TABLE III. Comparison of Weights with Age and Resistance of Mice.*

Age (wk)	Sex	Variations in avg wt (g) of age groups	Increase in avg wt (g) of age groups	Avg % fatalities of group
5- 9	♂	12.9-17.3	4.4	94.4
10		17.3-17.5	.2	52.0
11-15		17.5-21.3	3.8	59.2
16		21.3-21.4	.1	34.8
17-23		21.4-23.5	2.1	28.7
5- 7	♀	12.6-15.3	2.7	98.1
8		15.3-15.7	.4	56.0
9-14		15.7-19.0	3.3	55.3
15		19.0-19.3	.3	40.0
16-23		19.3-22.4	3.1	32.2

* Inoculated with 23 million yeast phase *H. capsulatum* in 0.5 ml mucin.

compared to 17 weeks in males. Between 8 to 14 weeks of age females appeared to be especially more resistant than males. This observation can probably be attributed to the fact that female mice mature more rapidly than males(4). Thus, before and after full development of sexual maturity the differences in susceptibility were not appreciable. These results are also comparable to those observed by Theiler(5) in which the morbidity and mortality rates in experimental encephalomyelitis of mice were lower in mice over 12 weeks of age. The recognition of such differences in susceptibility in different age and sex groups can assist in the evaluation of data in a variety of studies employing the mouse as the experimental animal.

Conclusions. Age, sex, and dose are important factors in comparative susceptibility of mice to fatal histoplasma infections. Both sexes may show lower mortality ratios with increasing age. Females develop resistance earlier than males. This difference is most apparent between 8 to 14 weeks.

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Received September 7, 1955. P.S.E.B.M., 1955, v90.

Laboratory and Clinical Observations on Mecamylamine as a Hypotensive Agent.* (22047)

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Currently available ganglionic blocking agents used for the treatment of hypertension produce an inconstant day to day reduction in blood pressure largely due to incomplete and variable absorption of the quaternary ammonium compounds (bisammonium) from the intestinal tract. Mecamylamine, a secondary amine† is the first known ganglionic blocking agent which is completely absorbed after oral administration. The hemodynamic effects have been studied both in the laboratory as well as in patients with hypertension.

Methods and materials. Laboratory observations: Observations on the blood pressure response and on ganglionic blockade were made on 29 dogs anesthetized with 30 mg/kg of pentobarbital. The dogs were divided into 2 groups. Group I consisted of 12 dogs on which observations were made relative to doses which effectively blocked the autonomic ganglia and consequently reduced the blood pressure. Group II consisted of 17 dogs on which observations on the effect on renal hemodynamics and the excretion rates of water and electrolytes were made. *Group I.* Arterial blood pressure was measured by direct intra-arterial manometry in these ani-

* Supported in part by a grant from the Houston Heart Assn.

† 3-Methylaminoisocamphane hydrochloride. Available as Inversine by Sharp & Dome, Division of Merck & Co., West Point, Pa.

mals. Following suitable control observations, dosage increments of .05, .5, 1 and 2 mg/kg of mecamylamine were given intravenously over a 5-minute period. Subsequently, observations on blood pressure were made for the ensuing 5 hours. During this period, the blood pressure responses to electrical stimulation of the peripheral end of the severed vagus and to carotid occlusion were made at regular intervals. At one hour intervals, norepinephrine was infused at the same rate as required to produce a rise in mean blood pressure of 20 mm Hg during the control period. This was done as a test for adrenergic blockade. *Group II.* (*Renal studies*). Seventeen female dogs ranging in weight from 9 to 15 kg were used. They were anesthetized with pentobarbital, 30 mg/kg body weight, given intravenously. Creatinine was used to measure glomerular filtration rate (GFR) and p-aminohippurate (PAH) for renal plasma flow (RPF). Sodium and potassium determinations were made using a Beckman flame photometer for analysis. Arterial blood, collected in heparinized syringes, was used for chemical analysis. Analytical methods and procedures have been described previously(1). Mean blood pressure (MBP) was measured by a damped mercury manometer connected through a manifold to an indwelling arterial needle.

Clinical observations. The clinical observations were made on 2 groups of patients with moderately severe to severe hypertension. Group I consisted of 12 patients who were observed in detail and in whom observations were made on single dosage responses giving the drug no more frequently than once every other day. Group II consisted of 50 patients who received the mecamylamine as therapy for their hypertension. *Group I.* The 12 patients in Group I consisted of hospitalized patients with moderate to severe hypertension. After suitable control observations were made on the day of the test, 5 mg of mecamylamine were given orally at 8 o'clock in the morning. Observations on blood pressure were again made in the supine and upright positions every 15 minutes for the first 3 hours and then every half hour for the remainder of the day. If an adequate reduction in blood pressure was not obtained, a larger dose was given 2 or more days later and the procedure repeated. The dose was thus increased in 5 mg increments until an effective reduction in blood pressure‡ was obtained for each patient. Subsequently, 5 of the patients were given the same dose (effective dose) by the parenteral route in order to compare the response by the 2 different routes of administration. *Group II.* (Out-patients with Hypertension): All patients in this group had received 1 mg of reserpine a day for several months before initiation of the current study. This was not altered. None of the patients had become normotensive and control observations for the current study were made 2 months or more after stabilization on reserpine. The reserpine was continued because it reduces the pulse rate and blocks the reflex orthostatic tachycardia which is frequently observed with patients given ganglionic blocking agents.

This study consisted of a group of 50 patients with moderate to severe essential hypertension treated as out-patients in the Hypertensive Clinic. All patients had control blood pressures, as measured in both the supine and upright positions, of 150/100 mm Hg or greater. Controls were established by taking the average of a minimum of 4 separate blood pressure and pulse rate determinations in the supine and upright positions while the patients received only placebo. The post drug observations (2 months or more) are the averages of all blood pressures and pulse rates taken weekly in both the supine and upright positions after the therapeutic dose of mecamylamine for each patient had been established (*i.e.*, after the titration period during which time blood pressure and drug dosage were being stabilized). Sixteen of the group were males and 34 were females. Five were white and 45 negro. Average age was 52 years, with a range of 34 to 69 years. The severity of the disease in this group is best indicated by a high incidence of complications and by the fact that 41 (82%) had the retinal

‡ An attempt was made to reduce the standing blood pressure to a level below 150/100 without prohibitive side reactions.

TABLE I. Mean Blood Pressure* Response to Graded Doses of Mecamylamine Given Intravenously to Dogs.

Dog No.	Control	Time after drug in min. 5	10	15	20	30	45	90	120	300	Dose, mg/kg
1	128	96	90	84	80	60	55	50	44	44	2
2	132	110	100	106	104	100	102	100	102	104	2
3	142	98	100	104	116	102	104	110	128	136	2
4	164	154	144	128	126	128	134	142	146	146	.5
5	115	108	106	100	90	84	70	65	70	88	.5
6	168	142	135	136	138	132	128	128	126	130	.5
7	140	132	128	116	114	96	94	94	112	104	1
8	128	120	100	85	82	80	90	80	95	95	1
9	110	65	65	60	50	54	60	58	76	88	1
10	138	140	140	138	130	134	130	126	128	128	.05
11	138	136	138	138	140	140	144	146	148	154	.05
12	160	160	158	156	164	160	162	158	160	160	.05

* Direct intra-arterial manometry.

changes of hypertensive vascular disease; 7 of these had retinal hemorrhages. The initial dose of mecamylamine was 5 mg given orally twice a day (after breakfast and supper). This dose was empirically chosen as one which would not produce excessive hypotension or side reactions. However, in some cases, this dose resulted in marked orthostatic hypotension and numerous side reactions. A more suitable starting dose would be 2.5 mg twice a day. In our experience, this dose rarely produces side reactions or excessive hypotension. The initial dose was gradually increased in a stepwise fashion until an adequate blood pressure response was obtained. To minimize the orthostatic side reactions from excessive hypotension, the blood pressures in the upright position were the guide to the weekly changes in dosage. In addition to the blood pressure observations, clinical manifestations of excessive hypotension such as dizziness on standing and weakness were considered when regulating the dosage schedule.

Results. General Laboratory Observations (*Group I*): A consistent blood pressure effect in dogs was not observed with doses of less than 0.1 mg/kg. Doses in excess of 0.5 mg/kg did not cause much greater reduction in blood pressure than the 0.5 mg/kg dose but the period of the depressor response was not as long with smaller doses as with the larger ones. Likewise, the onset of action was somewhat more rapid with larger doses. Following administration of 0.5 mg/kg or more, this delay period was 5 to 10 minutes before the blood pressure decreased, and maximum depression was observed after 30 to 45 minutes (Table I). Blockade of the depressor response to vagal stimulation was consistent at the 1 mg/kg level. Blockade of the carotid pressor reflex usually occurred at a dose of 0.5 mg/kg. When maximum reduction in blood pressure occurred, there was no evidence of adrenergic blockade. In fact, the dose of norepinephrine required to produce a rise in mean blood pressure of 20 mm Hg during the control period was usually excessive after the administration of mecamylamine, apparently a result of ganglionic blockade of vasopressor inhibitory reflexes which are mediated via the parasympathetics. These observations indicate that the vasodepressor effect is not due to adrenergic blockade. Ganglionic blockade (partial) is present, but an additional central component has not been ruled out.

Observations on Renal Hemodynamics (Group II): Doses of mecamylamine of 0.2 and 0.5 mg (approximately .03 to .05 mg/kg) had no effect on blood pressure, renal hemodynamics, or on water and electrolyte excretion. Doses of 0.5 to 2.0 mg/kg produced a significant reduction in blood pressure ($p < 0.001$) which was more prolonged after the 1 and 2 mg/kg doses than after the .5 mg/kg dose. However, the initial reduction in blood pressure appeared to be nearly the maximum response with the 0.5 mg dose and was not increased by giving a larger dose. The initial reduction in blood pressure was not associated with depression in glomerular filtration rate or in renal blood flow during the first 30 minutes after drug administration. Renal vasodilata-

TABLE IIA. Effect of Mecamylamine on Renal Hemodynamics.

Dog No.	Mean blood pressure, mm Hg				Glomerular filtration rate, ml/min.				Renal blood flow, ml/min.				Renal vascular resistance*				Dog wt, kg	Dose
	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3		
Sub-group A																		mg
1	126	131	140	147	38	27	34	38	177	216	216	196	.71	.61	.65	.75	13.0	.2 (Total)
2	158	157	104	115	35	35	31	30	198	194	222	218	.80	.81	.47	.53	16.5	.2 "
3	132	132	126	142	37	33	41	35	202	200	234	198	.65	.66	.54	.72	11.0	.2 "
Mean	139	140	123	135	37	32	35	34	192	203	224	204	.72	.69	.55	.67	13.5	.2
Sub-group B																		
4	163	159	163	160	62	57	56	66	318	363	402	342	.51	.44	.41	.47	18.0	.5 (Total)
5	135	136	139	152	64	65	64	66	437	452	354	289	.31	.30	.39	.53	18.8	.5 "
6	138	137	135	128	50	55	50	44	320	317	260	185	.43	.43	.52	.69	18.0	.5 "
Mean	145	144	146	147	59	59	57	59	358	377	339	272	.42	.39	.44	.56	18.3	.5
Sub-group C																		mg/kg
7	139	121	113	111	45	53	40	37	251	269	195	170	.55	.45	.58	.65	15.0	.5
8	123	88	90	97	49	47	40	44	328	354	316	250	.38	.25	.28	.39	18.5	.5
9	63	43	40	64	30	30	30	31	134	132	121	106	.47	.33	.33	.60	12.0	.5
10	138	123	95	107	50	50	47	39	266	292	313	202	.52	.42	.30	.53	14.0	.5
11	103	60	56	89	49	44	44	34	192	180	219	120	.54	.33	.26	.74	20.0	.5
12	116	102	66	85	47	47	33	25	283	276	192	157	.41	.37	.34	.54	12.5	1.0
13	162	132	137	144	37	35	33	33	204	169	135	132	.79	.78	1.01	1.09	12.0	1.0
14	159	136	138	129	83	87	74	55	495	562	459	317	.32	.24	.30	.41	22.0	1.0
15†	123	89	47	45	44	38	9	15	284	306	42	208	.43	.29	1.12	.22	11.0	1.0
16	119	106	105	101	27	26	25	26	185	146	112	116	.64	.73	.94	.87	13.0	2.0
17	141	102	113	132	48	44	42	41	313	281	233	200	.45	.36	.48	.66	15.0	2.0
Mean	126	100	91	100	46	46	38	35	267	270	212	180	.50	.41	.54	.61	15.0	1.0
% of control		79	72	79		100	83	76		101	79	67		82	108	122		
P value‡ (<)		.001	.001	.001		NS	.05	.01		NS	.05	.001		.01	NS	.05		

C = Avg of 3-10 min. periods; control. D_1 = Immediately after drug administration (avg of 2-10 min. periods). D_2 = One hr after drug. D_3 = 3 hr after drug.

* Renal vascular resistance $= \frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$.

† Dog died 8 hr later.

‡ $t = \bar{x}\sqrt{\frac{n(n-1)}{Sx_2}}$ (Sub-group C). Statistical analysis by R. A. Seibert, Ph.D.

TABLE IIB. Effect of Mecamylamine on Water and Electrolyte Excretion.

Dog No.	Urine vol, cc/min.				Sodium excretion, meq/min.				Potassium excretion, meq/min.				Hematocrit			
	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3
Sub-group A																
1	.6	1.9	1.1	.9	45	75	42	62	15	18	30	38	39	42	45	43
2	.5	.3	.7	.7	18	13	14	12	22	18	16	19	38	38	45	49
3	1.0	1.0	2.1	2.0	103	85	223	81	26	26	38	33	39	40	41	44
Mean	.7	1.1	1.3	1.2	55	58	93	52	21	21	28	30	39	40	44	45
Sub-group B																
4	1.0	1.6	1.8	5.5	45	68	62	60	24	32	42	62	32	35	35	34
5	1.8	2.5	2.2	1.7	285	382	302	182	43	64	64	70	41	40	41	43
6	3.7	2.7	1.6	1.6	269	272	170	175	30	29	23	27	35	35	35	33
Mean	2.2	2.3	1.9	2.9	200	241	178	139	32	42	43	53	36	37	37	37
Sub-group C																
7	3.0	1.8	2.4	1.5	257	135	84	47	43	49	44	40	37	36	36	39
8	1.2	1.2	2.1	2.2	190	152	183	166	42	38	56	51	39	39	37	38
9	.5	.6	.6	.9	25	37	39	44	19	22	24	31	41	38	34	36
10	1.5	1.8	1.4	1.2	178	215	137	75	28	41	38	36	39	39	38	35
11	7.1	5.9	6.7	2.2	722	639	678	188	97	111	110	61	41	39	36	35
12	.5	.5	.4	.6	18	37	15	24	27	41	16	24	40	41	40	40
13	1.0	1.1	1.3	2.1	47	61	62	80	22	23	21	19	51	48	45	43
14	3.6	7.3	5.7	4.1	291	403	173	103	74	73	57	58	35	35	36	40
15	1.0	.7	.3	.4	87	58	6	9	40	25	1	5	43	47	45	47
16	2.1	2.3	1.2	1.6	123	186	93	136	29	39	30	45	35	35	32	32
17	1.1	.7	1.4	1.5	50	92	87	122	41	42	37	38	39	38	37	37
Mean	2.1	2.2	2.1	1.7	181	183	142	90	42	46	39	37	40	40	38	38
% of control		105	100	81		101	78	50		110	93	88		100	95	95
P value* (<)		NS	NS	NS		NS	.10	.10		.20	NS	NS		NS	.05	.20

C = Control (avg of 3-10 min. periods). D_1 = First 20 min. after drug administration (avg of 2-10 min. periods). D_2 = One hr after drug administration (avg of 2-10 min. periods). D_3 = 3 hr after drug administration (avg of 2-10 min. periods).

$$* \; t = \bar{x} \sqrt{\frac{n(n-1)}{Sx^2}}$$ (Sub-group C).

tion (decreased renal vascular resistance), was adequate ($p<0.01$) to compensate for the reduction in blood pressure. However, with prolonged hypotension, there was significant reduction in glomerular filtration rate and in renal blood flow ($p<0.05$). This was probably enhanced by the anesthesia and the fact that the ganglionic blockade persisted throughout the period of observation in contrast to hexamethonium, which is active for a much shorter period of time(2,3). The reduction in glomerular filtration rate was not accompanied by alterations in water and electrolyte excretion.

Clinical observations on acute responses to single doses (Group I): The average single dose which would reduce the blood pressure to approximately normotensive levels in the upright position when administered orally was 19 mg but the range was 5 to 40 mg. The duration of action varied from 12 to 48 hours with an average of 18 hours. There was a latent period of 20 to 70 minutes after parenteral administration of mecamylamine and 30 minutes to 2 hours after oral administration. Table III shows that the final response to equal oral and parenteral dosages was about the same. After an effective dose was given, increasing the dose had very little additional effect on the supine blood pressure but markedly enhanced and prolonged the upright pressure response.

Out-patient treatment of hypertension (Group II): For purposes of analysis, the 50 patients have been divided into 2 sub-groups on the basis of their upright control diastolic blood pressure. Sub-group I consisted of 9 patients with less severe hypertension, *i.e.*, their control upright diastolic blood pressure was greater than 100 but less than 120 mm Hg.

TABLE III. Summary of Data for Single Dosage Response to Mecamylamine in 12 Patients with Hypertension.

Patient		Control blood pressure Supine S	Supine D	Upright S	Upright D	Blood pressure max response Supine S	Supine D	Upright S	Upright D	Onset blood pressure reduction (min.)	Duration blood pressure reduction (hr)	Dose (mg)*	Route	Side effects	Renal disease	Ocular fundi†	Age
D.D.	A	188	122	182	120	132	78	102	72	60	14	10	Oral	0	0	III	59
J.H.	A	220	140	200	130	200	130	140	100	90	16	15	"	0	+++	II	47
B.N.	A	230	110	230	110	150	100	70	50	90	24	5	"	+++‡	+++	II	61
F.H.	A	170	110	160	100	140	100	140	100	90	24	5	"	0	0	I	59
C.A.	A	200	120	190	110	180	110	110	80	30	14	20	"	0	++	II	56
P.M.	A	230	130	210	120	188	108	138	90	90	12	40	"	++‡	+++	III	58
J.R.	A	188	122	190	120	160	110	120	70	90	16	25	"	++‡	+++	III	66
I.T.	A	222	162	228	158	178	109	122	78	120	12	30	"	0	+++	III	44
	B	230	158	226	156	170	107	128	72	70	14	30	Intramusc.	0	—	—	—
T.R.	A	198	138	192	128	132	76	112	82	30	48	10	Oral	0	0	II	38
	B	188	140	190	120	140	72	118	78	60	48	10	Intramusc.	0	—	—	—
K.C.	A	232	144	218	148	190	118	138	108	90	12	40	Oral	0	+++	IV	34
	B	250	154	238	150	178	112	146	104	60	16	40	Intramusc.	0	—	—	—
J.M.	A	198	110	190	115	140	80	120	78	30	12	15	Oral	0	++	II	60
	B	186	112	188	112	146	88	116	76	20	15	15	Intramusc.	0	—	—	—
L.T.	A	236	138	225	134	190	106	128	88	120	18	10	Oral	N & V	+	II	42
	B	236	136	256	137	225	110	160	100	30	16	10	Intramusc.	N & V	—	—	—

* This dose (established by titration in 5 mg increments) would repeatedly reduce the blood pressure to normotensive levels while standing.
† Keith-Barker-Wagener classification.
‡ Side effects consisted primarily of marked weakness and dizziness (BN) when standing.
S = Systolic blood pressure. D = Diastolic blood pressure.
A = Observations after oral administration. B = Observations after parenteral administration using same dose as A.

TABLE IV. Comparison of Blood Pressure Response—Mecamylamine, Hexamethonium and Pentolinium.

	+ Rauwolfia +					
	Mecamylamine		Hexamethonium		Pentolinium	
	No.	%	No.	%	No.	%
No. patients treated	50	100	75	100	75	100
Responsive	46	92	57	76	59	79
Normotensive	12	24	28	37	25	33
Unresponsive	4	8	18	24	16	21
Avg daily dose of responders	17 mg		2307 mg		341 mg	

Sub-group II consisted of 41 patients with more severe hypertension (*i.e.*, control upright diastolic pressures greater than 120 mm Hg). The criterion for response was a fall in the mean control blood pressure of 20 mm Hg or more, or a return to normotensive levels (<150/100 mm Hg) in the upright position. The overall response rate was 92% and 24% of the patients became normotensive on a total daily dose of 17 mg of mecamylamine. Of the 9 patients with control diastolic pressures less than 120 mm Hg but greater than 100 mm Hg (Sub-group I), 7 (78%) responded while 2 (22%) of these became normotensive on an average dose of 13 mg of mecamylamine daily. In sub-group II (control diastolic blood pressures greater than 120 mm Hg in the upright position), 39 (95%) of the 41 patients were responsive and 10 (24%) returned to normotensive levels on an average daily dose of 19 mg of mecamylamine. The fall in blood pressure was greatest in the upright position; however, there was also a significant reduction in the supine blood pressure.

It is difficult to evaluate the beneficial effects of blood pressure reduction due to the short period of treatment with mecamylamine. However, the most outstanding symptomatic improvements were relief of headaches and angina pectoris which were present in two-thirds of the patients prior to therapy. About one-half of the patients with congestive heart failure showed symptoms of improvement during this short course of treatment.

The most annoying side effects with mecamylamine were constipation, weakness and dizziness. Constipation was adequately controlled by the use of cathartics such as milk of magnesia, cascara, and mineral oil. Although constipation was not marked in most cases, it is a serious side effect and should be treated actively to prevent fecal impaction and ileus. After continued therapy for several weeks, this side effect either lessens or disappears in most patients. Weakness was present in 38% of the group. In most patients, this was not marked and was hard to evaluate. Dizziness was present in 40% at some time during the course of therapy. In some cases, this was due to excessive orthostatic hypotension although syncope was not observed. Dizziness was marked in 3 patients and in these it was probably due to over zealous treatment. Nausea was present at some time during the course of therapy in 10 (20%) of the patients but only 3 (6%) vomited. Several other less serious side effects such as blurred vision and dry mouth were observed in a number of the patients. Comparison of the side effects of therapy with mecamylamine and 2 other ganglionic blocking agents reveals that the major side effects of ganglionic blockade are qualitatively comparable with the 3 drugs.

Summary and conclusions. Mecamylamine produced the same cardiovascular and renal hemodynamic effects on dogs as have been previously observed with such autonomic blocking agents as hexamethonium and pentolinium. When given to patients with hypertension, it produced a consistent reduction in blood pressure which was most marked in the upright position. The effect was about equivalent when given orally as when given parenterally, the average daily dose being approximately 19 mg. The onset of action ranged from ½ to 2 hours, and lasted 12 to 48 hours. The response was quite variable from patient to patient, but within the same patient, it was reproducible, thus minimizing one of the chief objections to ganglionic blocking agents for the treatment of hypertension.

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Received September 7, 1955. P.S.E.B.M., 1955, v90.