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Research Article

THE CARDIO-CIRCULATORY EFFECTS IN MAN OF NEO-SYNEPHRIN

(1-α-hydroxy-β-methylamino-3-hydroxy-ethylbenzene hydrochloride) [1]

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Neo-synephrin [2] differs chemically from epinephrine only in the absence of the hydroxy group in the para position on the benzene ring. The first pharmacological studies with this substance emphasized the conclusion that the pharmacological action of neo-synephrin resembles that of epinephrine in all respects, but the potency is less and the duration of effects is longer (12, 13, 21). Inspection of the data in these papers shows, however, that the pressor effect is relatively much more prominent than the cardio-accelerator action.

The pressor action of neo-synephrin has been utilized with some success in the treatment of surgical shock (10, 11, 17), in the prevention of the hypotension of spinal anesthesia (1, 2) and in the treatment of orthostatic hypotension (6, 8). Neo-synephrin is widely used as a local vaso-constrictor and may prevent cardiac standstill in patients with a hyperactive carotid sinus reflex (18). A prominent effect of this drug in normal man is the production of marked bradycardia (14).

MATERIALS AND METHODS

The subjects ranged from 16 to 60 years of age but the majority were from 18 to 30. Thirty-nine of them were men, 9 were women. With the exception of 10 cardiac patients they were all trained as experimental subjects, so that psychic effects were at a minimum.

The studies were carried out in the morning in the basal fasting state with an absolute minimum of exciting influences. In all but a few cases the room temperature was between 75° and 80° F. and humidity was between 40 and 70 per cent. Most of the experiments were made with the subject horizontal; in the others, the subject rested in a chair designed for x-ray studies. A period of at least one day was allowed to elapse between studies on any one subject.

The general procedure in all studies was the same. The subject rested quietly for 10 to 30 minutes and then measurements and observations were begun and continued for 10 minutes or more before the drug was administered. Observations were continued for 1 to 4 hours following the administration. In all cases blood pressure and pulse rate were measured at frequent intervals throughout the entire experimental period. The same observer measured blood pressures throughout any one experiment. Electrocardiograms were made in the majority of studies.

Roentgenkymograms (R.K.Gs.) were made in the posterio-anterior position at a distance of 66 inches and an exposure time of 1.5 seconds. The R.K.Gs. were measured and analyzed for heart size and stroke output by the methods of Keys and Friedell (15, 16); in most cases the systolic and diastolic outlines were drawn by their method *B* (1940, *op. cit.*). Three or four R.K.Gs. were made in each experiment in which this method was applied.

Minute output was measured by the acetylene method of Grollman (7). In those experiments in which this method was applied the sequence was: rest 15 minutes; measurement of oxygen consumption, acetylene rebreathing; rest 10 minutes; drug administration; wait 5 to 10 minutes; measurement of oxygen consumption (8 minutes), acetylene rebreathing, final measurement of oxygen consumption.

Venous pressure was measured in the horizontal position by the direct method with citrated saline in the manometer. Circulation time (arm-to-tongue) was measured by injection of 5 ml. of a 20 per cent solution of sodium dehydrocholate ("decholin"). For this purpose the syringe needle was inserted into the vein and a minute or two allowed to elapse before the injection was started. The injection was then made as rapidly as possible and the time was measured from the *start* of the injection until the first sensation of the bitter taste.

Threshold for subcutaneous injection

The threshold dose of neo-synephrin to produce cardiovascular effects was determined for subcutaneous injection in 36 experiments on normal adults. In each case injection was made under the skin on the outside of the upper arm; the site

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[2] Also known as meta- or m-sympatol and as meta synephrin.

of injection was very briefly massaged just after injection and then left undisturbed thereafter. The concentration of the drug was 1 per cent except that the least volume used was 0.2 ml.

The threshold effect of neo-synephrin in 11 instances was found to be a fall in pulse rate of 4 to 8 beats per minute below the normal minimum for the subject and a rise in blood pressure of 5 to 10 mm. Hg. In 4 instances only the bradycardia was certain, the blood pressure remaining practically constant.

The threshold dosage—for the environmental and physiological conditions used here—was from 0.8 to 1.5 mgm. neo-synephrin per square meter of body surface in all cases. The subcutaneous injection of a total of 1 mgm. never had a definite effect; 2 mgm. usually had an unmistakable effect; while 3 mgm. always had an effect even in very big persons.

The effects of subcutaneous injection of epinephrine in the same subjects under the same rigidly controlled conditions are of interest for comparison. The threshold dosage was 0.06 to 0.12 mgm. epinephrine and the threshold effect was a rise in pulse rate with little or no rise in blood pressure (9 cases), or even a fall, particularly in diastole (6 cases).

Blood pressure and pulse rate

The subcutaneous injection of 3 to 10 mgm. of neo-synephrin in normal persons always results in a rapid fall of pulse rate and a rise in both systolic and diastolic blood pressure. Maximal bradycardia occurred within 6 to 9 minutes after injection in all cases. Maximal hypertension occurred within 10 to 17 minutes after injection in all cases. Depending on the dosage, these effects persist in almost full intensity for 20 to 50 minutes and then slowly return to the original levels. In all cases the fall in heart rate and the rise in diastolic pressure *precede* the rise in systolic pressure; we were unable to find any time difference between the initiation of the changes in pulse rate and in diastolic blood pressure.

In 47 trials on 34 normal subjects with 5 mgm. neo-synephrin given subcutaneously, the average pulse rate fell from 70 to 44; the maximal declines varied from 16 to 34 beats per minute. The average blood pressure rose from 110/66 to 138/84; the maximal rises varied from 10 to 36 mm. in systole and from 10 to 30 mm. in diastole. In 16 trials with 14 normal subjects, 10 mgm. neo-synephrin given subcutaneously produced an average change of pulse rate from 64 to 40; the declines ranged from 17 to 32 beats per minute. In these experiments the blood pressure rose from an average of 109/66 to an average of 159/96; the maximal rises varied from 32 to 76 mm. in systole and from 20 to 33 mm. in diastole.

Rapid intravenous injection of 0.2 to 1.5 mgm. of neo-synephrin produces changes similar to the subcutaneous injection except that the heart rate varies greatly until a steady bradycardia sets in from 70 to 100 seconds after the injection is started. The heart rate usually returns to normal in 15 to 20 minutes but then continues to rise slightly—10 to 15 beats per minute—above the original resting level. Typical results are shown in Figure 2.

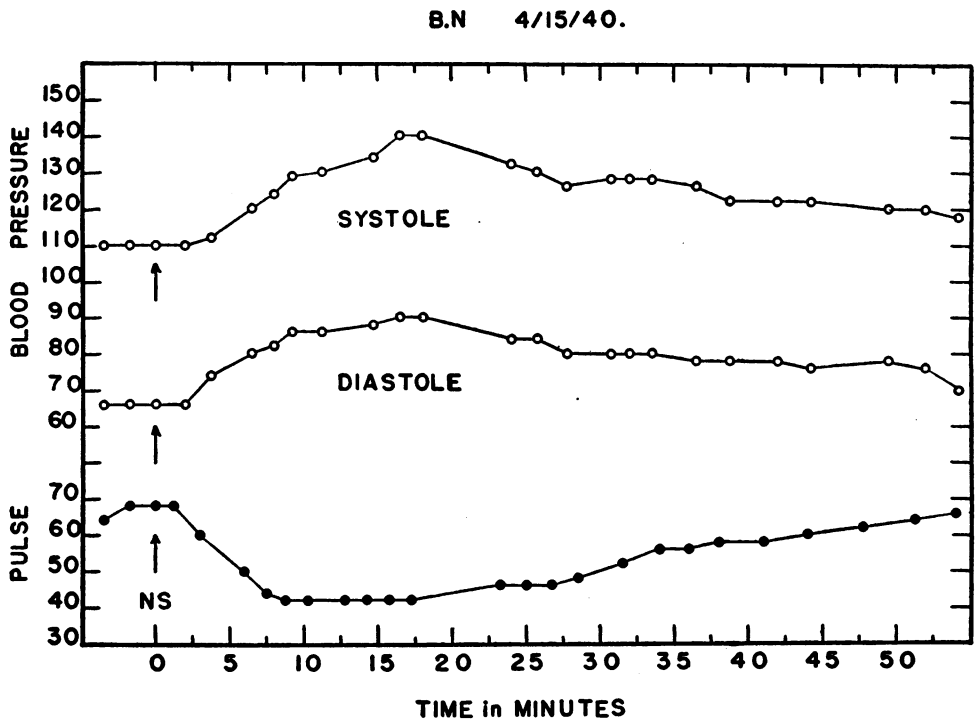
Oral administration

Neo-synephrin is effective when taken by mouth but relatively large amounts are necessary. In the basal state the threshold oral dosage is 40 to 60 mgm. in the average young adult—*i.e.*, about 25 mgm. per square meter of body surface or about ⅔ mgm. per kgm. body weight. Given by mouth, about 250 mgm. of neo-synephrin is roughly the equivalent of 5 mgm. given subcutaneously. In the basal state, 250 mgm. neo-synephrin produced the following average changes (7 subjects): pulse rate, decline to 46 from previous 67; blood pressure, increase from previous 112/71 to 143/96. The effects are slower in onset with oral administration and they last longer but otherwise they are entirely comparable to subcutaneous injection. A typical example is shown in Figure 3.

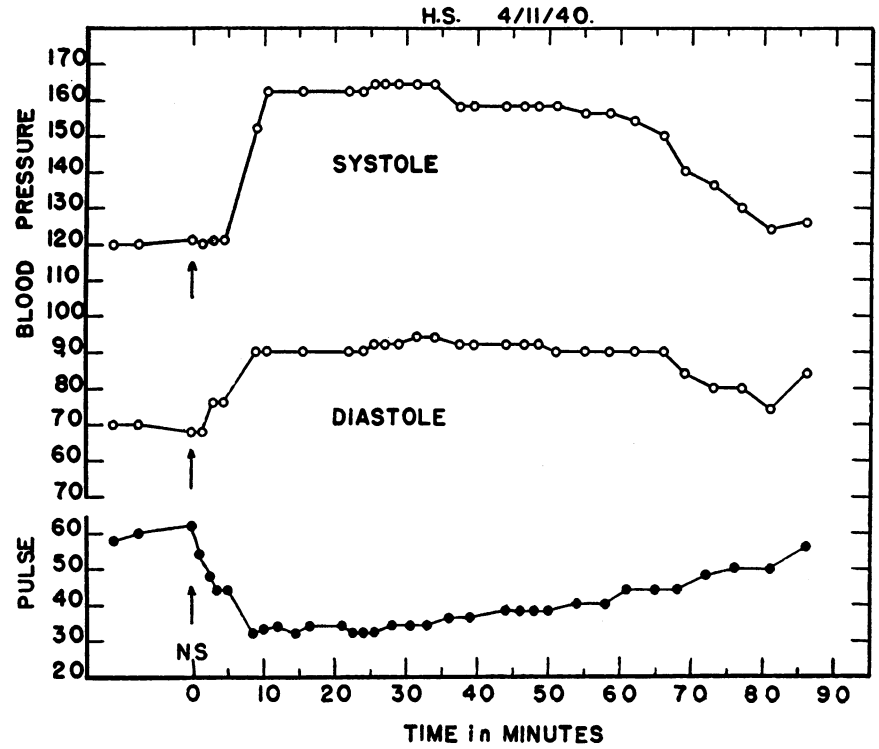
Electrocardiographic changes

In general, E.C.G. records made following subcutaneous injection appear perfectly normal except for the bradycardia and, indeed, resemble records made on athletes with very slow hearts. A typical example is shown in Figure 4.

Though the E.C.G. during neo-synephrin bradycardia usually is entirely normal, there are definite changes compared to E.C.Gs. made before injection of the drug. Table I summarizes the data



A. Subject B. N., 5 mgm. neo-synephrin subcutaneously at arrow.



B. Subject H. S., 10 mgm. neo-synephrin at arrow.

FIG. 1. BLOOD PRESSURE AND PULSE RATE CHANGES RESULTING FROM SUBCUTANEOUS INJECTION OF NEO-SYNEPHRIN IN NORMAL ADULTS UNDER BASAL CONDITIONS IN THE PRONE POSITION

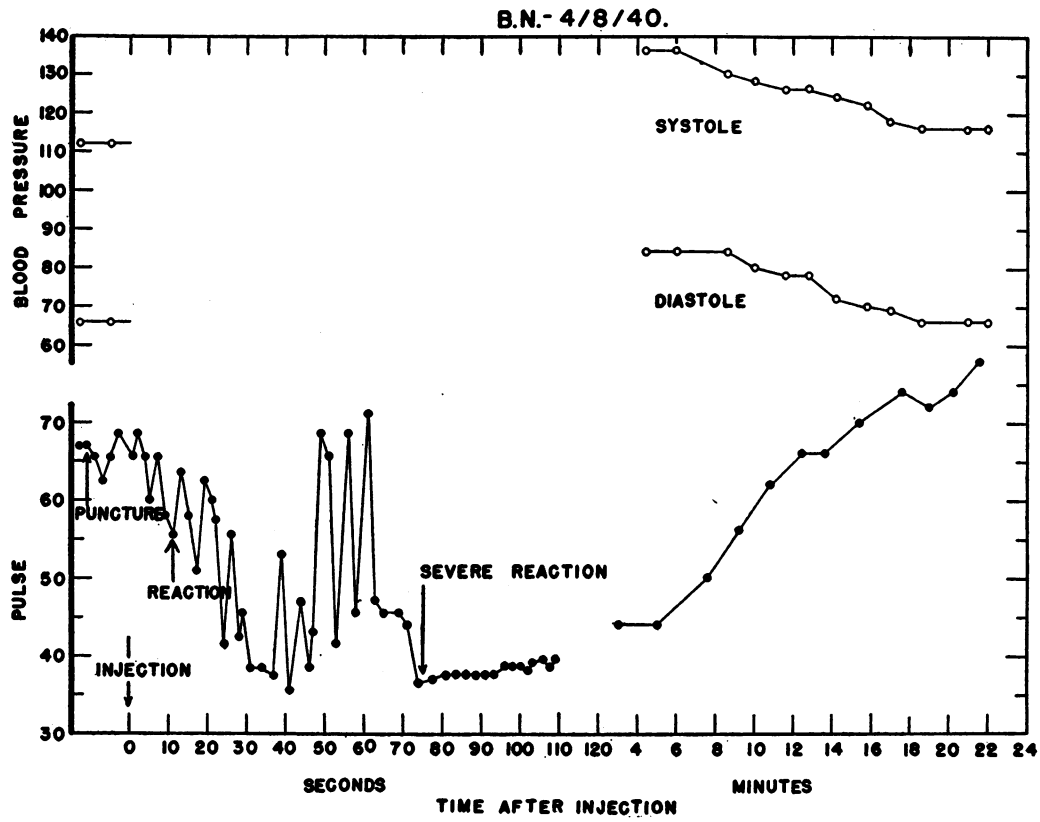


FIG. 2. BLOOD PRESSURE AND PULSE RATE CHANGES RESULTING FROM RAPID INTRAVENOUS INJECTION OF 1 MGM. NEO-SYNEPHRIN IN 0.5 CC. VOLUME

"Reaction" (12 seconds after start of injection) consisted of spastic contraction of voluntary muscles, particularly those of the toes. "Severe reaction" (75 seconds) consisted of involuntary muscle twitches, jerking extremities, facial tic.

from Lead II for dosages of 4 to 6 mgm. given subcutaneously. There is always an increase in the potential of the *T* wave and there is almost always a decrease in the potential of *P*. The potential changes in Leads I and III are, in general, similar to those observed in Lead II—the potential of *P* is decreased and that of *T* is increased. In 3 cases with large doses—more than 7 mgm. neosynephrin per square meter of body surface—the *P* wave disappeared, or became isoelectric, in all leads. In 2 instances, doses of 7 to 8 mgm. per square meter produced records indicating complete auriculo-ventricular dissociation.

One of the interesting features of the neosynephrin bradycardia is the relative constancy of the heart rate with all but very large doses. Not only do irregularities fail to appear but the normal respiratory sinus arrhythmia is usually reduced; in 5 experiments the heart rate became practically independent of respiration.

The reduction in heart rate is almost entirely the result of an extension of the diastolic pause.

TABLE I

Electrocardiographic changes resulting from the subcutaneous injection of 4 to 6 mgm. neo-synephrin in 32 experiments

Representative normal young adults in basal rest, values before and after injection, the latter at the time of greatest bradycardia. Data from Lead II only here. Q-T interval in seconds, potentials in millivolts (corrected for calibration).

	Pulse rate	Q-T interval	Potentials		
			P	R	T
Average before.....	68	0.38	0.124	1.10	0.324
Average after.....	45	0.42	0.091	1.08	0.461
Maximum increase..	−17	0.12	0	0.15	0.47
Minimum decrease..	33	0	0.15	0.21	−0.02

The drug appears to have no effect on the conduction or spread of the nervous impulse from its normal origin.

The circulation rate

The arm-to-tongue circulation time was measured before neo-synephrin injection and again after the bradycardia was well established. With all dosages greater than 3.5 mgm. there was an increase in the circulation time, usually slight but occasionally very marked (*cf.* experiments numbered 7, 8, 10, 13).

R.K.G. measurements—heart size and output

It was suspected beforehand that, because of the increased duration of diastole, the diastolic filling of the heart would be increased with a corresponding increase in stroke output. In general, this was found to be true. An unexpected effect observed was the frequent increase in *both* diastolic and systolic size of the heart. The transverse diameter of the heart sometimes increased by more than a centimeter. It is obvious that not only does the heart fill more completely during diastole but that it empties less completely and there is a small amount of true dilatation.

TABLE II

Effect of subcutaneous injection of neo-synephrin on arm-to-tongue circulation time in normal subjects as measured with sodium dehydrocholate

"Time decholin" indicates the time, in minutes, after the neo-synephrin injection when the second injection of sodium dehydrocholate was made.

Subject	Dose	Before			Time decholin	After		
		Heart rate before circulation time	Blood pressure arm	Circulation time		Heart rate before circulation time	Blood pressure arm	Circulation time
	mgm.			*seconds*				*seconds*
F.M. July 31	2.5	62	110/58	16	23′	68	114/68	16
V.M. December 5	3.5	72	120/76	14	14′	60	130/82	14
E.B. December 28	3.5	72	106/62	14	15′	52	118/76	16
L.C. December 19	5.0	58	111/70	18	16′	46	128/90	25
H.S. June 7	5.0	66	116/60	19	25′	42	144/82	23
Z.M. June 8	5.0	66	120/70	21	16′	38	154/90	23
C.S. June 8	5.0	76	108/58	22	17′	48	120/74	30
E.B. June 10	5.0	60	104/62	19	13′	42	132/90	24
Z.M. June 10	5.0	66	114/72	16	15′	44	132/84	19
L.R. June 11	5.0	66	118/64	17	13′	46	128/74	25
O.H. December 24	8.0	62	104/68	19	15′	42	139/94	21
N.S. February 1	8.0	70	118/66	19	18′	48	138/84	22
H.S. January 22	10.0	56	114/66	16	13′	34	188/100	24
Averages:		66	112/66	17.7	17′	47	136/84	21.7

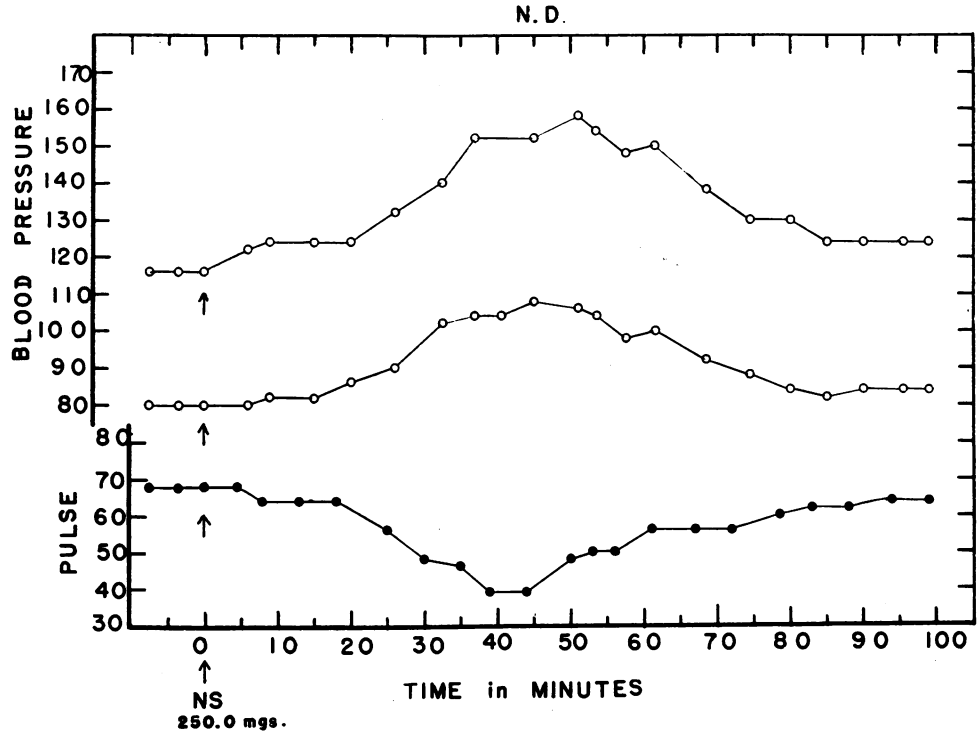


FIG. 3. BLOOD PRESSURE AND PULSE RATE CHANGES RESULTING FROM ORAL ADMINISTRATION OF 250 MGM. NEO-SYNEPHRIN IN SUBJECT N. D., NORMAL MALE IN THE BASAL STATE

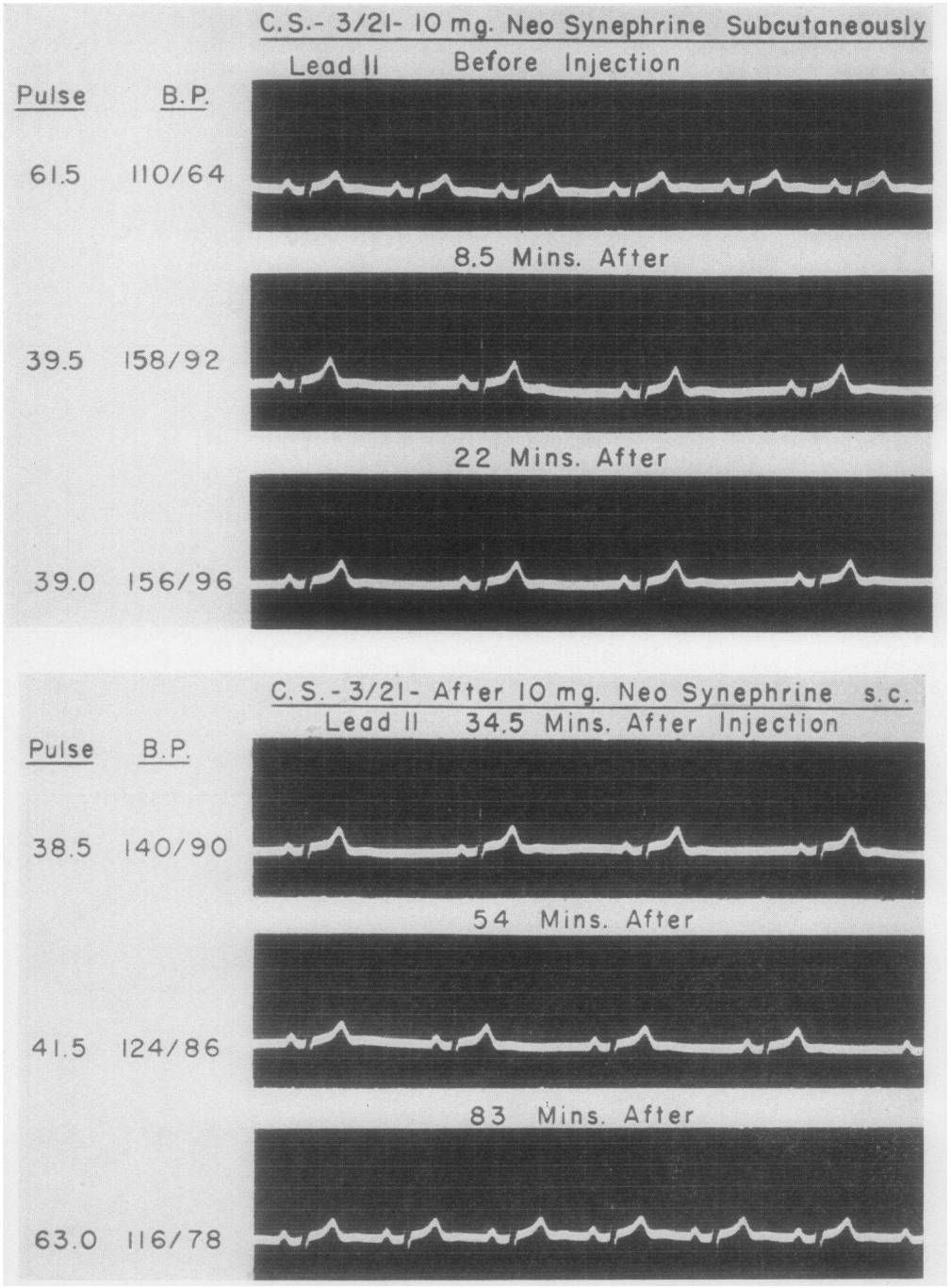


FIG. 4. ELECTROCARDIOGRAPHS (LEAD II) BEFORE AND AT INTERVALS AFTER SUBCUTANEOUS INJECTION OF 10 MGM. NEO-SYNEPHRIN IN A NORMAL MALE

Circulation by the acetylene method

The results of 14 experiments in which the cardiac output was measured by the acetylene method are summarized in Table IV.

The results from the acetylene method are in substantial agreement with the R.K.G. measurements. There was almost invariably a large increase in stroke output, amounting on the average

TABLE III

The effect of neo-synephrin on the size and stroke of the heart as measured by roentgenkymographic methods

Seated position throughout. "Dose" in mgm. injected subcutaneously. Heart volumes and stroke outputs in cc., minute volumes in liters.

Subject	Dose	Before					After				
		Heart rate	Heart volume		Stroke volume	Minute volume	Heart rate	Heart volume		Stroke volume	Minute volume
			Diastolic	Systolic				Diastolic	Systolic		
VO-1	3.5	68	656	597	76	5.1	63	691	628	81	5.1
LC-1	3.5	81	682	631	65	5.3	54	708	650	74	4.0
LC-2	3.5	82	681	629	67	5.5	53	701	646	70	3.7
DA	3.5	83	561	509	67	5.6	69	571	503	87	6.0
LR	4.0	84	497	454	55	4.6	64	521	471	64	4.1
BN-1	5.0	75	576	531	58	4.4	50	590	540	64	3.2
NS	5.0	75	754	699	70	5.3	53	809	746	81	4.3
EH	5.0	69	519	474	58	4.0	58	526	467	76	4.4
BN-2	5.0	76	559	505	69	5.2	47	591	538	68	3.2
DW	5.0	86	600	552	61	5.2	56	658	598	77	4.3
WAT	5.0	72	549	509	51	3.7	55	580	517	81	4.5
ZM	5.0	70	585	526	75	5.3	45	623	552	91	4.1
VO-2	5.0	80	597	550	60	4.8	54	640	578	79	4.3
LC-3	5.0	76	684	632	67	5.1	51	746	686	77	3.9
WIL	6.0	74	527	491	47	3.5	46	597	551	59	2.7
HS	10.0	82	768	724	56	4.6	55	810	753	73	4.0
VO-3	10.0	84	622	582	51	4.3	57	671	616	70	4.0
BE	10.0	75	603	555	61	4.6	42	628	568	77	3.2
Averages		77	612	564	62	4.8	54	648	589	75	4.1

TABLE IV

Measurements by the acetylene method of the minute output of the heart before injection and during neo-synephrin bradycardia

Minute volumes in liters of blood per minute, stroke outputs in cc.

Subject	Dose	Before			After		
		Heart rate	Stroke output	Minute volume	Heart rate	Stroke output	Minute volume
L.C. December 12	3.5	81	64	5.20	54	70	3.78
GAS December 30	3.5	82	53	4.31	67	62	4.16
L.R.* May 6	4.0	85	59	5.05	67	58	3.87
B.N. April 10	5.0	62	82	5.12	42	136	5.70
B.N. April 15	5.0	66	84	5.56	42	89	3.74
DWil* April 22	5.0	82	64	5.27	58	78	4.52
DWat* April 24	5.0	76	62	4.75	58	91	5.26
Z.M. June 10	5.0	77	90	6.92	45	96	4.32
VOM December 13	5.0	79	84	6.68	75	83	6.24
L.C. December 22	5.0	73	49	3.56	50	75	3.74
DWil May 2	6.0	75	65	4.88	51	110	5.61
L.R. May 20	6.0	80	48	3.84	48	127	6.10
H.S. April 11	10.0	62	71	4.56	33	108	3.56
VOM December 18	10.0	81	85	6.91	55	70	3.84
Averages:		76	68.8	5.19	53	89.4	4.60

* "After" determinations made during period of return of heart rate toward normal from maximum bradycardia.

to 30.0 per cent of the pre-injection value. The average increase in stroke volume was considerably greater in the measurements by the acetylene method than indicated in the experiments in which the R.K.G. method was used. This difference may be a result of the fact that the acetylene measurements were made with the subject recumbent, while the x-ray films were always taken with the subject seated upright. We have noticed that signs of circulatory insufficiency never appeared after neo-synephrin injection when the subjects were recumbent, but in the upright seated position vertigo resulted on several occasions and once actual syncope intervened.

Effects in the atropinized subject

Ten normal subjects were used, each of whom was studied on different occasions with: (*1*) 4 to 10 mgm. neo-synephrin given subcutaneously, (*2*) 0.65 to 1.3 mgm. ($\frac{1}{100}$ to $\frac{1}{50}$ grain) atropine given subcutaneously, and (*3*) atropine followed by neo-synephrin. With neo-synephrin alone all of these subjects responded in the characteristic manner described earlier in this paper. Atropine alone had slight but characteristic effects on the pulse rate in all cases. An initial slight fall persisted for about 20 or 25 minutes and then was succeeded by a rise to 10 to 15 beats per minute above the basal value. Atropine alone had no significant effect on the blood pressure. As judged by the characteristic flush, dry mouth and dilated pupils, the full atropine effect was obtained in about 40 minutes and lasted 40 to 60 minutes after this.

When neo-synephrin was injected after atropinization had been established, the blood pressure in both systole and diastole immediately rose and reached higher values than those produced by neo-synephrin alone in the same subjects. The pulse rate immediately declined and then rose rapidly to 120 or more in the presence of full atropinization. With incomplete atropinization the pulse rate likewise immediately declined after injection of neo-synephrin and then rose above the basal rate and tended to remain moderately elevated. Typical results illustrating these points are summarized in Figures 5 and 6.

With a standard dosage of 5 mgm. neo-synephrin given subcutaneously, the average maximum effect in these particular subjects was an increase of 22 mm. in the systolic and 13 mm. in the diastolic blood pressure. With the same dosage in the same subjects after atropinization, the average maximum effect of neo-synephrin was an in-

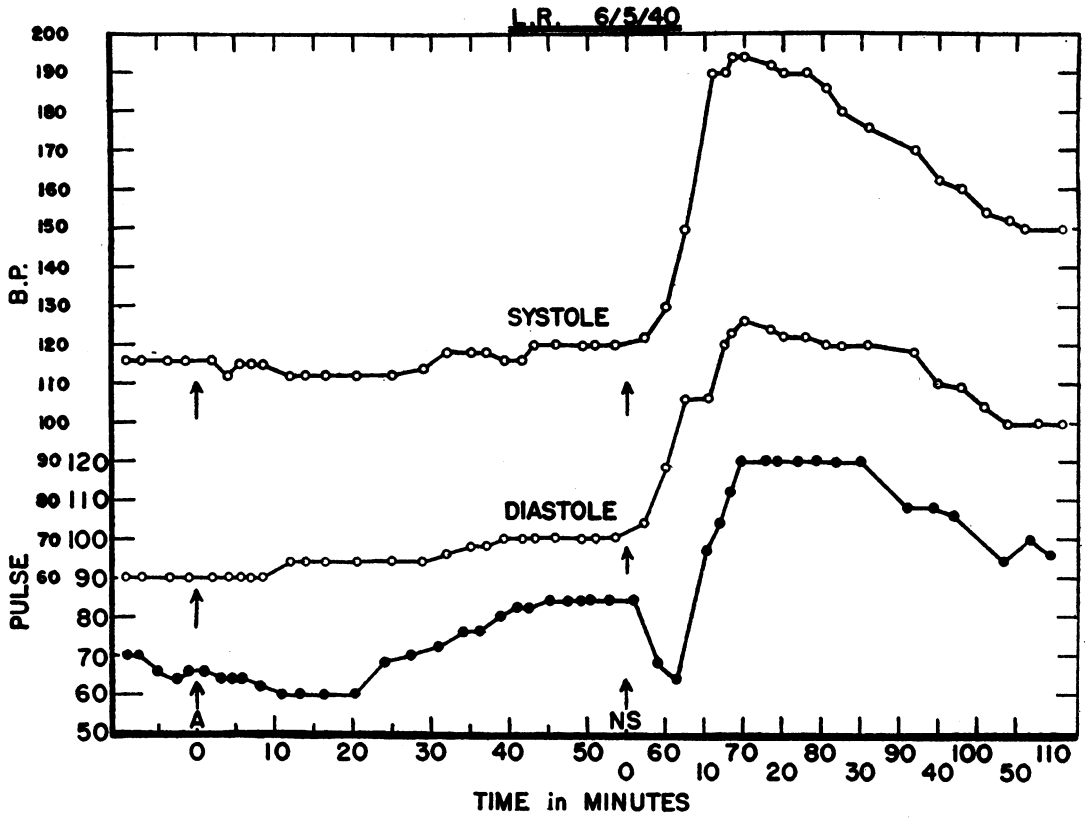


FIG. 5. EFFECT OF NEO-SYNEPHRIN IN THE FULLY ATROPINIZED NORMAL SUBJECT
At *A* 1.28 mgm. (1/50 grain) atropine subcutaneously. At *NS* 5.0 mgm. neo-synephrin subcutaneously.

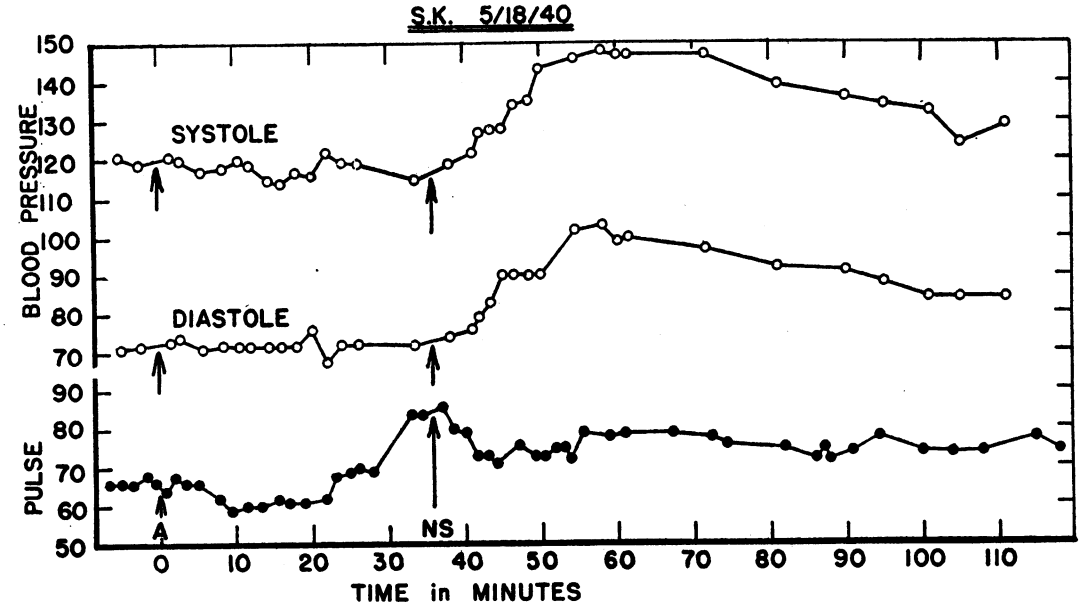


FIG. 6. EFFECT OF NEO-SYNEPHRIN IN THE PARTLY ATROPINIZED NORMAL SUBJECT
At *A* 1.28 mgm. (1/50 grain atropine subcutaneously. At *NS* 4.0 mgm. neo-synephrin subcutaneously.

crease of 62 mm. in the systolic and 52 mm. in the diastolic blood pressure. The "decholin" circulation time was measured in 5 atropinized subjects receiving 5 mgm. neo-synephrin subcutaneously. In all cases the "decholin" circulation time was shortened; the average was a reduction from 21.1 seconds to 16.9 seconds.

Patients with cardiac abnormalities

The effects of subcutaneous and intravenous injection of neo-synephrin were observed in patients presenting various types of tachycardia and of bradycardia.

In general, the results with these patients were entirely consistent with our belief that the normal effect of neo-synephrin on the heart rate operates through the vagus nerve on the sinus node. The drug was practically without effect on the heart rate in 5 cases of ventricular and supra-ventricular tachycardia. In one case of the latter, where the heart rate alternated from a rate of 60 to 70 to paroxysms of 170 lasting from 5 to 30 minutes, a total subcutaneous dosage of 25 mgm. in 50 minutes appeared to be entirely without effect except for a slight rise in blood pressure.

In another case of supra-ventricular tachycardia, the heart rate had been 180 for 12 hours before neo-synephrin was administered. Subcutaneous injection of first 5 and then 10 mgm., followed by 2 mgm. intravenously, was without effect on either blood pressure or heart rate. Further intravenous injection of 10 mgm. neo-synephrin over a period of 5 minutes increased the blood pressure by 30 mm. but still had no effect on the pulse rate.

In paroxysms of tachycardia of sinus origin, however, neo-synephrin injection has a prompt and satisfactory result. We have used the drug, in 5 mgm. subcutaneous injection, on 4 subjects who are prone to spells of sinus tachycardia but are otherwise entirely normal. On every occasion the paroxysm of tachycardia was rapidly dispelled, the heart rate dropping from a rate of 120 to 140 to 60 to 80 in 5 to 8 minutes.

According to our limited experience, more severe sinus tachycardias are likewise readily controlled with the drug. For example, Mrs. A., University of Minnesota Hospital Number 698875, who had a history of occasional very prolonged and exhausting paroxysms of tachycardia, suddenly developed a heart rate of 160 to 180 per minute. After 16 hours the heart rate was 160, blood pressure 110/90. The E.C.G. showed the tachycardia to be of sinus origin. Subcutaneous injection of neo-synephrin, 0.2 cc., 1 per cent solution, elevated the blood pressure to 125/100 in 7 minutes with no change in heart rate. Twenty minutes after the first injection, 0.5 cc. of 1 per cent solution of neo-synephrin was injected subcutaneously. In 8 minutes the blood pressure rose to 150/105 and the pulse rate dropped abruptly to 96 and declined further to 88; in the next 5 minutes the blood pressure fell to 140/95. This patient showed no further tachycardia during her stay in the hospital.

Sinus bradycardia responds to neo-synephrin with a further decline in the pulse rate. This was noted in 3 subjects with athletic bradycardia and was particularly well shown in a case of sinus bradycardia of unknown origin in a young man with no other discernible abnormality. Before injection the heart rate was 42, blood pressure 120/62. After subcutaneous injection of 5 mgm. neo-synephrin, the heart rate fell to 34 to 36 and the blood pressure to 112/64. The E.C.G. was entirely normal at all times. The fall in blood pressure in this case is interesting though unexplained.

Subjective sensations

The administration of epinephrine in amounts sufficient to produce a pronounced pressor effect is attended by sensations of acute anxiety, cardiac oppression and throbbing blood vessels. These sensations are frequently referred to the elevated blood pressure. With a dosage as large as 10 mgm. neo-synephrin given subcutaneously, there may be a sense of cardiac oppression and fullness in the neck and chest but the feeling of anxiety is almost entirely absent. Ordinary injections of neo-synephrin—5 mgm. subcutaneously—produce no subjective sensations at all in spite of the bradycardia and hypertension.

In the atropinized subject the sudden rise of blood pressure and pulse rate following injection of neo-synephrin gives rise to a sensation of cardiac oppression and fullness in the neck and chest and may be attended with sharp pains in the head

which disappear quickly. Even in these cases, however, the typical anxiety of epinephrine injection is absent.

Neo-synephrin in large dosage—more than 8 mgm. subcutaneously—has a marked effect on the pilomotors of the skin. The hair "stands on end" and the subject usually remarks on a prickly sensation, particularly at the hair line of the forehead. In some cases "goose pimples" appear over an area of 20 to 40 sq. cm. around the site of injection.

Animal experiments

Experiments were made on dogs and rabbits for comparison with human beings and to test the interpretation of several points. Normal unanesthetized animals responded precisely like human beings to intravenous and to subcutaneous neo-synephrin—the blood pressure rose and the pulse rate fell.

The dominant rôle of the vagus in the bradycardia of neo-synephrin was shown in experiments in which the vagi were sectioned or in which the perfused isolated heart was used. In all experiments of this type the effect of neo-sypnephrin on the heart rate was qualitatively not to be distinguished from that of epinephrine.

DISCUSSION

By any method of administration the duration of action of neo-synephrin is longer than obtained with epinephrine. All of the subjects used in the present experiments were also tested with epinephrine; in general, the effective duration of action of neo-synephrin was from 2 to 4 times as long as that of epinephrine.

The qualitative resemblance between neo-synephrin and epinephrine is apparent in several important effects on the heart. Kuschinsky (12) reported that the coronary flow is markedly increased with neo-synephrin and later (13) demonstrated a marked dilatation of the coronaries in perfused preparations with constant blood pressure. We have also observed that neo-synephrin produces a pronounced increase in blood flow from the coronary sinus in heart-lung preparations of dogs and in isolated perfused hearts of rabbits.[3] If the degree of positivity of the *T* wave of the E.C.G. may be taken as an indication, we may assume a similar effect on coronary flow in man. Even in the absence of true coronary dilatation we should expect a considerable augmentation of the coronary blood flow from neo-synephrin because of the increased blood pressure and the prolongation of the diastolic period during which most of the coronary flow takes place.

Neo-synephrin has a direct stimulatory action on the denervated, isolated or vagotomized heart, both as to rate and force of contraction (*cf.* 4, 5, 22). However, the cardiac-accelerating potency is relatively much less than the pressor potency, so that even in the completely denervated heart it is possible to inject neo-synephrin at a rate which produces a pressor response without cardiac acceleration (22).

It might be suggested that neo-synephrin sensitizes or potentiates the pressure receptors in the carotid sinus and aortic arch and causes bradycardia by enhancing the reflex to hypertension. Against this view is the finding of Nathanson (18) that neo-synephrin prevents cardiac standstill produced by mechanical pressure on the carotid sinus in sensitive persons. Another significant fact is that neo-synephrin can produce definite bradycardia in man when the blood pressure is practically unaffected.

The observed increase in stroke volume resulting from neo-synephrin is accounted for by direct stimulation of the myocardium and prolongation of the period of diastolic filling of the heart. This latter effect also accounts for the increased diastolic size of the heart. The increased systolic size of the heart indicates, of course, an increase in the amount of residual blood in the heart.

The work done by the heart per beat is increased by neo-synephrin. The total work per minute is also increased on the average. With a dosage of about 5 mgm. given subcutaneously, the product of mass of blood times pressure is usually slightly increased. Moreover, since the systolic discharge period is practically unaltered and the stroke volume is increased, there must be an increase in the velocity of systolic flow in the aorta and therefore an increase in the kinetic work done.

In comparison with epinephrine and other sympathomimetic amines the action of the heart is remarkably regular with neo-synephrin. Orth *et al.* (20) compared a number of sympathomimetic

[3] We are grateful to Dr. Gordon K. Moe for help in these experiments.

amines under cyclopropane anesthesia and found that neo-synephrin did not cause acceleration and was the least apt to produce cardiac irregularities. Cranston and Bieter (3) studied rabbits under spinal anesthesia and reported that the effective pressor dose/"toxic" dose ratio for neo-synephrin is lower than for other sympathomimetic drugs except synephrine; cardiac irregularity was the principal criterion of toxicity.

We have noted that the systolic volume of the heart is somewhat increased by neo-synephrin. This suggested the possibility that the pressure in the atria might be increased owing to less complete ventricular discharge in systole. Accordingly, direct venous pressure measurements were made in a series of experiments.

In 7 normal adults the venous pressure rose slightly after injection of neo-synephrin, being from 2 to 8 cm. (average 4.5 cm.) higher at the time of maximum effect of the drug with dosage of 5 or 6 mgm. subcutaneously. Iglauer and Altschule (9) have reported a similar but greater rise in venous pressure resulting from paredrine. They suggest that this effect in the case of paredrine, at least, is a result of "venous constriction," but we are unable to understand how peripheral venous constriction, if it occurs, can raise the venous pressure central to the valves in the veins. In the case of neo-synephrin the drug increases the output per beat of the heart but it appears that this augmentation is gained partly at the cost of a dilatation which requires a greater average venous pressure for filling the heart.

The action of neo-synephrin as a vasoconstrictor in local application is widely used. It might be thought, then, that it has a specially powerful action on the cutaneous vessels but this is not strictly true. With subcutaneous or intravenous injection, administration of neo-synephrin never produces generalized blanching and pallor like that obtained with epinephrine in equal pressor dosage.

The results of the present study indicate that neo-synephrin stimulates effectors of both sympathetic and parasympathetic nervous systems—the action of the drug is partly adrenergic and partly cholinergic. A predominance of the adrenergic action is evident in the pressor action, augmentation of the heart contraction, dilatation of the coronaries and excitation of the pilomotor system. A predominant cholinergic action on the vagus best explains the bradycardia. Another cholinergic action is suggested in the reports of physiologically trained persons tested with neo-synephrin who state that large dosages cause definite sensations of excitation of the detrusor muscle of the bladder and inhibition of the sphincter vesicae. A relative balance of adrenergic and cholinergic effects in a number of organs is indicated in the absence of marked changes in respiration, pupil size, sweat secretion and splenic contraction. (Hemoglobin concentration is constant.)

SUMMARY

The threshold dosage of neo-synephrin in the average adult is about 2 mgm. subcutaneously, 0.4 mgm. intravenously and 50 mgm. orally. The threshold effect is a decline in pulse rate and usually a slight increase in blood pressure.

The average dosage of neo-synephrin for satisfactory pressor and cardiac effect is about 5 mgm. subcutaneously, 0.8 mgm. intravenously or 250 mgm. orally. With these dosages the pulse rate declines 15 to 35 beats per minute, the systolic blood pressure rises 15 to 40 mm., and the diastolic blood pressure rises 10 to 30 mm.

The upper limit for safe and comfortable dosage of neo-synephrin in normal adults is about 10 mgm. subcutaneously, 1.5 mgm. intravenously, and 300 mgm. per os. With rare exceptions no sensations or symptoms other than pilomotor excitation are elicited by dosages below these levels.

Neo-synephrin increases the positivity of the T wave, decreases that of P, and prolongs the diastolic pause; otherwise the E.C.G. is essentially unchanged. Cardiac irregularities, extrasystoles and escape phenomena do not occur except in rare cases with the largest doses.

Neo-synephrin produces an increase in the size of the heart in both diastole and systole. The stroke output of the heart is increased but the minute output of the heart is generally somewhat decreased. There is a slight prolongation of the circulation time and a slight increase in venous pressure. The total work of the heart is increased.

In the atropinized subject the pressor effect of neo-synephrin is augmented and tachycardia is produced. The same result is obtained in vagotomized animals and in the isolated or denervated heart.

Tachycardia of sinus origin is readily controlled with neo-synephrin but tachycardia of ventricular or supra-ventricular origin is not affected. Sinus bradycardia responds to neo-synephrin with a further decrease in pulse rate.

Neo-synephrin differs from epinephrine in its smaller pressor and cardiac potency, its longer duration of action and in its stimulatory effect on some of the parasympathetic effectors, notably those of the cardiac vagus.

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