

A COMPARISON OF THE EFFECTS OF *L*-NOR-EPINEPHRINE, SYNTHETIC *L*-EPINEPHRINE, AND U.S.P. EPINEPHRINE UPON CEREBRAL BLOOD FLOW AND METABOLISM IN MAN¹

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(Submitted for publication November 17, 1952; accepted December 10, 1952)

Nor-epinephrine, a pressor amine known to exist normally in the mammalian body, is identical with epinephrine except for the absence of a methyl group in its chemical structure. Since methylation occurs readily in the body, it has been suggested that nor-epinephrine functions chiefly as a precursor to epinephrine (1-5). Nevertheless, it possesses potent pharmacologic properties which differ in many respects from those of epinephrine (6-9). Epinephrine raises systolic blood pressure, increases cardiac output and accelerates the heart rate; it constricts blood vessels in certain areas of the circulatory bed, dilates them in others, with an over-all effect of dilatation and a decrease in total peripheral vascular resistance. Nor-epinephrine increases systolic and diastolic blood pressure, has little or no effect on cardiac output and decreases cardiac rate. It constricts blood vessels in all areas of the circulation in which its effect has been studied.

Little is known, however, of the effects of nor-epinephrine and epinephrine upon the cerebral circulation in man. A clear understanding of their effects on this important segment of the circulation should provide information bearing on a number of physiologic, pathologic, and therapeutic questions. Because of the similarity of the hemodynamic changes in essential hypertension to those induced experimentally by the administration of *l*-nor-epinephrine, it has been suggested that *l*-nor-epinephrine may play an important role in the pathogenesis of essential hypertension (6). A measure of support for this hypothesis would be gained if nor-epinephrine-induced hypertension

could be shown to be associated with changes in the cerebral circulation similar to those accompanying essential hypertension. If, on the other hand, *l*-nor-epinephrine affects the cerebral circulation in some unique or distinctive way, this information might be of some value in the clinical recognition and detection of certain hypertensive states associated with abnormally high concentrations of *l*-nor-epinephrine in the adrenal gland, *i.e.*, pheochromocytoma (10, 11). Furthermore, nor-epinephrine has been employed therapeutically as a pressor agent in a variety of conditions characterized by acute hypotension including operative, hemorrhagic, and traumatic shock; to maintain blood pressure after thoracolumbar sympathectomy; and in the circulatory collapse that may accompany acute myocardial infarction (12, 13). A clear understanding of its effect on the cerebral circulation would be essential to a proper assessment of its over-all therapeutic value in these conditions. Obviously, if the increase in systemic arterial blood pressure is accompanied by a disproportionate increase in cerebral vascular resistance, a further reduction in blood flow to the brain would ensue. Such an effect would, no doubt, detract from its usefulness in the treatment of these hypotensive states.

This report deals with studies made to determine the effect of *l*-nor-epinephrine, and *l*-epinephrine on the cerebral circulation in normal, healthy males. Since U.S.P. epinephrine has been shown to contain significant amounts of *l*-nor-epinephrine (14, 15), it was necessary to determine the effect of both U.S.P. epinephrine and uncontaminated synthetic *l*-epinephrine.

METHOD

The cerebral blood flow (CBF) was determined by the nitrous oxide method of Kety and Schmidt (16), as modi-

¹ Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

TABLE I
The effect of *l*-nor-epinephrine on cerebral circulatory functions

Subject	Age	Dosage μg.	CBF cc./min./100 gms.		CVR mm. Hg/cc./min./100 gms.		CMR O ₂ cc./min./100 gms.		MABP mm. Hg	
			Control	Exper.	Control	Exper.	Control	Exper.	Control	Exper.
H. W.	29	1,000	54	49	1.35	2.02	4.28	4.35	73	99
A. R. H.	21	1,000	58	45	1.36	2.00	4.80	4.22	79	90
H. L. B.	27	1,400	61	52	1.44	2.09	4.10	5.16	88	109
W. C. C.	40	1,000	67	54	1.10	1.94	4.11	4.16	74	105
C. W.	26	800	42	33	1.90	3.06	3.02	2.86	80	101
A. M. M.	33	800	83	51	0.81	1.86	4.43	3.85	67	99
R. B.	23	800	50	34	1.72	3.09	4.02	2.96	86	105
W. L. P.	32	1,000	45	43	1.46	1.95	2.98	2.85	66	84
J. F. C.	27	1,000	60	43	1.15	2.58	3.68	3.07	69	111
R. H. H.	23	1,000	62	57	1.16	1.77	3.81	4.78	72	101
J. W. B.	21	700	83	56	0.96	1.64	4.93	3.84	80	92
G. D.	36	800	68	54	1.16	1.83	4.07	3.47	79	99
R. A. P.	24	800	63	59	1.11	1.47	3.91	3.85	70	86
Mean	28		61	48*	1.28	2.10*	4.01	3.80	76	99*
S.D.			11.94	8.05	.28	.48	.55	.71	6.73	8.07
S.E.			3.44	2.32	.08	.13	.15	.20	1.94	2.33
P value				<0.01		<0.01		>0.20		<0.01

* Indicates statistically significant change.

fied by Scheinberg and Stead (17). The cerebral oxygen consumption (CMR_{O₂}) was calculated from the CBF and the arterio-cerebral venous oxygen difference. The cerebral vascular resistance (CVR) was calculated from the CBF and the mean arterial blood pressure, which was measured directly in a peripheral artery, usually the femoral, with a damped mercury manometer. Arterial and cerebral venous blood samples were drawn simultaneously immediately before each blood flow determination. Blood oxygen and carbon dioxide content were determined manometrically (18). The cerebral blood

flows were measured in the morning with the subject fasting and in the recumbent position. Immediately following a control determination, *l*-nor-epinephrine, synthetic *l*-epinephrine,² or U.S.P. epinephrine in oil was administered intramuscularly in amounts varying from 600 μg. to 1,400 μg. Fifteen or twenty minutes later, when

² Generous quantities of *l*-nor-epinephrine (Levophen) and *l*-epinephrine (Suprarenin) were supplied by Kenneth M. Smoot, Dept. of Medical Research, Winthrop-Stearns, Inc.

TABLE II
The effect of *l*-nor-epinephrine on arterial and cerebral venous blood constituents

Subject	Age	Dosage μg.	Arterial blood				Internal jugular venous blood				A-V O ₂ Vol. %		Oxygen extraction ratio ER O ₂ %	
			CO ₂ content vol. %		O ₂ content vol. %		CO ₂ content vol. %		O ₂ content vol. %		Control	Exper.	Control	Exper.
			Control	Exper.	Control	Exper.	Control	Exper.	Control	Exper.				
H. W.	29	1,000	42.23	40.13	20.07	20.94	49.63	48.81	12.15	12.07	7.92	8.87	39	42
A. R. H.	21	1,000	44.50	42.54	22.72	22.75	52.13	51.10	14.44	13.38	8.28	9.37	36	41
H. L. B.	27	1,400	45.48	39.13	20.38	22.37	51.31	48.73	13.58	12.43	6.80	9.94	33	44
W. C. C.	40	1,000	46.10	44.39	17.60	19.16	52.86	53.76	11.46	11.44	6.14	7.72	35	40
C. W.	26	800	44.91	43.39	21.25	21.82	51.68	51.37	14.05	13.14	7.20	8.68	34	40
A. M. M.	33	800	46.95	43.78	18.13	19.14	51.05	51.10	12.79	11.59	5.34	7.55	29	39
R. B.	23	800	49.26	48.09	20.38	20.74	56.96	56.99	12.34	12.01	8.04	8.73	39	42
W. L. P.	32	1,000	49.10	46.22	18.69	19.65	55.47	54.00	12.06	12.43	6.63	7.22	35	37
J. F. C.	27	1,000	47.94	45.45	17.97	19.17	53.38	51.69	11.84	12.02	6.13	7.15	34	37
R. H. H.	23	1,000	51.88	47.94	19.16	20.26	53.40	55.67	13.00	11.87	6.16	8.39	32	41
J. W. B.	21	700	51.41	48.50	18.94	19.54	55.54	55.08	14.15	12.69	4.79	6.85	25	35
G. D.	36	800	48.85	48.82	18.67	19.08	54.24	54.76	12.68	12.66	5.99	6.42	32	34
R. A. P.	24	800	47.86	46.95	18.36	18.36	53.07	53.45	12.15	11.82	6.21	6.54	34	36
Mean	28		47.42	45.03*	19.41	20.23*	53.13	52.81	12.82	12.27*	6.59	7.96*	34	39*
S.D.			2.66	3.02	1.41	1.33	1.96	2.46	.92	.55	1.00	1.07	3.62	2.92
S.E.			.76	.87	.40	.38	.56	.71	.26	.16	.28	.31	1.04	.84
P value				<0.01		<0.01		>0.30		<0.01		<0.01		<0.01

* Indicates statistically significant change.

TABLE III
The effect of synthetic *l*-epinephrine on cerebral circulatory functions

Subject	Age	Dosage μg.	CBF cc./min./100 gms.		CVR mm. Hg/cc./min./100 gms.		CMR O ₂ cc./min./100 gms.		MABP mm. Hg	
			Control	Exper.	Control	Exper.	Control	Exper.	Control	Exper.
B. G. T.	25	1,000	43	45	1.76	1.66	4.20	3.61	76	75
J. W. F.	27	1,000	57	64	1.33	1.07	3.82	4.34	76	69
E. B.	29	600	60	59	1.27	1.24	3.77	4.08	76	73
M. L. A.	33	1,000	50	56	1.62	1.32	3.84	4.35	81	74
J. E. B.	33	800	68	67	1.04	0.95	5.20	4.95	71	66
J. L. P.	27	1,400	49	49	1.31	1.27	4.01		64	62
B. W. M.	28	1,000	68	54	1.04	1.22	3.82	2.42	71	66
T. R. E.	33	1,000	68	58	1.07	1.24	4.09	3.34	73	72
J. W. N.	28	1,000	68	76	1.10	0.88	4.39	5.02	75	68
E. R. B.	32	1,000	60	54	1.32	1.35	4.57	3.77	79	73
C. E. B.	30	1,400	69	69	1.23	1.13	3.80	4.28	85	78
E. L. M.	35	1,200	40	38	1.70	1.60	2.68	2.56	68	61
J. M. H.	22	1,000	98	97	0.72	0.69	4.51	4.37	71	67
I. W.	23	600	95	78	0.65	0.78	5.28	4.18	62	61
E. L.	24	1,200	95	79	0.87	1.01	4.40	5.79	83	80
Mean	29		66	63	1.20	1.16	4.16	4.08	74	70*
S.D.			17.57	14.73	.31	.26	.60	.87	6.30	5.76
S.E.			4.69	3.93	.08	.07	.16	.24	1.68	1.54
P value				>0.10		>0.30		>0.50		<0.01

* Indicates statistically significant change.

the blood pressure had become stabilized, the cerebral blood flow measurement was repeated. Previous experience with the intramuscular administration of *l*-nor-epinephrine had shown that a consistent pressor response occurs when the site of injection is massaged immediately after the administration of the drug. The blood pressure gradually rises for 15 to 20 minutes, becomes stabi-

lized at an essentially constant level for an additional 10 to 20 minutes, and then gradually returns to normal. The second cerebral blood flow in each case was measured during the stable plateau period. The mean of four blood pressure measurements made immediately preceding and four made immediately following the blood flow determination was used as the mean arterial pressure during the

TABLE IV
The effect of synthetic *l*-epinephrine on arterial and cerebral venous blood constituents

Subject	Age	Dosage μg.	Arterial blood				Internal jugular venous blood				A-V O ₂ Vol. %		Oxygen extraction ratio ER O ₂ , %	
			CO ₂ content vol. %		O ₂ content vol. %		CO ₂ content vol. %		O ₂ content vol. %		Control	Exper.	Control	Exper.
			Control	Exper.	Control	Exper.	Control	Exper.	Control	Exper.	Control	Exper.	Control	Exper.
B. G. T.	25	1,000	44.20	45.35	21.80	21.72	53.23	53.25	12.03	13.69	9.77	8.03	45	37
J. W. F.	27	1,000	43.59	41.27	18.35	18.53	49.73	48.26	11.65	11.75	6.70	6.78	37	37
E. B.	29	600	47.23	46.77	18.15	18.42	52.73	53.76	11.87	11.51	6.28	6.91	35	38
M. L. A.	33	1,000	47.73	47.81	20.09	19.72	55.05	55.70	12.40	11.95	7.69	7.77	38	39
J. E. B.	33	800	45.31	46.19	21.15	21.46	52.66	53.59	13.50	13.77	7.65	7.69	36	36
J. L. P.	27	1,400	47.18		21.27		55.49		13.07		8.20		38	
B. W. M.	28	1,000	46.20	45.52	20.31	20.57	51.10	50.87	14.68	16.08	5.63	4.49	28	22
T. R. E.	33	1,000	43.34	46.01	17.95	17.95	49.48	51.12	11.93	12.19	6.02	5.76	34	32
J. W. N.	28	1,000	49.30	50.10	18.01	17.88	55.64	56.44	11.54	11.28	6.47	6.60	36	37
E. R. B.	32	1,000	46.33	46.27	20.98	21.01	53.43	53.18	13.36	14.03	7.62	6.98	36	33
C. E. B.	30	1,400	48.46	47.50	17.26	17.52	53.89	53.80	11.75	11.31	5.51	6.21	32	35
E. L. M.	35	1,200	44.37	43.16	15.50	16.25	50.79	49.50	8.80	9.50	6.70	6.75	43	42
J. M. H.	22	1,000	47.21	48.35	17.73	17.69	52.11	53.44	12.92	13.19	4.81	4.50	27	25
I. W.	23	600	48.25	49.58	17.72	17.89	53.12	55.18	12.16	12.52	5.56	5.37	31	30
E. L.	24	1,200	42.54	42.28	17.85	18.22	47.59	50.17	13.21	10.89	4.64	7.33	26	40
Mean	29		46.08	46.15	18.94	18.92	52.40	52.73	12.32	12.40	6.62	6.51	35	35
S.D.			2.01	2.47	1.77	1.61	2.23	2.32	1.26	1.58	1.33	1.08	5.22	5.47
S.E.			.53	.68	.47	.44	.59	.64	.33	.43	.35	.30	1.39	1.51
P value				>0.50		>0.05		>0.10		>0.50		>0.50		>0.50

* Indicates statistically significant change.

TABLE V
The effect of U.S.P. epinephrine on cerebral circulatory functions

Subject	Age	Dosage µg.	CBF cc./min./100 gms.		CVR mm. Hg/cc./min./100 gms.		CMR O ₂ cc./min./100 gms.		MABP mm. Hg	
			Control	Exper.	Control	Exper.	Control	Exper.	Control	Exper.
C. E. L.	36	800	79	59	0.89	1.20	4.78	4.52	70	71
J. B. H.	39	1,000	42	50	1.83	1.34	2.73	3.38	77	67
J. C. H.	30	800	58	61	1.28	1.05	2.91	3.58	74	64
B. E. C.	38	800	69	51	1.04	1.43	5.44	4.12	72	73
W. M. J.	34	1,200	97	84	0.76	0.82	5.07	4.10	74	69
J. J.	32	1,200	67	69	1.00	0.90	3.93	3.53	67	62
R. A. A.	30	1,000	80	84	1.01	0.88	3.76	5.39	81	74
E. F. J.	31	1,000	85	94	0.99	0.84	5.28	5.59	84	79
E. L. C.	28	1,000	71	63	0.95	1.00	4.54	3.57	68	64
N. G. W.	41	1,000	76	73	1.09	0.99	4.59	4.41	83	72
J. M. M.	25	1,000	69	64	1.28	1.28	4.02	4.18	89	92
A. A. B.	34	1,000	50	49	1.74	1.69	3.62	3.26	87	83
C. D. D.	25	1,000	82	73	0.96	1.05		4.67	79	77
Mean	33		71	67	1.14	1.11	4.22	4.18	77	73*
S.D.			14.24	13.52	.30	.25	.84	.70	6.91	8.10
S.E.			4.11	3.90	.08	.07	.25	.20	1.99	2.33
P value				>0.10		>0.50		>0.50		<0.01

* Indicates statistically significant change.

procedure. Blood pressure values before and after measurement of CBF did not vary more than a few millimeters in any case.

RESULTS

l-Nor-epinephrine. The data (Tables I and II) indicate that *l-nor-epinephrine* is a potent cerebral vasoconstrictor. The disproportionate increase (64 per cent) in calculated mean CVR ($p = < 0.01$)

above MABP (31 per cent), eventuates in a 21 per cent reduction in CBF ($p = < .01$). Nevertheless, the CMR_{O₂} is unaffected because the fall in CBF is compensated by an increase in the oxygen extraction ratio (34 to 39 per cent) and in mean arterio-cerebral venous oxygen difference (6.59 vol. per cent to 7.96 vol. per cent) ($p = < .01$). The increase in A-V oxygen difference is the re-

TABLE VI
The effect of U.S.P. epinephrine on arterial and cerebral venous blood constituents

Subject	Age	Dosage µg.	Arterial blood				Internal jugular venous blood				A-V O ₂ Vol. %		Oxygen extraction ratio ER O ₂ , %	
			CO ₂ content vol. %		O ₂ content vol. %		CO ₂ content vol. %		O ₂ content vol. %		Control	Exper.	Control	Exper.
C. E. L.	36	800	47.37	46.24	17.93	18.63	53.77	52.73	11.88	11.91	6.05	6.72	34	36
J. B. H.	39	1,000	47.75	49.48	18.80	18.46	54.77	56.06	12.30	11.71	6.50	6.75	35	37
J. C. H.	30	800	46.74	47.50	17.03	16.71	51.88	53.72	12.01	10.84	5.02	5.87	29	35
B. E. C.	38	800	47.83	48.73	20.36	20.38	55.93	56.45	12.47	12.30	7.89	8.08	39	40
W. M. J.	34	1,200	48.17	49.68	17.85	17.70	53.62	55.34	12.62	12.82	5.23	4.88	29	28
J. J.	32	1,200	39.38	40.27	15.65	15.67	45.74	45.53	9.78	10.56	5.87	5.11	38	33
R. A. A.	30	1,000	52.10	50.54	18.38	20.02	56.75	56.55	13.67	13.60	4.71	6.42	26	32
E. F. J.	31	1,000	47.39	48.55	20.00	19.95	54.02	54.40	13.79	14.00	6.21	5.95	31	30
E. L. C.	28	1,000	44.16	46.91	16.34	15.37	51.20	52.60	9.94	9.69	6.40	5.68	39	37
N. G. W.	41	1,000	48.32	49.09	16.75	16.32	54.80	56.00	10.71	10.28	6.04	6.04	36	37
J. M. M.	25	1,000	48.46	49.00	16.68	16.63	54.49	55.93	10.84	10.10	5.84	6.53	35	39
A. A. B.	34	1,000	46.75	46.90	20.23	20.13	53.77	54.46	13.03	13.48	7.23	6.65	36	33
C. D. D.	25	1,000		48.03		21.10		53.82		14.70		6.40		30
Mean	33		47.04	47.76	18.00	18.24	53.40	54.12*	11.92	12.00	6.08	6.24	34	34
S.D.			2.87	2.46	1.52	1.88	2.72	2.79	1.28	1.57	.85	.77	4.07	3.58
S.E.			.86	.71	.45	.54	.82	.80	.38	.45	.25	.22	1.22	1.03
P value				>0.05		>0.50		<0.02		>0.30		>0.50		>0.40

* Indicates statistically significant change.

sult of a significant increase in arterial O_2 content (19.41 vol. per cent to 20.23 vol. per cent) and a decrease in cerebral venous oxygen content (12.82 vol. per cent to 12.27 vol. per cent). Mean arterial CO_2 content decreased significantly (47.42 vol. per cent to 45.03 vol. per cent) apparently as a result of mild hyperventilation.

Synthetic l-epinephrine. In contrast to *l-nor-epinephrine*, this substance had no significant effect on mean cerebral hemodynamics or metabolism (Table III); nor were any changes in blood gases noted (Table IV). The only change of significance was a small but consistent reduction in MABP from 74 mm. Hg to 70 mm. Hg ($p = < 0.01$).

U.S.P. epinephrine. The results of studies made with U.S.P. epinephrine are listed in Table V and Table VI. With one exception they are identical with the findings in the synthetic epinephrine series, *i.e.*, a slight but significant reduction in MABP (77 mm. Hg to 73 mm. Hg; $P = < .01$) without changes in CBF, CVR, CMR_{O_2} , arterial or venous oxygen content. With both synthetic and U.S.P. epinephrine there was an increase in mean cerebral venous CO_2 content which on statistical analysis proved to be of significance only with U.S.P. epinephrine.

DISCUSSION

These experiments demonstrate that the administration of *l-nor-epinephrine* results in powerful cerebral vasoconstriction in normal healthy males. The increase in cerebral vascular resistance induced by this substance exceeds the accompanying increase in perfusion pressure; as a consequence, the blood flow to the brain is diminished. This decrease in CBF, however, does not eventuate in a reduction in cerebral oxygen consumption because of the compensatory increase in the extraction of oxygen from arterial blood by the brain, *i.e.*, the arterio-cerebral venous oxygen difference increases.

The increase in cerebral vascular resistance is most likely due to a direct vasoconstricting effect of *l-nor-epinephrine* upon cerebral vessels. However, this vasoconstricting action could be augmented by changes in O_2 tension, CO_2 tension or pH of the arterial blood (19). King, Sokoloff, and Wechsler (20) have shown that the intra-

venous infusion of *l-nor-epinephrine* is not accompanied by a change in pH of the blood. However, a rise in arterial oxygen content and a fall in arterial carbon dioxide content occurs when the drug is administered by either the intramuscular or intravenous route. These changes in blood gases are attributed to the mild hyperventilation that was observed in most of the subjects. However, they are not of sufficient magnitude to account for the marked increase in cerebral vascular resistance and could contribute only in a small way, if at all, to the total increase in cerebral vascular resistance (19). It seems very unlikely that reduced arterial CO_2 tension is causally related to the cerebral vasoconstriction induced by *l-nor-epinephrine* although it is possible that slight changes in blood CO_2 tension incident to hyperventilation might tend to augment the direct vasoconstricting effect of the drug. There is the further possibility that acute hypertension resulting from the administration of *l-nor-epinephrine* may be associated with an increase in intracranial pressure, and in this way further augment the resistance to blood flow in the brain.

These studies disclosed a striking difference between the cerebral circulation in essential hypertension and the acute hypertension induced by *l-nor-epinephrine*. In the former there are parallel increases in cerebral vascular resistance and blood pressure; the CBF, therefore, remains unaltered (21). In the latter, the augmentation of CVR is out of proportion to the increase in blood pressure; the blood flow is reduced. This does not, however, constitute strong evidence against the suggestion that *l-nor-epinephrine* may be involved in the pathogenesis of essential hypertension, since the hypertension noted in this study was acute and the state of the cerebral circulation under these circumstances not necessarily comparable to that in chronic essential hypertension. Furthermore, there is the possibility, indicated above, that indirect and secondary factors not present in essential hypertension may augment the increase in cerebral vascular resistance consequent to the acute administration of *l-nor-epinephrine*.

The demonstration that the pressor response of *l-nor-epinephrine* is accompanied by a reduction in cerebral blood flow in normotensive subjects suggests that this drug should be used with cau-

tion as a therapeutic agent in acute hypotensive states when a reduction in blood flow to the brain may not be desirable.

Other vital segments of the circulation have been shown to be similarly affected by the administration of this substance. Renal and hepatic blood flow are diminished and calculated renal and splanchnic vascular resistance increased during the administration of nor-epinephrine (22-25). Until it can be shown that the cerebral, as well as the renal and hepatic, circulations in patients with acute hypotension respond differently to *l*-nor-epinephrine than in normotensive subjects, its use here should be considered potentially harmful.

These studies with epinephrine confirm the previous assumption that the quantities of nor-epinephrine present in U.S.P. epinephrine do not alter the effect of the latter (5), and they demonstrate yet another difference in the hemodynamic effects of nor-epinephrine and epinephrine. The intramuscular administration of epinephrine leads to a slight reduction in mean arterial blood pressure but does not alter cerebral vascular resistance, cerebral blood flow or cerebral oxygen consumption. These findings are in disagreement with those of King, Sokoloff, and Wechsler (20) who found that the intravenous infusion of epinephrine was accompanied by an increase in blood pressure, cerebral blood flow and cerebral oxygen consumption; cerebral vascular resistance was not changed. The differences in blood flow and blood pressure responses can be adequately accounted for by the difference in mode of administration of epinephrine in the two studies. Our experimental blood flows were determined 25 to 30 minutes after the intramuscular administration of epinephrine when there were clear-cut clinical manifestations of its effect such as tremulousness, tachycardia, palpitation, pallor, excitement, and apprehension; no special attempt was made to produce a pressor response in the subjects. In the studies of King, Sokoloff, and Wechsler (20) epinephrine was administered by intravenous infusion, the rate of which was adjusted to provide a pressor response before the experimental studies were done. The concentration of circulating epinephrine obtained as a result of the slow absorption from an intramuscular deposit of epinephrine in oil was no doubt inadequate to cause an increase in cardiac output of

sufficient magnitude to overcome the over-all vasodilating effect of epinephrine. Since epinephrine by either route of administration does not alter cerebral vascular resistance, its effect upon the blood flow to the brain will depend directly upon its effect upon blood pressure.

The results of the two studies regarding cerebral oxygen utilization, however, cannot be attributed to the difference in mode of administration. Excitement, apprehension, palpitation, tremulousness, pallor, etc., occurred in most of the subjects after the intramuscular administration of *l*-epinephrine and U.S.P. epinephrine, and in many instances these manifestations were quite prominent. Cerebral oxygen consumption, however, was unaffected by these agents. No change in mean CMR_{O_2} was observed in groups who received either *l*-epinephrine or U.S.P. epinephrine. Nor were there individual instances in either group in which there appeared to be a relationship between changes in cerebral oxygen consumption and the severity of the subjective sensations experienced by the subjects.

The results in this respect are similar to those of Scheinberg and Stead (17) who found that cerebral blood flow and cerebral oxygen consumption were unaltered by apprehension and anxiety in normal young males, and they tend to support the suggestion of Scheinberg (26) that cerebral metabolism normally functions at nearly its maximum rate. Apprehension and anxiety, whether occurring spontaneously or induced by the intramuscular administration of epinephrine, do not appear to be associated with changes in cerebral oxygen consumption.

SUMMARY

1. The effect of the intramuscular administration of *l*-nor-epinephrine, synthetic *l*-epinephrine, and U.S.P. epinephrine on cerebral circulatory and metabolic function has been determined in normal healthy males.
2. *l*-Nor-epinephrine increases mean arterial blood pressure and reduces cerebral blood flow in normotensive males by virtue of its potent constricting effect upon cerebral blood vessels. Cerebral oxygen utilization is not altered.
3. Epinephrine, when administered intramuscularly in dosage of from 600 μ g. to 1,400 μ g.,

slightly lowers mean arterial blood pressure; does not affect cerebral blood flow, cerebral vascular resistance or cerebral oxygen utilization.

4. The cerebrovascular effects of synthetic *l*-epinephrine and U.S.P. epinephrine are identical.

ACKNOWLEDGMENTS

This work was done with the technical assistance of Mrs. Angeline M. Hayes and Miss Mildred T. Brennan. Mr. Tyree Loving also gave valuable assistance.

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