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CARDIOVASCULAR AND RENAL RESPONSES TO THE COMBINATION OF HEXAMETHONIUM AND 1-HYDRAZINOPHTHALAZINE (APRESOLINE®) IN HYPERTENSIVE SUBJECTS¹

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1-Hydrazinophthalazine has been demonstrated to cause a fall in peripheral artery pressure, to possess slight adrenergic blocking properties, to increase renal plasma flow (1-8), and to cause a proportional increase in cardiac output (8). It has been stated that the cardio-stimulating effects of 1-hydrazinophthalazine are mediated *via* the autonomic nervous system, since they can be blocked by sympathectomy or ganglionic blockade (9, 10).

These cardiac stimulating qualities of 1-hydrazinophthalazine may account for many of the undesirable side effects reported. Angina (11, 12), electrocardiographic changes (9), and myocardial infarction (13), have been reported during clinical therapy of hypertension with this agent. Though such evidence is at best only circumstantial, the use of 1-hydrazinophthalazine alone would seem to be of somewhat questionable value, particularly in the many patients suffering from hypertension complicated by coronary artery disease.

However, if the above side effects could be prevented by the prior administration of a ganglionic blocking agent, the combined use of 1-hydrazinophthalazine and hexamethonium, first proposed by Schroeder (14), would represent a satisfactory combination: the hypotensive qualities of 1-hydrazinophthalazine would be enhanced, while the cardiac stimulating effects would be blocked.

The purpose of the present study was twofold: (a) to evaluate the cardio-vascular and renal adjustments to 1-hydrazinophthalazine in a group of hypertensive patients; (b) to retest these adjustments when a ganglionic blocking agent,

hexamethonium,² was administered just prior to the 1-hydrazinophthalazine.

MATERIAL AND METHODS

A total of eighteen patients with hypertension was studied. Three of these were thought to have hypertension secondary to renal disease, as determined by history and clinical evaluation. The remainder had "essential" hypertension.

A. Experiments utilizing 1-hydrazinophthalazine alone

Ten of the patients underwent a total of fifteen experimental studies with 1-hydrazinophthalazine alone. All were given the compound in rapid single intravenous doses of 0.20 to 0.50 mgm. per Kg. body weight. Repeated basal determinations of blood pressure and pulse were made before the 1-hydrazinophthalazine injection, and at intervals of 2 to 5 minutes thereafter for one to two hours.

1. *Renal clearance determination.* Renal plasma flow (C_{PAH}), and glomerular filtration rate (C_{IM}), were measured simultaneously in eight hypertensive patients by Smith's clearance techniques (15), but the data were not corrected for extraction values. The recorded data before administration of the drug represent the average of at least three successive urine collection periods of 12 to 20 minutes each. Following the administration of the drug, at least four similar successive urine collections were made.

2. *Hemodynamic studies.* Cardiac catheterization was performed in seven hypertensive patients after 1-hydrazinophthalazine. Five of these patients had renal clearance values determined just prior to the hemodynamic studies. Cardiac output was measured by the determination of oxygen consumption and A-V oxygen difference. Pulmonary and systemic arterial pressures were recorded by means of capacitance electromanometers or strain gauges.

B. Experiments utilizing hexamethonium and 1-hydrazinophthalazine

Ten of the patients underwent a total of seventeen experimental studies involving both these drugs.

² Hexamethonium (Esomid®) supplied by Ciba Pharmaceutical Products, Inc.

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1. *Renal clearance determination.* Using the same techniques, renal plasma flow and glomerular filtration rate were measured in nine patients before and after intravenous administration of 10 to 12.5 mgm. of hexamethonium ion, and again after the additional intravenous administration of 0.21 to 0.40 mgm. per Kg. of 1-hydrazinophthalazine. The latter drug was given within 45 to 60 minutes of the hexamethonium in each case. The clearance values represent the average of at least three 12 to 20-minute successive urine collections.

In one patient, T. G., the renal clearance determinations were measured simultaneously with the cardiovascular hemodynamic responses to the two drugs.

Only two of these nine patients had been studied before with 1-hydrazinophthalazine alone. Previous studies from this laboratory (8), however, would tend to indicate a fairly consistent renal response to this drug in hypertensive patients. In the previous series five of eight patients had responded with a significant rise in renal plasma flow following the 1-hydrazinophthalazine administration. (The other three patients had developed circulatory collapse.)

2. *Hemodynamic studies.* Using the techniques mentioned above, cardiac output and vascular pressures were obtained in patients before and after the administration of both hexamethonium and 1-hydrazinophthalazine. At least three determinations of cardiac output were made before and after the administration of each drug and were done at 10 to 15-minute intervals after stabilization of blood pressure readings. The 1-hydrazinoph-

thalazine was given within 30 to 45 minutes after the hexamethonium in each case.

It should be emphasized that the effects of the two hypotensive agents were additive and alarming degrees of hypotension were encountered even in the recumbent position when 0.5 mgm. per Kg. of 1-hydrazinophthalazine was administered following the hexamethonium. In fact, five of the ten patients studied with the two drugs developed circulatory collapse and shock (E. C., O. W., A. L. P., V. G., I. B.). Each received only a moderate dose of 1-hydrazinophthalazine. It was, therefore, not prudent to insist on a full dose of 1-hydrazinophthalazine. It was thought, however, that definite increase in renal blood flow and in cardiac output had been satisfactorily demonstrated even with suboptimal doses of 1-hydrazinophthalazine (8), and for these reasons, the results of the present study were considered to be interpretable.

RESULTS

A. Experiments using 1-hydrazinophthalazine alone

1. *Renal clearances.* Average values for renal plasma flow, glomerular filtration rate, and filtration fraction in eight patients before and after the 1-hydrazinophthalazine administration are recorded in Table I together with the maximal changes in pulse rate and blood pressure.

TABLE I
Changes in B.P., pulse rate, CP_{RH} , C_{IN} , and F.F. in eight hypertensive subjects following intravenous administration of 1-hydrazinophthalazine

PT.	AGE	SEX	DX	DOSAGE		B.P.	PULSE	CP_{RH}	% CHGE	C_{IN}	% CHGE	F.F.	COMMENTS
				MG/ML	MG								
C.E.	57	M	E.H.	.40	24	170/110 120/80	76 96	552 712	+29	98 85	-13	.18 .12	
S.W.	54	M	E.H.	.35	22	174/102 140/80	72 72	430 562	+30	93 74	-21	.21 .15	
O.S.	48	M	E.H.	.40	25	190/130 150/100	72 96	369 464	+23	88 89		.25 .20	
P.W.*	39	M	E.H.	.20	15	140/80 110/64	76 84	541 458*	-16	125 106	-15	.23 .23	*This patient had been on oral Apresoline for several months with good result (See Discussion)
F.B.	40	M	E.H.	.20	14	250/130 190/110	72 80	220 182	-17	58 55		.26 .30	
E.C.	62	F	E.H.	.35	22	210/140 **86/60	96 64	301 62	+80	82 11	-87	.27 .18	**Marked Shock like picture.
E.K.	44	M	E.H.	.40	24	230/150 140/70	80 96	74 36	-52	16 8	-50	.21 .22	
G.K.	46	M	E.H.	.21	15	170/100 170/90	80 90	23 22		13 22	+63	.59 .41	

LEGEND

E.H. = Essential Hypertension
R.H. = Renal Hypertension

Values for CP_{RH} (renal plasma flow) expressed in c.c./Min/1.73 M² B.S.A.

Values for C_{IN} (glomerular filtration rate) expressed in c.c./Min/1.73 M² B.S.A.

The uppermost figure in each pair of figures represents the control value. The other figure corresponds to the maximal change following the drug.

TABLE II

Changes in cardiovascular hemodynamics in seven hypertensive subjects following intravenous administration of 1-hydrazinophthalazine

PT	AGE	SEX	DOSAGE		C.O.	C.I.	% CHGE	PULSE	STR. VOL.	S.A.P.	P.A.P.
			MM/KILO	MM							
S.W.	54	M	.50	31	5.0	2.9	+119	60	82	190/110	25/8
					10.9	6.5		84	129	155/95	36/16
G.S.	48	M	.50	35	4.4	2.5	+127	84	52	210/140	26/5
					10.0	5.9		100	100	160/110	34/9
E.C.	62	F	.50	30	3.2	2.0	+25	86	37	260/150	30/12
					4.0	2.5		100	40	130/86	59/20
E.K.	44	M	.25	15	3.0	1.8	+73	60	50	230/126	25/4
					5.2	3.1		60	81	180/90	22/4
G.K.	46	M	.25	15	5.7	3.4	+44	80	71	180/110	44/22
					8.2	4.9		96	85	160/100	45/22
A.B.	34	M	.35	18	4.0	4.0	+82	76	52	215/140	30/16
					7.3	7.3		90	81	168/98	30/15
M.C.	49	F	.50	30	6.0	4.4	+18	76	79	180/100	26/14
					7.1	5.2		54	131	80/46	30/12

LEGEND

C.O. = Cardiac output in Litres/Min.
 C.I. = Cardiac output/M² B.S.A.
 STR. VOL. = Stroke volume
 S.A.P. = Systemic arterial pressure
 P.A.P. = Pulmonary arterial pressure

The uppermost figure in each pair of figures represents the control value.
 The other figure corresponds to the maximal change following the drug.

Four patients (G. S., C. E., S. W., P. W.) had normal or near normal resting values for renal plasma flow and glomerular filtration rate. Of these, three (G. S., C. E., S. W.) experienced an appreciable increase in renal plasma flow following intravenous injection of 1-hydrazinophthalazine. In the patient, P. W., renal plasma flow was observed to fall slightly after the drug had been administered. Either no change, or slight decline in glomerular filtration rate was noted in these four patients. In consequence, a decrease in the filtration fraction occurred in the three subjects who manifested a rise in renal plasma flow. In the other four patients (E. K., E. C., G. K., F. B.) control values for renal plasma flow and glomerular filtration rate were well below normal and none responded with an increase in renal plasma flow following the administration of the drug. Two of these patients (E. K., G. K.) had such extreme impairment of renal function that without correction for changes in extraction, the renal

clearance values are recognizably inaccurate. However, these patients were purposely studied to determine whether or not 1-hydrazinophthalazine might have the reported effect in the presence of severe renal impairment. One might expect such patients to be the ones most likely to benefit from an increased renal blood flow. One patient, E. C., had moderate reduction of renal plasma flow before administration of the drug, but an acute hypotensive episode followed the injection of the 1-hydrazinophthalazine. In this subject values for renal plasma flow suggested virtual cessation of flow during this period.

2. *Hemodynamic studies.* Table II presents the hemodynamic changes observed on seven hypertensive patients. The average of three resting levels of cardiac output is compared with the maximal response within two hours after the 1-hydrazinophthalazine.

Five of the seven hypertensive patients (S. W., G. S., E. K., G. K., A. B.) experienced an obvious

rise in cardiac output following the drug injection. None of these patients had ever revealed clinical evidence of heart failure. All responded with a moderate decrease in arterial pressure with a concomitant rise in pulse rate. Only in one patient, G. K., was the mean pulmonary artery pressure elevated at rest and this level was not influenced by 1-hydrazinophthalazine.

The other two patients (M. C., E. C.) did not demonstrate as striking a rise in cardiac output, although optimal doses of the agent were given. Both had recently exhibited evidence of heart

failure. Another probable reason for the different responses in these two patients is that both of them developed hypotension with symptoms of shock. In E. C., who developed this shock-like state following the injection of .5 mgm. per Kg. of 1-hydrazinophthalazine, a marked rise in mean pulmonary artery pressure occurred, suggesting either an episode of acute left ventricular failure or pulmonary venous spasm, or both. She recovered promptly and without treatment except oxygen inhalation. This same subject developed an identical state of collapse when given a

TABLE III

Changes in renal plasma flow (C_{PAH}), glomerular filtration rate (C_{IN}), and filtration fraction (F.F.) following single intravenous injections of Hexamethonium and 1-hydrazinophthalazine (at 45-60 minute intervals).

PT.	AGE	SEX	DX	DOSAGE		C _{PAH}	% CHGE	C _{IN}	% CHGE	F.F.	S.A.P.	PULSE
				HEXAM.	HYDRAL							
G.S.	48	M	E.H.	12.5		332		85		.17	190/130	68
						280	-21	69	-16	.20	155/110	68
					.25	415	+25	75	-12	.18	140/100	76
E.C.	62	F	E.H.	10		294		81		.27	220/108	66
						239	-19	72	-11	.30	180/100	56
					.28	298	NIL	69	-15	.23	150/80	80
A.P.	49	M	E.H.	12.5		534		121		.23	170/110	80
						444	-18	88	-27	.20	170/100	92
					.21	926	+73	124	NIL	.14	140/80	88
C.R.	46	M	E.H.	12.5		516		157		.30	170/110	80
						350	-32	84	-47	.24	140/100	96
					.25	716	+39	148	NIL	.20	134/94	96
M.C.	49	F	E.H.	10		300		52		.17	200/100	60
						238	-21	49	NIL	.20	180/80	76
					.25	210	-30	42	-17	.20	154/74	88
O.W.	65	F	E.H.	12.5		451		113		.25	210/110	72
						380	-16	80	-30	.21	160/100	80
					.25	282*	-37	52*	-54	.18	96/60	80
A.L.P.	61	M	E.H.	12.5		299		67		.22	180/100	64
						303	NIL	60	NIL	.20	170/100	64
					.27	267	-11	40	-40	.15	120/70	68
T.G.	46	M	E.H.	12.5		360		100		.29	190/130	72
						490	+38	145	+45	.29	175/115	76
					.40	425	+18	94	-6	.22	150/100	80
I.B.	56	F	E.H.	12.5		306		85		.28	180/110	68
						234	-24	54	-36	.23	170/90	76
					.30	290	-5	53	-36	.18	90/70	80

LEGEND

E.H. - Essential hypertension
 HEXAM - Hexamethonium
 HYDRAL - 1-Hydrazinophthalazine
 S.A.P. - Systemic arterial pressure

All Values for C_{PAH} and C_{IN} Expressed as cc/Min/1.73 Square Meters Body Surface Area.
 (The uppermost figure of each group of three represents the control value. The second figure represents the change after hexamethonium and the third figure, the change following 1-hydrazinophthalazine.)

* Shock-like State Present.

TABLE IV

Changes in cardiovascular hemodynamics following single intravenous injections of Hexamethonium and 1-Hydrazinophthalazine in six hypertensive subjects (Injections 30-45 minutes apart).

PT.	AGE	DOSAGE		C.O.	C.I.	% CHGE	PULSE	STR. VOL.	S.A.P.	P.A.P.
		HEXAM. MG	HYDRAZ. MG/KG							
G.S.*	48	12.5	.40	5.3	3.0		64	83	170/120	25/5
				4.8	2.7		76	63	148/108	27/7
				4.6	2.6		72	64	150/90	29/9
G.S.*	48	12.5	.50	4.1	2.3		60	68	180/125	28/18
				3.8	2.2		84	45	170/107	22/5
				6.1	3.5	+ 48	100	61	125/70	26/17
E.G.	62	10	.30	2.1	1.3		66	32	190/110	35/14
				2.1	1.3		60	35	160/96	33/17
				2.5	1.5		66	38	140/90	34/14
A.P.**	49	10	.22	7.9	4.1		86	92	155/100	30/12
				7.1	3.7		92	77	120/80	18/10
				7.7	4.0		96	80	120/70	21/11
A.P.**	49	10	.40	6.8	3.7		90	75	185/120	15/5
				6.0	3.4		96	62	150/85	18/6
				5.6	2.9		76	74	80/50	25/15
A.L.P.	62	10	.20	4.1	2.2		76	54	150/100	25/7
				4.6	2.4		76	61	145/90	27/8
				4.5	2.4		68	66	110/70	20/7
T.O.	46	12.5	.40	5.8	2.7		64	90	180/120	34/15
				5.2	2.4		90	58	165/110	25/10
				8.2	3.8	+ 40	76	100	125/70	25/10
V.O.	47	12.5	.40	6.3	2.95		80	79	185/100	40/15
				6.2	2.9		84	74	140/80	28/10
				***			66		80/60	

* - Same patient

** - Same Patient

*** - Severe shock. Procedure discontinued

LEGEND

HEXAM - Hexamethonium ion
 HYDRAZ - 1-Hydrazinophthalazine
 C.O. - Cardiac output in litres/min.
 C.I. - Cardiac index in litres/min/M² body surface area
 STR. VOL. - Stroke volume
 S.A.P. - Systemic arterial pressure
 P.A.P. - Pulmonary arterial pressure

The uppermost figure of each group of three represents the control value. The second figure represents the change after hexamethonium and the third figure, the change following 1-hydrazinophthalazine.

slightly smaller dose of the drug during evaluation of her renal function.

B. Experiments using 1-hydrazinophthalazine and hexamethonium in combination

Approximately 10 to 12.5 mgm. of hexamethonium were required in each case to produce autonomic blockade with a moderate reduction of the supine blood pressure. With this fall in blood pressure, little or no reflex rise in pulse

rate was observed. The rise in pulse rate usually associated with 1-hydrazinophthalazine effect was absent when the hexamethonium had been administered first. This, we assumed, indicated at least some degree of blockade of sympathetic ganglia.

1. *Renal clearances.* Table III presents the changes in glomerular filtration rate and renal plasma flow (average of at least three samples), before hexamethonium, within 45 to 60 minutes

after hexamethonium and then within 60 to 75 minutes after 1-hydrazinophthalazine. Most of these nine patients experienced a slight fall in renal plasma flow and glomerular filtration rate following hexamethonium administration. These changes occurred simultaneously with a fall in blood pressure and have been reported previously (16-18). Following the 1-hydrazinophthalazine injection, only three of the patients (G. S., A. P., C. R.), experienced a significant rise in renal plasma flow. In these patients the control renal plasma flow levels were normal or nearly normal. In one patient (O. W.) the resting renal plasma flow was normal. However, on administration of the 1-hydrazinophthalazine, this patient became severely hypotensive and, like E. C., developed a shock like picture with further reduction of renal clearance values. No tachycardia was noted during the hypotensive period in any of these patients.

The remainder of the patients (M. C., E. C., A. P., T. G., I. B.) had reduced renal plasma flow prior to the drug injections. In one of these patients (E. C.) renal plasma flow fell slightly after the 1-hydrazinophthalazine and it did not change significantly in the remaining subjects.

It would seem, therefore, that patients capable of increasing renal plasma flow may do so and that this effect following 1-hydrazinophthalazine may not be blocked by hexamethonium in the range of dosage given. The blood pressure changes in the patients studied after the one drug and in those studied after the two drugs were comparable.

2. *Hemodynamic studies.* Table IV represents the cardiovascular adjustments observed in eight experiments on six hypertensive patients who were given both hexamethonium and 1-hydrazinophthalazine.

All patients experienced a fall in arterial pressure with little change in pulse rate. Two of the patients (A. L. P., V. G.) developed alarming hypotension lasting 3 to 4 hours after the 1-hydrazinophthalazine was given within 30 to 45 minutes of the hexamethonium. The expected rise in cardiac output following administration of 0.2 to 0.5 mgm. per Kg. of 1-hydrazinophthalazine was blocked, although incompletely in two patients (G. S. and T. G.) who received maximal doses of this drug. No changes in pulmonary artery pressure occurred. Two patients (G. S. and

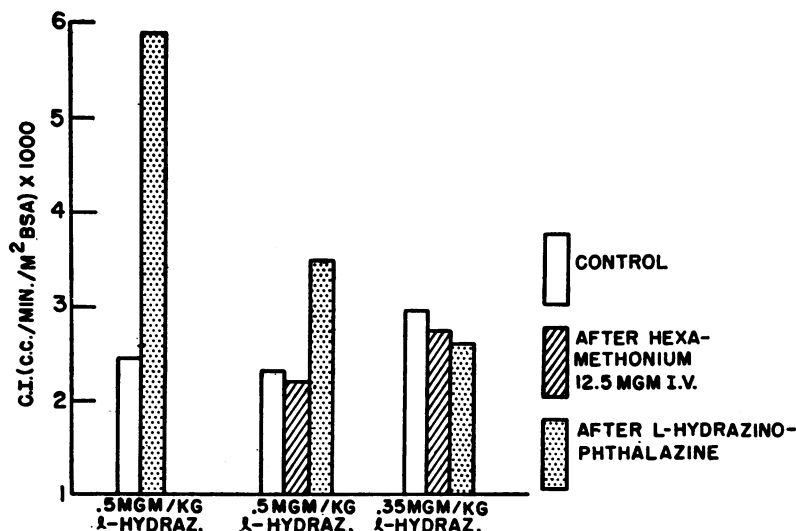


FIGURE 1

This 48-year-old male (G. S.) received a .5 mgm. per Kg. of 1-hydrazinophthalazine, i.v., which resulted in a striking increase in cardiac output. This effect could be partially blocked by hexamethonium. No increase in cardiac output was noted when the dose of 1-hydrazinophthalazine was slightly reduced after hexamethonium had been given. Injections of as little as 0.20 mgm. per Kg. of 1-hydrazinophthalazine always resulted in an appreciable elevation of cardiac output, (8), when not preceded by the administration of an autonomic blocking agent.

A. P.), were studied twice with different doses of the 1-hydrazinophthalazine each time. This was to demonstrate that within the dose range used the cardio-stimulating properties of 1-hydrazinophthalazine are blocked nearly completely by the hexamethonium.

Figure 1 records these changes in one hypertensive patient (G. S.) studied on three different occasions, first with 1-hydrazinophthalazine alone, then when hexamethonium was given prior to .5 mgm. per Kg. of 1-hydrazinophthalazine, and on a subsequent occasion when .35 mgm. per Kg. of 1-hydrazinophthalazine was administered after the hexamethonium.

DISCUSSION

1-Hydrazinophthalazine (Apresoline®) has been shown by several observers to increase renal plasma flow and cardiac output while reducing systemic arterial pressure (1-7). It has been suggested that these effects may also occur with oral administration of the drug (9).

The mechanism whereby these changes are produced is not clearly understood. It was thought that the increased renal plasma flow represented but another manifestation of the increased cardiac output (8). However, when the rise in cardiac output is partially or completely prevented by prior administration of a ganglionic blocking agent, the renal plasma flow may still increase in response to the 1-hydrazinophthalazine. This then may indicate that 1-hydrazinophthalazine has a selective effect on renal vessels which is independent of the level of cardiac output.

There is some evidence suggesting that only patients with relatively normal renal function are capable of responding to 1-hydrazinophthalazine by an increase in renal plasma flow. The patients with moderate or severe decrease in renal function did not experience a rise in estimated renal plasma flow following this drug. One might surmise that these subjects were incapable of responding to the drug by an increase in renal plasma flow because of irreversible vascular pathology.

While an increased renal plasma flow was associated in each case with a blood pressure decline, patients who developed severe hypotension invariably had a very marked fall in renal plasma flow regardless of the resting clearance level.

The lack of renal response to 1-hydrazinophthalazine given intravenously to a patient who had been receiving the drug orally for a long time (P. W., Table I) has been noted previously by Moyer (9). Here one might postulate that the oral medication had already resulted in a maximal renal-vascular response or that the patient had become insensitive to the drug.

In the patients receiving hexamethonium first, then 1-hydrazinophthalazine, the same theoretical mechanisms would seem to operate. Though the number of patients studied is too small to draw definite conclusions it is suggestive that only those patients with normal, or nearly normal, resting renal plasma flow were able to significantly increase their flow rates. 1-Hydrazinophthalazine, when administered parenterally, increases cardiac work by increasing cardiac output, even in the face of a decline in blood pressure. This, it appears, is true for normal subjects as well as for patients with systemic arterial hypertension. It has been noted with doses as low as 0.20 mgm. per Kg. We have observed that these properties of 1-hydrazinophthalazine can be blocked by prior administration of a small amount of hexamethonium given intravenously. The combination of the two drugs necessitated small doses of hexamethonium and in some instances doses of 1-hydrazinophthalazine which were smaller than those given to other subjects who had not been primed with hexamethonium. In all instances, however, dosages were given that remained within the effective level or which had produced effects in the same patient previously. The partial or complete blocking of the rise in cardiac output by a ganglionic blocking agent would indicate that these actions of 1-hydrazinophthalazine are mediated over the sympathetic nervous pathways.

This study may then offer a rational basis for such a therapeutic combination of drugs as has been proposed (11, 12, 14, 19, 20). The hypotensive effects are greater, the increase in renal plasma flow (when possible) still occurs, but the increase in cardiac output and cardiac work is partially or completely blocked. No information is available which would explain the observed increase in cardiac output following 1-hydrazinophthalazine and the blocking of this effect by hexamethonium. Following 1-hydrazinophthalazine widespread vasodilation of the arteriolar bed

seems to take place resulting in a decrease of total peripheral resistance in the face of increased total flow. Whatever mechanisms come into play, central, venomotor, or cardiac, they may perhaps be considered compensatory. Their interference by hexamethonium suggests that they are linked to the autonomic nervous system.

SUMMARY AND CONCLUSIONS

Eighteen hypertensive patients were studied in order to evaluate the renal and cardiovascular adjustments to 1-hydrazinophthalazine when given alone and after the administration of hexamethonium. The following observations were made:

1. 1-Hydrazinophthalazine seems to increase renal plasma flow only in patients with normal or nearly normal resting renal plasma flow.

2. The prior administration, parenterally, of a moderately hypotensive dose of hexamethonium, did not alter the ability of 1-hydrazinophthalazine to increase renal plasma flow in some patients.

3. 1-Hydrazinophthalazine caused an increase in cardiac output in all patients to whom it was given.

4. The prior administration of hexamethonium was capable of blocking the rise in cardiac output following the 1-hydrazinophthalazine.

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