EFFECT OF DOPA ON THE CATECHOLAMINE CONTENT OF DOG HEART AFTER HEMORRHAGIC HYPOTENSION

YUICHI HASHIMOTO* AND HELMUT LYDTIN**

Department of Pharmacology, Medical College of Georgia, Augusta, Georgia, U.S.A.

Received for publication June 24, 1965

It has been noted that there is evidence of myocardial failure following the reinfusion of blood into animals after hemorrhagic hypotension (1-3). Glaviano and Coleman have shown in rabbits that the norepinephrine content of the left ventricle was markedly decreased and its epinephrine content increased after hemorrhagic hypotension. They suggested that myocardial failure after hemorrhagic hypotension could be due to norepinephrine depletion in the heart (4). Gomerz and Hamilton (5, 6) were unable to show cardiac failure immediately after the hypotensive period, but 40 to 120 minutes later the heart showed signs of damage if the blood pressure was kept at a normotensive level. Therefore, it seemed advisable to investigate the successive changes in the catecholamine content of the heart after subjection to hemorrhagic hypotension and also to study the effect of DOPA infusion on the myocardial catecholamine content after hemorrhagic hypotension.

It is well known that there is a marked increase in the release of epinephrine and norepinephrine from the sympathoadrenal system during hemorrhagic hypotension (7-9). This may play an important role in producing vasoconstriction, causing irreversible tissue damage and then deterioration of cardiac efficiency (10, 11). Therefore, it is understandable that adrenergic blocking agents protect animals from the fatal outcome caused by hemorrhagic hypotension.

The present experiments were also designed to determine if pretreatment with dibenzylamine had an effect on myocardial catecholamine synthesis and/or storage in the heart after hemorrhagic hypotension, and further if this compound protected the tissues from damages in shock.

METHODS

Fifty-two mongrel dogs of both sexes, weighing 13 to 20 kg, were used. They were anesthetized with 5 mg/kg morphine followed by 20 mg/kg sodium pentobarbital. The right femoral artery and vein were cannulated for bleeding and retransfusion. Pressures

橋本 裕一

Present address : * Department of Pharmacology, Faculty of Medicine, Osaka University, Kita-ku, Osaka, Japan.

** Medizinische Poliklinik der Universität München (Munich), Germany.

A preliminary report of this work appeared in the *Pharmacologist* ; 5, (2), 257, 1963.

in the left femoral artery and right atrium were monitored via catheters attached to Statham strain gauges on DR 8 recorder from Electronics for Medicine. Then half the animals received a 20 minutes infusion of 100 ml of normal saline containing 1 mg/kg dibenzylamine. About 10 minutes after the infusion, artificial respiration was begun via an intratracheal tube. The chest was opened in the midline and a myocardial sample of about 1 gram was taken from the right ventricle. Half the dogs were bled rapidly into a reservoir containing heparin until the mean arterial pressure reached 35 ± 5 mm Hg, and then the pressure was maintained at this level for 90 minutes or in some animals for 180 minutes. At the end of these periods the blood was retransfused into the animals over a 5 minutes period, and during the following 10 minutes, a second myocardial sample was taken from the right ventricle. After 30 minutes the animals were sacrificed

FIG. 1. Experimental groups.

() : Number of dogs.

FIG. 2. Scheme of procedure.

S : Sample, LV : Left ventricle, RA : Right atrium, LA : Left atrium.

and myocardial samples were taken from all four chambers. Care was taken that the samples came from the same topographical regions. During the 30 minutes period after the retransfusion, a 20 minutes infusion of 10 mg/kg DOPA was given to half the animals. Control groups were treated in exactly the same way except that they were not subjected to hemorrhagic hypotension. Figs. 1 and 2 give a summary of the procedure.

Total norepinephrine and epinephrine content was determined by the trihydroxyindole method. Exactly 1 gram of each sample was homogenized with sand and extracted with 0.4 N perchloric acid. The catecholamines in the tissue extract were adsorbed on aluminum hydroxide and passed through a CG-50 resin column to remove DOPA. Eluates from this column were analyzed according to the modified trihydroxyindole method. The trihydroxyindole fluorescence due to total norepinephrine and epinephrine at 410 m μ was measured at 540 m μ in a Farrand fluorometer. The total norepinephrine and epinephrine content was expressed as microgram of norepinephrine per gram of cardiac tissue, and is called the catecholamine content in this paper. Preliminary tests

TABLE 1. Initial and later bleeding volumes of hypotensive dogs with and without dibenzyline treatment.

	Dog No.	Weight (pound)	Weight (kg)	Initial bleeding volume	ml/kg	Later bleeding volume	ml/kg
Without dibenzyline	6	29	13.1	300	22.9	530	40.5
	7	38	17.2	—	—	—	—
	8	32	14.5	—	—	—	—
	10	32	14.5	450	31.0	600	41.5
	11	32	14.5	350	24.2	700	48.3
	12	40	18.1	—	—	—	—
	13	39	17.7	600	33.9	750	42.5
	21	34	15.4	275	17.9	400	26.0
	23	42	19.0	400	21.0	500	26.4
	25	37	16.8	410	24.4	580	34.6
	32	32	14.5	180	12.4	180	12.4
	35	30	13.6	300	22.0	540	39.7
With dibenzyline	36	34.5	15.7	290	18.5	430	27.4
	37	37	16.8	0	0	25	1.48
	39	40	18.1	390	21.5	700	38.8
	41	45	21.0	200	9.5	500	13.8
	43	35	15.9	200	12.6	450	27.3
	46	34	15.4	0	0	220	14.3
	48	44	20.0	200	10.0	530	26.5
	50	32	14.5	150	10.4	450	31.0
	52	33	15.0	430	28.7	640	42.7
	56	31	14.1	60	4.3	290	20.6
	57	28.5	12.9	200	15.5	420	32.6
	58	31	14.1	140	9.9	300	21.2
	60	36.5	16.6	280	16.9	600	36.2

showed that the epinephrine content was less than 10% of the norepinephrine content. Statistical analysis of data was done according to the Students t-test. Significant differences were given at levels of 5% or less than 5%.

RESULTS

Table 1 and Fig. 3 showed the bleeding volume at early and late stages of the hypotensive period in dogs with and without dibenzyline pretreatment. The initial bleeding volume was markedly lower in the dibenzyline pretreated animals. The same relation can be seen at the end of the hypotensive period. In both groups, the final bleeding volume was larger than the initial one.

FIG. 3. Comparison of the initial and later bleeding volumes of hypotensive dogs with and without dibenzyline treatment.

The close correlations between of the catecholamine contents of the right and left ventricle in paired observations (see Table 2) are shown in Fig. 4. Therefore, it was felt that changes in the catecholamine content of the right ventricle are representative of that in the left ventricle.

The successive changes in the right ventricular catecholamine contents are given in Table 2 and Fig. 5, the vertical bar on the left in Fig. 5 shows the standard deviation of sample 1, and indicates the wide scatter of normal values for the catecholamine content of the heart in dogs when the chest is opened. The observed values ranged from 0.274 to 1.53 $\mu\text{g/g}$ cardiac tissue.

There is significant increase in cardiac catecholamine content between sample 1 and sample 2, both in control and hypotensive animals, which is small in comparison with

TABLE 2. Successive changes of the catecholamine contents of control and hypotensive dogs.

	Dog No.	Weight (pound)	S ₁ (μ g/g)	S ₂	S ₃	LV	RA	LA
Control + saline	15	30	0.498	0.596	0.590	0.560	1.83	1.88
	16	35	0.486	0.670	0.609	0.613	1.42	1.92
	18	32	0.912	0.940	0.940	0.829	2.06	2.06
	19	33	0.624	0.705	0.572	0.646	1.54	1.83
	20	43	0.736	0.733	0.521	0.623	1.54	1.68
	31	36	0.488	0.851	0.845	0.880	2.14	2.22
Control + DOPA	4	41	1.530	1.490	1.710	1.280	2.63	3.70
	5	38	0.456	0.554	0.536	0.457	0.980	1.25
	14	44	0.816	0.833	1.120	1.120	2.12	3.32
	22	34	0.914	1.070	1.400	1.320	4.85	4.26
	26	37	0.510	0.716	0.795	0.905	2.63	2.10
	33	35	0.560	0.794	0.840	0.703	1.80	2.42
Hypotension + saline	10	32	0.274	0.420	0.362	0.326	0.918	1.52
	11	32	0.900	1.370	1.310	0.090	4.55	4.76
	12	40	0.865	0.996	1.030	1.100	3.48	4.43
	23	42	0.594	0.730	0.600	0.580	1.70	1.58
	25	37	0.916	0.930	0.895	0.507	2.25	1.82
	32	32	1.006	1.150	1.060	0.925	3.10	3.08
Hypotension + DOPA	6	29	0.435	0.619	0.631	0.569	2.32	2.12
	7	38	0.466	0.825	0.780	0.516	1.68	2.03
	8	32	1.060	1.070	1.120	1.060	3.26	3.17
	13	39	1.100	1.100	1.200	1.090	3.02	3.50
	21	34	0.880	0.905	0.955	0.790	2.38	2.38
	35	30	0.985	1.062	0.912	0.895	2.81	2.88

S : Sample, RA : Right atrium, LV : Left ventricle, LA : Left atrium.

the standard deviation of the normal values. A significant increase in myocardial catecholamine content was found between samples 2 and 3 only in the control dogs infused with DOPA. On the other hand, a small but significant decrease in cardiac catecholamine content was observed between samples 2 and 3 only in the hypotensive dogs which were not treated with DOPA. There was also a significant difference between the myocardial catecholamine contents of the control and hypotensive animals treated with DOPA, but no significant difference between the decrease in catecholamine content in the control and hypotensive dogs which were not treated with DOPA.

Table 3 and Fig. 6 showed the same relations in the experimental groups pretreated with dibenzyline. There was no significant difference in the cardiac catecholamine contents of sample 1 and sample 2 in either the control or hypotensive animals, and after DOPA treatment there was also no significant difference between samples 2 and 3 in both control and hypotensive animals. However, a significant decrease was observed in both control and hypotensive dogs without DOPA treatment. There was

FIG. 4. Comparison of the left and right ventricular catecholamine contents of dogs.

FIG. 5. Successive changes of the catecholamine contents of the right ventricle of control and experimental dogs without dibenzylamine treatment.

TABLE 3. Successive changes of the catecholamine contents of control and hypotensive dogs with dibenzylamine treatment.

	Dog No.	Weight (pound)	S ₁ (μ g/g)	S ₂	S ₃	LV	RA	LA
Control + saline	38	35	0.690	0.670	0.681	0.660	2.50	2.36
	42	33	1.260	1.190	1.040	0.973	4.08	4.00
	47	36	0.702	0.699	0.661	0.655	2.20	2.82
	51	39	0.774	0.770	0.706	0.724	2.35	2.31
	55	32	1.050	1.230	1.150	0.875	2.77	3.52
	61	38	0.782	0.678	0.560	0.644	2.73	2.50
Control + DOPA	40	32	0.913	0.958	0.999	1.020	3.46	2.96
	45	29	0.892	0.905	0.915	0.932	3.15	3.16
	49	31	0.865	0.853	0.927	0.922	3.62	3.83
	53	31	1.248	1.160	1.338	1.165	2.95	3.30
	54	32	1.430	1.400	1.320	1.350	3.12	3.19
	59	37.5	0.608	0.607	0.789	0.750	1.81	2.74
Hypotension + saline	37	37	0.789	0.785	0.868	0.865	2.30	2.59
	41	45	1.280	1.300	1.140	1.030	4.35	3.18
	46	34	0.741	0.665	0.545	0.476	1.94	2.74
	50	32	0.588	0.675	0.580	0.610	1.91	2.28
	57	28.5	0.821	0.996	0.824	0.820	2.06	2.55
	60	36.5	0.766	0.660	0.540	0.564	1.62	2.52
Hypotension + DOPA	36	34.5	0.394	0.410	0.631	0.524	1.73	2.41
	39	40	0.735	0.700	0.815	0.775	0.93	1.44
	43	35	1.330	1.290	1.100	1.150	3.03	2.60
	48	44	0.771	0.854	0.756	0.763	3.61	3.88
	52	33	0.794	0.799	0.835	0.858	2.16	2.97
	56	31	0.386	0.442	0.552	0.547	1.68	1.66
	58	31	0.377	0.375	0.556	0.559	1.57	1.84

S : Sample, RA : Right atrium, LV : Left ventricle, LA : Left atrium.

also no significant difference between the decrease in the control and the hypotensive animals without DOPA treatment, and also between the increase in the control and the hypotensive animals with DOPA.

Tables 4 and 5, and Fig. 7 show the arterial blood pressures during the experiments. The difference between the arterial pressure after sample 2 and before sacrifice was compared. There is a statistically significant fall of arterial pressure with and without dibenzylamine pretreatment in hypotensive animals which received DOPA. There was no significant difference in this DOPA induced fall in arterial pressure in hypotensive animals with and without dibenzylamine pretreatment. Therefore, dibenzylamine does not have any effect on this fall in arterial blood pressure. During the same period the right atrial blood pressure was not found to change appreciably.

Fig. 8 summarizes the relation between arterial blood pressure and right ventricular catecholamine in sample 2 and sample 3. DOPA increased the catecholamine content

FIG. 6. Successive changes of the catecholamine contents of the right ventricle of control and experimental dogs with dibenzyline treatment.

in control animals but had little or no effect on their arterial blood pressure. However, it increased the catecholamine content of hypotensive animals less and caused a larger decrease of arterial pressure than in controls. Without DOPA only the catecholamine content of hypotensive animals showed a significant decrease, whereas the arterial blood pressure did not change significantly. Pretreatment with dibenzyline had essentially no effect on this relation. However, without DOPA, the catecholamine content decreased significantly in both control and hypotensive animals though the arterial blood pressure did not decrease significantly.

DISCUSSION

Significant increases in the survival rate of animals subjected to various types of shock have been demonstrated and discussed using many different drugs and procedures to induce vasodilation (12). For example, dibenzyline, which is an adrenergic blocking agent, was found to prevent death of animals in a state of shock. Some investigators ascribed this protective effect of dibenzyline to a reduction in the bleeding volume which could be withdrawn for maintaining the blood pressure at a required hypotensive level. This explanation is controversial, but seems to be supported by our data. Reduction in the bleeding volume could protect vital organs from severe damage.

TABLE 4. Change of arterial blood pressure (mean) in control and experimental dogs.

	Dog No.	Weight (pound)	Before S ₁ (mmHg)	Hypotension	Before S ₂	Beginning of DOPA infusion	Before sacrifice
Control + saline	15	30	87.0	—	102.0	93.8	99.4
	16	35	112.8	—	95.6	90.8	88.3
	18	32	—	—	87.0	96.0	99.0
	19	33	93.0	—	105.0	102.0	105.0
	20	43	115.0	—	123.0	105.0	108.0
	31	36	—	—	—	80.0	75.0
Control + DOPA	4	41	100.0	—	105.0	100.0	87.5
	5	38	80.0	—	75.0	62.5	70.0
	14	44	87.5	—	78.0	64.1	56.8
	22	34	75.0	—	62.7	48.7	42.0
	26	37	91.6	—	89.8	81.0	74.6
	33	35	—	—	—	78.2	75.5
Hypotension + saline	10	32	—	—	—	75.0	70.5
	11	32	78.6	41.0	83.8	83.8	77.5
	12	40	112.0	50.0	97.5	80.0	50.0
	23	42	102.3	37.9	72.6	71.5	59.2
	25	37	66.8	37.5	88.5	84.0	93.5
	32	32	—	—	—	71.5	39.6
Hypotension + DOPA	6	29	115.0	37.5	—	46.9	30.0
	7	38	135.0	35.0	100.0	94.0	33.0
	8	32	—	54.0	—	65.0	31.0
	13	39	105.0	38.2	—	84.0	54.3
	21	34	—	35.6	80.3	44.6	24.8
	35	30	—	—	—	76.3	50.9

Left ventricular biopsy was technically almost impossible, because ventricular fibrillation occurred, followed by death. However, the correlation found between the left and right ventricular catecholamine contents made it possible to use the catecholamine content of the right ventricle as an indicator of the change in that of the left ventricle. So, right ventricular biopsy was made. These operations induced almost no physiological changes in the arterial blood pressure or right atrial blood pressure. The significant increases observed in the myocardial catecholamine contents of both hypotensive and control animals during the 90 minutes experimental period might be due to severe stress caused by the experimental procedures rather than to hemorrhagic hypotension. The absence of a significant difference between the values of the control and hypotensive animals supports this explanation. This increase in myocardial catecholamine content was due to increased plasma epinephrine released from the adrenal medulla (7-9).

These increases were prevented by pretreatment with dibenzylamine. The explanation for this may be as follows: 1) The bleeding volume was reduced so that there was not a severe shock, which induces an increase in plasma epinephrine. 2) Binding of epinephrine to cardiac tissue was inhibited. Further experiments are required to solve this

TABLE 5. Change of arterial blood pressure (mean) of control and experimental dogs with dibenzylamine treatment.

	Dog No.	Weight (pound)	Before S ₁ (mmHg)	Hypotension	Before S ₂	Beginning of DOPA infusion	Before sacrifice
Control + saline	38	35	83.0	—	55.9	45.2	50.9
	42	33	85.8	—	67.9	72.2	71.5
	47	36	53.0	—	58.0	60.6	61.5
	51	39	86.0	—	86.5	73.6	71.3
	55	32	75.0	—	66.3	66.0	71.5
	61	38	87.0	—	105.5	103.0	100.0
Control + DOPA	40	32	67.5	—	66.8	64.4	61.9
	45	29	60.0	—	63.0	58.1	63.9
	49	31	61.2	—	68.5	62.4	62.4
	53	31	54.1	—	53.0	51.1	31.5
	54	32	69.7	—	78.6	71.5	98.2
	59	37.5	89.0	—	78.5	83.5	70.0
Hypotension + saline	37	37	87.6	32.2	45.2	31.1	28.8
	41	45	53.6	38.2	90.0	79.0	65.4
	46	34	45.3	37.6	51.2	55.5	42.7
	50	32	50.3	31.3	95.3	55.0	47.3
	57	28.5	54.3	34.8	81.6	61.6	48.8
	60	36.5	—	—	102.0	78.3	93.9
Hypotension + DOPA	36	34.5	73.0	37.8	—	48.9	38.8
	39	40	96.9	38.3	98.1	93.9	69.3
	43	35	75.5	37.2	83.6	78.5	36.0
	48	44	68.5	34.2	86.1	60.0	45.4
	52	33	68.0	36.5	95.1	84.5	50.0
	56	31	60.3	33.5	72.5	53.0	15.7
	58	31	51.0	36.0	61.0	54.0	42.0

problem.

DOPA caused a significant increase in the cardiac catecholamine content of control animals but not in that of hypotensive animals. This difference may be due to a metabolic change during hemorrhagic hypotension. Tissue anoxia especially may cause serious disorders in metabolic processes in various organs. The chief of these have been reported to be glycogen breakdown, dephosphorylation of glucose and reduced production of ATP in the mitochondria (13). Thus, it is conceivable that there is a disturbance of synthesis of myocardial norepinephrine from DOPA in hypotensive animals. In addition, ionic imbalance, changed pH in the tissues, and fluid shift may also lead to deterioration of enzymes during hypotensive shock (14).

However, in preliminary experiments it was observed in dogs subjected to prolonged hemorrhagic hypotension that the decreased myocardial norepinephrine was increased to the normal level after DOPA infusion (15). This increase was suggested to be due to *de novo* synthesis in the heart, because Chidsey *et al.* reported that synthesis of nor-

FIG. 7. Difference between the arterial blood pressures of control and experimental dogs "after sample 2" and "before sacrifice".
I ; Standard error of mean difference.

epinephrine from DOPA was observed in isolated dog heart (16). Therefore, in addition to some disturbance in myocardial norepinephrine synthesis, it was suggested in this experiment that the almost complete absence of an increase in the myocardial catecholamine content of hypotensive dogs following DOPA injection was also due to disorders in the myocardial norepinephrine storage mechanism in the heart.

After pretreatment with dibenzylamine, DOPA did not cause a significant increase in the myocardial catecholamine content of either hypotensive or control animals. Without DOPA, myocardial catecholamine in both the control and hypotensive animals decreased significantly during a 30 minutes period after retransfusion of blood when the arterial blood pressure was kept at the normotensive level. There have been no reports showing that dibenzylamine has any effect on norepinephrine synthesizing enzyme systems. However, it has been reported that dibenzylamine blocks the uptake of released norepinephrine at receptive sites in the splenic nerve of the cat (17). Therefore, our data might be interpreted in the following way. Normally DOPA is converted to dopamine, which is then taken up and stored in the small particles (18, 19), but dibenzylamine inhibits the uptake of dopamine by such particles. Increased cardiac function after retransfusion of

FIG. 8. Relation between the arterial blood pressure and the catecholamine content of the right ventricle of control and experimental dogs.

blood is supposed to induce the increased discharge of myocardial norepinephrine, which is not recaptured by storage sites in the presence of dibenzyline. This might cause a gradual decrease in the myocardial norepinephrine level of the dog after dibenzyline treatment.

Pretreatment with dibenzyline did not prevent a marked fall in arterial blood pressure in hypotensive animals following DOPA treatment. There is no significant difference between the fall in blood pressure observed in hypotensive animals with and without pretreatment with dibenzyline. Dibenzyline, therefore, does not seem to prevent the disorder in cardiovascular function induced by DOPA infusion after hemorrhagic hypotension.

DOPA infusion into hypotensive animals either with or without dibenzyline caused a remarkable fall in arterial blood pressure and death. However, during this period there was no obvious change in atrial blood pressure. So, in these cases it is thought that DOPA infusion may cause a shock in hypotensive dogs just as epinephrine causes

the so-called epinephrine shock (10, 20-22). On gross examination, a marked increase in subendocardial hemorrhage in the left ventricle in hypotensive animals was observed after DOPA treatment. However, hemorrhages such as these were hardly ever observed in dogs pretreated with dibenzylamine.

The observed changes in the myocardial catecholamine contents of the heart following hemorrhagic hypotension are small but their direction is consistent with the idea that there is a disturbance in myocardial catecholamine synthesis and/or storage in the heart. Evidence for such a disturbance was also obtained from comparison of the effects of DOPA infusion in hypotensive and control animals.

From our data it is impossible to conclude that myocardial norepinephrine depletion after hemorrhagic hypotension leads to myocardial failure. However, it is possible that hemorrhagic hypotension produces fundamental disorders in the heart and other vital organs, which result in a lowering of the myocardial norepinephrine content and also cause myocardial failure. This would explain why DOPA infusion was fatal in hypotensive animals, although the myocardial norepinephrine level increased.

SUMMARY

After hemorrhagic hypotension in dogs, myocardial norepinephrine synthesis and storage were apparently disturbed. Dibenzylamine seemed to prevent death of animals subjected to hemorrhagic hypotension by causing a reduction in the bleeding volume. However, dibenzylamine did not prevent a fall in arterial blood pressure during DOPA infusion after hemorrhagic hypotension. It is suggested that fundamental damage occurred during hemorrhagic hypotension, which caused the depletion of myocardial norepinephrine content, and also produced cardiovascular failure.

Acknowledgements : This work was supported by a grant HTS 5044 from the U.S. Public Health Service and also by a grant from the American Heart Association. The authors wish to express their sincere gratitude to Prof. W.F. Hamilton, Prof. R.P. Ahlquist and Prof. P. Dow of the Departments of Physiology and Pharmacology, Medical College of Georgia, for their guidance during this work. They are also much indebted to Prof. R. Imaizumi and Assistant Prof. H. Yoshida of the Department of Pharmacology, Faculty of Medicine, Osaka University for help in preparing this manuscript.

REFERENCES

- 1) WIGGERS, C.J. AND WERLE, J.M. : *Amer. J. Physiol.* **196**, 421 (1947)
- 2) SARNOFF, S.J., CASE, R.B., WAITHE, P.T. AND ISAACS, J.P. : *Ibid.* **176**, 439 (1954)
- 3) EDWARDS, W.S., SIEGEL, A. AND BING, R.J. : *J. clin. Invest.* **33**, 1646 (1954)
- 4) GLAVIANO, V.V. AND COLEMAN, B. : *Proc. Soc. exp. Biol., N.Y.* **107**, 761 (1961)
- 5) GOMERZ, O. : *Fed. Proc.* **21**, 117 (1962)
- 6) GOMERZ, O. AND HAMILTON, W.F. : Personal communication
- 7) WATTS, D.T. AND BRAGG, A.D. : *Proc. Soc. exp. Biol., N.Y.* **96**, 609 (1957)
- 8) WALKER, W.F., ZILELI, M.S., PEUTTER, F.W., SHOEMAKER, W.C., FRIEND, D. AND MOORE, F.D. : *Amer. J. Physiol.* **197**, 773 (1959)

- 9) WATTS, D.T. AND WESTFALLY, V. : *Proc. Soc. exp. Biol.*, N.Y. **115**, 601 (1964)
- 10) FREEMAN, N.E., FREEDMAN, H. AND MILLER, C.C. : *Amer. J. Physiol.* **131**, 545 (1941)
- 11) HACKEL, D.B. AND GOODALE, W.T. : *Circulation* **11**, 628 (1955)
- 12) NICKERSON, M. : "Shock" *Pathogenesis and Therapy, An International Symposium*, Edited by BOCK, K.D., p. 356, Academic Press Inc., New York (1962)
- 13) MIGONE, L. : *Ibid.* p. 76 (1962)
- 14) LEVENSON, S.M., EINHEBER, A. AND MALM, O.J. : *Fed. Proc.* **20**, Suppl. **9**, 99 (1961)
- 15) HASHIMOTO, Y. : THIS JOURNAL **15**, 317 (1965)
- 16) CHIDSEY, C.A., KAISER, G.A. AND BRAUNWALD, E. : *Science* **139**, 828 (1963)
- 17) BROWN, G.L. : Ciba Foundation Symposium Jointly with Committee for Symposia on Drug Action on "Adrenergic Mechanisms", Editor for the British Pharmacological Society, p. 116, Churchill Ltd., London (1960)
- 18) POTTER, L.T. AND AXELROD, J. : *J. Pharmacol.* **142**, 291 (1963)
- 19) POTTER, L.T. AND AXELROD, J. : *Ibid.* **142**, 299 (1963)
- 20) ERLANGER, J. AND CASSER, H.S. : *Amer. J. Physiol.* **49**, 345 (1919)
- 21) SCHOLZ, D.E., SCHULTZ, J.C., PLEUNE, F.G., FINK, K., STEADMAN, L.T. AND WARREN, S.L. : *J. clin. Invest.* **24**, 154 (1945)
- 22) SZAKACS, J.E. AND CANNON, A. : *Amer. J. clin. Path.* **30**, 425 (1958)