which appears to correspond to a large fraction of the systolic discharge. During respiration these passive movements are obscured by the active movements of the diaphragm but if the stroke volume is large and respiration is very quiet traces may still be visible in the R.K.G.

Summary. In man during respiratory pause there are changes in the position of the diaphragm during the cardiac cycle so that in ventricular systole the total thoracic volume is smaller than in diastole. Calculation of the net thoracic changes involved integration of measurements of both vertical and horizontal components of motion in posterior-anterior and lateral projections. The reduction in thoracic volume amounts to a large and apparently rather constant fraction of the cardiac stroke output.

11338

Production of Bradycardia in Normal Man by Neosynephrin* (l-α-hydroxy-β-methylamino-3-hydroxy-ethylbenzene hydrochloride).

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It is well known that heart rate and blood pressure do not rise in equivalent degree after administration of different sympathomimetic drugs. Ethylnor-suprarenin (3-4 dihydroxy-phenyl-1-amino-2-butanol-1) produces a rise in pulse rate and a fall in blood pressure (Cameron, *et al.*[1]). Neosynephrin (3-hydroxyphenyl-1-methylamino-2-ethanol-1) increases the blood pressure with a relative fall in the pulse rate (Johnson[2]).

The production of relative bradycardia by sympathomimetic drugs has generally been ascribed to reflexes produced by the elevated blood pressure arising in the aortic arch and the carotid sinus. Such an effect can be demonstrated in man when small doses of epinephrine are used; the heart rate and blood pressure rise together but after some minutes the rate may fall while the blood pressure is still

* This work has been supported by a fellowship grant to the University of Minnesota by Frederick Stearns and Company.

1 Cameron, W. M., Crismon, J. M., Whitsell, L. J., and Tainter, M. L., *J. Pharm.*, 1937, **62**, 318.

2 Johnson, C. A., *Surgery, Gyn., Obst.*, 1936, **63**, 35.

above normal. When continuous electrocardiographic records are made before, during and after injection of a small dose of epinephrine in man, we have found an immediate but very transient slowing of the heart (Fuchs[3]). Large doses of some of these drugs may produce ventricular bradycardia as a result of block, cryptosystole and general cardiac damage.

We have studied the cardiac and vasomotor responses in normal man to epinephrine, neosynephrin hydrochloride and synephrin tartrate (d-α-hydroxy-β-methylamino-4 hydroxy-ethylbenzene tartrate). All studies were made in basal rest on 14 trained subjects, who received subcutaneous injections at intervals of several days. Each subject was studied at various dosages of all 3 drugs.

Synephrine tartrate produced no effects on pulse, blood pressure or the electrocardiogram in doses up to 60 mg. Epinephrine produced the classical results as well as the very transient slowing and occasionally the late reflex slowing mentioned above.

Neosynephrin consistently produced an immediate marked bradycardia which persisted from 30 to 90 minutes. Relative tachycardia never appeared except occasionally in very slight degree as the last effects of the drug were wearing off. The results were not changed

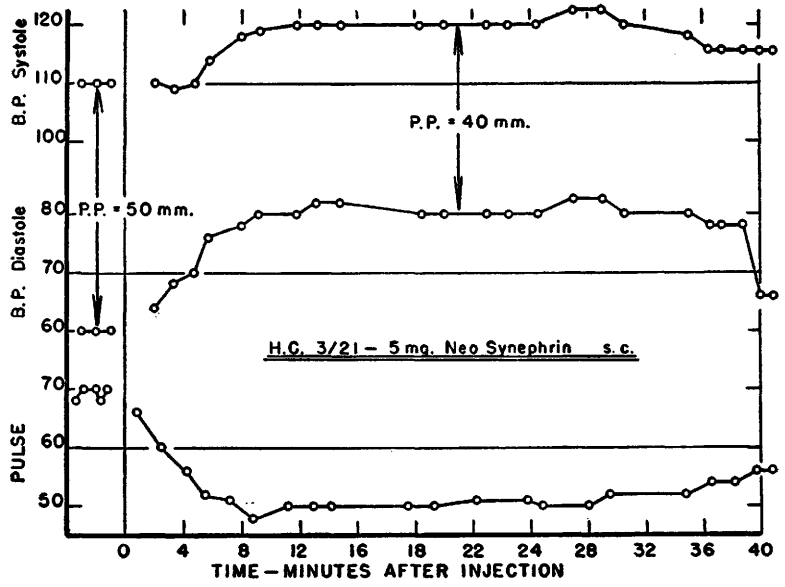

FIG. 1.

Typical course of blood pressure and pulse following subcutaneous injection of 5 mg of neosynephrin in a normal young man in the basal state.

[3] Fuchs, R. T., *J. Pharm.*, 1938, **63**, 143.

when the subject was kept seated instead of prone. The threshold subcutaneous dose was from 1 to 2.5 mg in young adults from 110 to 180 lb in weight.

Fig. 1 shows the typical changes resulting from a rather small dose of neosynephrin. The pulse immediately starts to decline, reaching a constant low level at 7 to 10 minutes after injection. At the same time the diastolic blood pressure rises but the systolic pressure does not rise until the diastolic pressure and pulse changes are well established. With these rather small doses the systolic pressure rise is small and the pulse pressure is generally diminished. With a 10 mg injection (as is frequently used for the clinical dose) the initial time course is the same but the systolic pressure continues to rise so that the pulse pressure is eventually increased above normal. With the 10 mg dose the pulse rate may fall to 30 beats per minute and be maintained at 35 to 45 for as long as 80 minutes.

The electrocardiographic records are interesting. The rhythm is perfectly normal with no change in the PR interval though the RT interval (duration of systole) may be very slightly prolonged. There is no slurring of QRS in any of the leads at any time. Very rarely there may be inversion of P, especially in lead 3. Aside from the extreme bradycardia, the most notable change is a marked elevation of the T wave in all leads and a diminution of the P wave. In several cases the P wave practically disappeared and the E.C.G. would indicate A.V. nodal rhythm. Neither A.V. nor bundle branch block appeared. In a single case when a 10 mg dose was given to a small athletic woman there was a short period when the E.C.G. record could be interpreted as showing retrograde conduction or complete A.V. dissociation at equal rhythm.

The general appearance is that neosynephrin produces a primary bradycardia by inhibition of the sino-auricular node and this is relatively independent of blood pressure reflexes over the vagus nerve. Neosynephrin does not appear to accentuate the carotid sinus reflex; Nathanson[4] reported it is effective in preventing syncope resulting from pressure on the carotid sinus. No distress or subjective excitement was reported by the subjects, several of whom were trained observers, in these extreme bradycardias.

Summary. Neosynephrin injected subcutaneously into normal, trained subjects in the basal state produces an immediate bradycardia and rise in diastolic pressure; systolic pressure rises later. The threshold is from 1 to 2.5 mg and pulse rates from 30 to 45, per-

[4] Nathanson, M. H., *Arch. Internal Med.*, 1936, **38**, 683.

sisting for as long as 80 minutes, are produced by 5 to 10 mg. The E.C.G. remains normal with no change in A.V. or ventricular conduction time but there is a fall in the potential of the P wave and a rise in the T wave.

11339

A Method of Separating Small Quantities of the Coproporphyrin Isomers 1 and 3.

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Quantitative separation of the naturally occurring coproporphyrin isomers (1 and 3) has hitherto been impossible. Crystallization has usually permitted identification of the porphyrin predominating in any given mixture, such as obtained for instance from urine and feces.[1-4] This, however, has required that relatively large amounts of porphyrin be available. The present investigation was undertaken with the purpose of finding a means by which mixtures consisting of as little as 5-10 γ of total coproporphyrin could be resolved quantitatively.

We have found that the methyl esters of coproporphyrins 1 and 3 are quantitatively adsorbed on Brockmann's Al_2O_3* under the conditions noted in the following. The ester of coproporphyrin 3 may be eluted quantitatively with 35% acetone in water while that of copro-1 remains adsorbed, and is later removed by elution with pure acetone. The various steps in the procedure are as follows: (1) Esterification of the total, free porphyrin mixture in methyl alcohol saturated with HCl gas. (2) Dilution with equal volumes of distilled water, followed by neutralization of the HCl with a saturated aqueous solution of sodium acetate, which is added drop by drop with constant stirring until the solution no longer turns Congo paper blue. Ten percent NH_4OH is then added drop by drop until the mixture becomes pink to phenol red. (A few drops of an aqueous

1 Watson, C. J., *J. Clin. Invest.*, 1935, **14**, 106.
2 Watson, C. J., *J. Clin. Invest.*, 1936, **15**, 327.
3 Dobriner, K., *J. Biol. Chem.*, 1936, **113**, 1.
4 Watson, C. J., *J. Clin. Invest.*, 1937, **16**, 383.
*Merck and Company, Inc.