension.

hormonal aberrations, in one large series of patients with Cushing's syndrome hypertension was found to be absent in about 25 per cent of the affected individuals (15). Among patients with acromegaly, hypertension was found about 3 times as commonly as would have been expected from the age and sex distribution of the 103 patients: but two-thirds of the patients were not classed as hypertensive (16).

If the hypothesis proposed here is valid, first degree relatives of patients with high blood pressure should also have high blood pressure more frequently than similar relatives of patients with normal blood pressure. This is so well established for "essential" hypertension that documentation is no longer necessary. This correlation now appears to be firmly established for pyelo-

nephritis as well: in patients with both hypertension and pyelonephritis, hypertension is found significantly more often among first degree relatives than among similar relatives of non-hypertensive patients with pyelonephritis (17–19). Two recent studies of hypertension which developed during pregnancy also showed familial aggregation of elevated blood pressure (20, 21) and the same may be true for patients with chronic nephritis (19). In sum, there is a considerable body of clinical evidence that is compatible with the experience derived from experimental models.

CONCLUSIONS

Two strains of selectively inbred rats were demonstrated previously to have opposite genetic predisposition to develop hypertension from NaCl ingestion (1, 2), DOCA-NaCl (3), and unilateral renal artery compression without NaCl (3).

Using these same strains, similar disparate responses were elicited with two other models for inducing experimental hypertension, namely cortisone and adrenal regeneration.

On the basis of these experiences, it is proposed that the genetic substrate will be found to modify significantly the influence of all non-genetic factors considered to play a primary role in the etiology of experimental hypertension.

Furthermore, it is suggested that similar genetic and non-genetic factors interact to produce hypertension in man. An hypothesis has been elaborated that is compatible with the experimental data and there is some clinical evidence to support this hypothesis.

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