macological reactions are eagerly sought. It would seem to be of considerable biochemical interest to attack a lethal process already well underway and to nullify and reverse it. The reversal of the lethal action of nitrogen mustards in mice appears to be such an example. It would seem that fruitful and perhaps practically significant clinical findings await further clarification of the interrelationships suggested here.

Summary. The intraperitoneal administration of a pyrazolone compound before and after a single intraperitoneal nearly-lethal dose of nitrogen mustard had been given to mice produced a marked reduction of the mortality expected from the nitrogen mustard. Furthermore the leukopenia resulting from the nitrogen mustard was considerably less in extent and duration.

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Renal Effects of Renin in Normal and Buffer-Nerve Sectioned Dogs.* (27689)

F. DEL GRECO,† A. C. CORCORAN‡ AND I. H. PAGE
Research Division, Cleveland Clinic Foundation, Cleveland, Ohio

The effect of renin on urine flow and composition is not as well defined in the dog as in other laboratory animals(1). Previous studies in normal dogs and in those with diabetes insipidus have shown that following renin injection urine flow increases(2), decreases(3, 4) or does not change(5). These disparate observations are probably attributable to differences in experimental procedures. The present study was therefore undertaken to reexamine the effects of renin in normal dogs under standardized conditions. The condition selected was that of osmotic (mannitol) diuresis during hydropenia since water and electrolyte excretion tends, in this situation, to be relatively stable(6). Then, since section of the carotid sinuses and aortic depressor nerves in dogs (abbreviated below as buffer-nerve sectioned dogs) enhances the pressor response to renin and angiotensin(7), similar experiments were performed in dogs so prepared.

Material and methods. Ten normal and 6 buffer-nerve sectioned dogs, weighing from 6 to 20 kg, were used. The latter dogs were studied at least one month after section of the buffer-nerves, and after daily measurements of blood pressure in the resting, unanesthetized state had shown sustained hypertension.

The effects of renin were determined in all the animals after induction of anesthesia by intravenous sodium pentobarbital (15 to 30 mg/kg/B wt), in the course of osmotic (mannitol) diuresis and hydropenia. The procedures employed have been described(8).

Three to 5 consecutive control clearance periods were obtained at 10-15-minute intervals. Renin,§ diluted in the infusion fluid used for the study of kidney function, was then administered at a constant rate. The urine collected during the first 5 to 10 minutes of renin infusion was discarded. Subsequently, 3 to 5 consecutive clearance periods were determined. After the administration of renin was discontinued and after a 5-10-minute discard period, another 3 to 5 clearance periods were again determined.

Throughout the experiments mean blood

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† Present address: Passavant Memorial Hospital, Chicago, Ill.

‡ Present address: St. Vincent Charity Hospital, Cleveland, Ohio.

§ Hog renin, partially purified by several ammonium sulfate precipitations and assayed according to Goldblatt *et al.*(9), contained 30 pressor units (P.U.) per ml.

TABLE I. Effects of Renin on Renal Function of Normal Dogs.*

Dog No.	Wt, kg		Renin, P.U./min/kg	B.P., mm Hg	C_{PAH}, ml/min per 1.0 m² B.S.A.	C_M, ml/min per 1.0 m² B.S.A.	FF, %	R	V, ml/min	$U_{Na}V$, μeq/min per 1.0 m² B.S.A.	U_KV, μeq/min per 1.0 m² B.S.A.	$U_{Cl}V$, μeq/min per 1.0 m² B.S.A.
1	8.5	C		136	182	63	34	.7	3.0	56	44	51
		I	.09	174	126	44	35	1.3	2.7	28	37	30
		R		134	131	53	41	1.0	3.0	30	40	23
2	6.4	C		114	316	83	26	.3	4.7	260	43	300
		I	.20	148	288	71	35	.5	3.2	110	49	126
		R		122	307	68	27	.4	4.5	100	63	105
3	11.4	C		137	201	72	36	.6	2.6	50	22	46
		I	.05	151	162	64	38	.9	2.1	53	27	40
		R		122	172	76	44	.7	2.1	62	36	38
4	12.0	C		132	324	122	36	.4	1.6	27	33	10
		I	.06	151	244	110	45	.6	1.5	16	34	10
		R		140	270	127	47	.5	1.7	8	29	8
5	9.6	C		111	357	102	29	.3	4.3	70	47	76
		I	.10	143	350	125	35	.4	5.8	126	126	118
6	14.1	C		138	242	68	28	.5	3.0	120	30	155
		I	.07	166	158	65	41	1.0	4.4	170	84	230
		R		139	137	56	40	1.0	4.4	90	74	220
7	16.2	C		136	160	54	33	.8	5.1	268	200	77
		I	.07	147	172	55	32	.8	5.3	280	214	92
		R		121	137	47	34	.8	3.5	96	110	64
8	18.4	C		131	189	63	33	.7	3.7	69	64	38
		I	.05	158	159	58	36	.9	3.1	77	28	38
		R		135	149	57	37	.9	3.2	48	44	41
9	14.4	C		109	272	91	34	.4	2.8	290	132	57
		I	.07	152	246	101	41	.6	4.7	480	307	86
		R		121	264	100	37	.4	4.7	245	200	83
10	15.0	C		123	306	84	27	.4	4.0	174	158	57
		I	.05	173	246	59	40	.7	2.7	54	22	54
		R		128	254	68	40	.5	3.0	34	41	78

* All values are avg of three to five determinations.

P.U. = pressor unit
B.S.A. = body surface area (M^2)
B.P. = mean blood pressure
C_{PAH} = sodium p-aminohippurate clearance
C_M = mannitol clearance
FF = renal filtration fraction, C_M/C_{PAH} (%)
R = renal vascular resistance, B.P.—5/C_{PAH}
V = urine flow
$U_{Na}V$ = urinary sodium output
U_KV = urinary potassium output
$U_{Cl}V$ = urinary chloride output
C = control
I = infusion
R = recovery

pressure (BP) was measured from a damped mercury manometer connected to a cannula inserted into a femoral artery. Glomerular filtration rate was measured as the mannitol clearance (C_M), and renal plasma flow as the sodium p-aminohippurate clearance (C_{PAH}).

Plasma and urinary PAH and mannitol, as well as urinary Na, K and Cl were measured by methods previously described(8).

Results. The average data and dosage rates of renin infused are listed in Tables I and II.

Blood pressure. The control blood pressure (BP) in the resting, unanesthetized state, ranged in normal dogs between 110 and 140 mm Hg and in the buffer-nerve sectioned dogs between 180 and 200 mm Hg. Upon induction of anesthesia BP did not change in the normal dogs, but it dropped by an average of 50 mm Hg in the buffer-nerve sectioned dogs. This fall occurred although the amount of sodium pentobarbital given these animals was about half that administered to normal dogs.

The infusion of renin caused a rapid rise in BP during the first 10 to 20 minutes. Then, BP tended to decrease gradually although remaining above normal levels by an average of 29 mm Hg in the normal dogs and by an average of 45 mm Hg in the buffer-nerve sectioned dogs.

TABLE II. Effects of Renin on Renal Function of Buffer-Nerve Sectioned Dogs.*

Dog No.	Wt, kg		Renin, P.U./min/kg	B.P., mm Hg	C_{PAH}, ml/min per 1.0 m² B.S.A.	C_M, ml/min per 1.0 m² B.S.A.	FF, %	R	V, ml/min	$U_{Na}V$, μeq/min per 1.0 m² B.S.A.	U_KV, μeq/min per 1.0 m² B.S.A.	$U_{Cl}V$, μeq/min per 1.0 m² B.S.A.
11	22.5	C		128	153	42	28	.8	3.1	35	36	51
		I	.04	152	136	40	30	1.1	4.2	88	44	97
		R		132	117	33	28	1.1	3.6	34	36	32
12	16.4	C		151	206	57	38	.7	4.4	381	51	275
		I	.06	214	155	52	33	1.3	7.9	1020	89	660
		R		159	104	37	36	1.5	3.4	300	47	241
13	11.4	C		128	206	65	32	.6	4.8	346	41	381
		I	.09	195	172	59	35	1.1	10.7	1000	82	996
		R		156	80	35	45	1.9	5.8	460	57	424
14	9.7	C		129	235	53	22	.5	3.3	63	46	42
		I	.10	140	170	55	31	1.0	6.5	316	65	436
		R		111	144	41	38	.7	5.3	139	42	130
15	21.1	C		106	188	62	33	.5	2.8	105	46	80
		I	.05	148	137	56	41	1.0	3.6	130	41	122
		R		136	132	48	56	1.0	2.8	117	38	26
16	11.5	C		168	237	57	24	.7	3.1	123	49	
		I	.08	235	141	45	32	1.6	4.1	160	53	
		R		171	123	39	32	1.3	2.7	57	35	

* Abbreviations are explained in legend to Table I.

Upon cessation of renin infusion BP returned to or near control levels in all the experiments.

Renal hemodynamics. Renin produced a decrease in C_{PAH} of about 15 per cent in the normal dogs and of 26 per cent in the buffer-nerve sectioned dogs. Consequently, renal vascular resistance (R, calculated as BP–5/C_{PAH}) rose more in the latter animals. C_M was less consistently affected by renin infusion, since in normal dogs it fell by 10 to 30 per cent in 6 experiments, while remained unchanged in the other 4 (Table I, No. 5, 6, 7 and 9). In the buffer-nerve sectioned dogs (Table II) C_M decreased by 4 to 9 per cent. Filtration fraction (FF) rose in all the experiments.

After the infusion of renin was discontinued C_{PAH} and C_M remained depressed or tended to fall further, while FF and R persisted elevated.

Urine flow and electrolyte excretion. In the 6 experiments in normal dogs exhibiting a decreased C_M during the infusion of renin, urine flow (V) fell by an average of 21% and the minute excretion of Na, K and Cl ($U_{Na}V$, $U_{Cl}V$, U_KV) decreased by nearly 50%. However, in the 4 experiments in which C_M was not affected by renin (Table I, No. 5, 6, 7 and 9) V rose by an average of 34%, $U_{Na}V$ and $U_{Cl}V$ by 40%, and U_KV by 80%. In all the buffer-nerve sectioned dogs in spite of the slight reduction in C_M V nearly doubled, $U_{Na}V$ and $U_{Cl}V$ increased by an average of 160 and 180%, respectively, while U_KV rose by only 32%.

After cessation of renin infusion V, $U_{Na}V$, $U_{Cl}V$ and U_KV returned to control levels or decreased further in all but 4 experiments (Table I No. 6 and 9; Table II No. 13 and 14) in which they persisted slightly elevated.

Discussion. The considerable fall in blood pressure noted in the buffer-nerve sectioned dogs upon induction of anesthesia is consistent with previous observations(6,10), which also revealed that the depth of pentobarbital anesthesia did not significantly affect the pressor response to vasoactive agents. The observed changes in C_{PAH} confirm previous studies(2,4,5) and indicate that renin, like angiotensin(11), reduces considerably renal blood flow. This effect, however, is not consistently associated with similar decreases in glomerular filtration rate. Indeed, in some of the present experiments C_M was unchanged or reduced proportionately less than C_{PAH}. The finding of diminished C_{PAH} and C_M after renin infusion was discontinued should be at-

tributed to the effects of prolonged anesthesia and fluid loss.

In 6 experiments in normal dogs renin infusion caused antidiuresis and sodium retention. Since in all these experiments C_M decreased, it is possible that this change accounts for the reduction in urine flow and salt excretion. However, in the other 4 experiments in normal dogs in which C_M was unchanged a moderate but definite diuresis and natriuresis occurred. This diuretic and natriuretic effect was even more manifest in all the buffer-nerve sectioned dogs in spite of a slight reduction in C_M. These findings suggest that the diuretic effect of renin was probably due to diminished tubular reabsorption. This interpretation is further supported by the observation of persisting diuresis in some of the above experiments (No. 4, 9, 13 and 14) after cessation of renin infusion in presence of a falling glomerular filtration rate.

Renin injection causes increased water and salt excretion in rats and rabbits(12,13,14). In most patients with hypertension or cirrhosis and ascites the infusion of angiotensin II produces similar effects(15,16,17,18). Many of the present findings are consistent with these observations and indicate that section of the buffer-nerves enhances the pressor as well as the diuretic and natriuretic effects of renin in the dog.

The mechanism of renin diuresis is obscure. Although the available data suggest that renin causes diuresis by direct tubular inhibition of water and salt reabsorption, it is entirely possible that renin diuresis represents response to changes in environmental factors. In this regard it is noteworthy that the greatest increases in water and salt excretion were found in the buffer-nerve sectioned dogs in which the pressor response to renin was also greatest. Considered in this context renin diuresis would resemble the effect of increased renal perfusion pressure, as described by Selkurt (19). Another hypothesis might be that renin diuresis is due to ill defined changes in the intrarenal circulation affecting the tubular reabsorption mechanism.

Summary. The effects of renin infusion were studied in anesthetized normal and buffer-nerve sectioned dogs during osmotic (mannitol) diuresis and hydropenia. Renin produced a rise in blood pressure and a decrease in C_{PAH}. These changes were more marked in buffer-nerve sectioned dogs. C_M fell by an average of 15% in 6 normal dogs in which urine and salt excretion also decreased. However, in another 4 normal dogs in which C_M remained unchanged during renin infusion, water and salt excretion increased moderately. In all the buffer-nerve sectioned dogs renin caused significant diuresis and natriuresis although C_M decreased slightly. The results show that buffer-nerve sectioned dogs are more sensitive than normal dogs to the diuretic action of renin. The possible mechanisms of this action have been discussed.

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Inactivation of the Skin-Sensitizing Antibodies of Human Allergy by Thiols. (27690)

JOHN P. LEDDY,† GERALDINE L. FREEMAN,*‡ ASUNCION LUZ* AND RICHARD H. TODD
(Introduced by L. H. Muschel)
Department of Immunochemistry, Walter Reed Army Institute of Research, and Allergy Training Program, The Children's Hospital, Washington, D.C.

The skin-sensitizing antibody or reagin is considered to be an important pathogenetic factor in human atopic allergy. Although many of the unique characteristics of this antibody are well known, a clear understanding of its physicochemical properties has been impeded by discordant findings(1). One method which has contributed valuable insights into antibody structure and classification is *in vitro* exposure to sulfhydryl (SH) compounds (2). This treatment inactivates high molecular weight (19S) antibodies(3), dissociating them into 7S subunits, presumably through reductive cleavage of disulfide bridges(2). Ordinary 7S (γ_2-globulin) antibodies are not affected(3) unless a denaturing agent is used in conjunction with SH treatment(4). Since the effect of SH compounds on the activity of human reagins was unknown, this investigation was undertaken. Data will be presented to show that *in vitro* SH treatment of the reagin-containing sera of allergic patients destroys the skin-sensitizing activity of these sera.

Materials and methods. After screening donors for a history of hepatitis, Wassermann negative sera from 16 allergic children and adults were selected for their ability to passively sensitize non-atopic human skin to subsequent challenge with the appropriate allergen(s) (the Prausnitz-Küstner or P-K reaction). The sera were sterilized by Seitz or Millipore filtration and stored at 4°C. The reagins represented included those to pollens, animal danders, molds and foods. The thiols employed in the majority of experiments were β-mercaptoethanol (ME) and DL-penicillamine; L-cysteine and β-mercaptoethylamine (MEA) were also used in certain later studies.

In a typical experiment, to each allergic serum diluted 1:3 with triethanolamine buffered saline (TBS) (pH 7.35, $\mu = 0.15$) was added an equal volume of 0.2M thiol which had been freshly prepared in TBS and adjusted, when necessary, to pH 7.2-7.3. Thus, the final thiol concentration was 0.1M and the final serum dilution was 1:6, giving a protein concentration of approximately 1%. Untreated controls consisted of aliquots of the same sera diluted equally with TBS alone and thereafter handled identically to the thiol-treated aliquots. Incubation in sterile, closed tubes was usually at room temperature for 24-48 hours in experiments with ME or MEA, and at 37°C for 24 hours with penicillamine or cysteine. After incubation, treated and control sera were dialyzed (separately) for 36-48 hours at 4°C against TBS with sufficient changes to reduce the calculated thiol concentration to 10^{-8}M or less. The dialyzed sera were then sterilized by Millipore or Seitz filtration. After 48 hours were allowed for bacterial cultures, bioassays were begun.

Antibody activity in the control and treated sera was assayed, usually without further dilution of the sera, by the P-K reaction in normal, non-allergic human volunteers unreactive in direct intradermal skin tests with the allergens concerned. Each treated serum and its untreated control were uniformly

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† Present address: Dept. of Medicine, University of Rochester Med. Center, Rochester, N. Y.
‡ Present address: Dept. of Pediatrics, Univ. of Colorado School of Med., Denver.