and ethereal sulfates on these diets was estimated. 2. The extent of the synthesis of the mercapturic acid and of the ethereal sulfates is apparently a function of the nutritive state of the animal: when the animal was deprived of dietary sulfur, a decrease in the output of mercapturic acid and an increase in the output of ethereal sulfates was noted. 3. The results offer further support to the previous suggestion that the dietary sulfur is not the immediate source which is used for the detoxication of bromobenzene in dogs.

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Action of Parahydroxyphenylisopropylamine on Induced Cardiac Standstill.

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The pressor response of the experimental animal has been used almost exclusively in the investigation of the comparative pharmacological actions of the epinephrine-like compounds (the sympathomimetic amines).[1] In previous studies,[2] the cardiac standstill which may be induced in many individuals by pressure over the right carotid artery in the neck (carotid sinus reflex) was used as a basis for the investigation of the comparative activities of these substances on the human heart. In susceptible subjects a cardiac arrest of many seconds' duration can be induced consistently by compression of the carotid sinus. The standstill is the result of an active reflex stimulation of the vagus nerve so that the heart is temporarily deprived of its pacemaker, the sinus node.

Upon administration of drugs of the epinephrine series the cardiac standstill could be prevented due to the development of new centers of stimulus formation, usually in the ventricles. This effect on cardiac rhythmicity is definitely a sympathomimetic action as it could be produced by a number of sympathomimetic compounds and could not be affected by a variety of unrelated substances. The rate of the ectopic pacemaker was as an index of the intensity of the effect, and this served as a method for the comparative study of these substances using the human heart as the test object. As an illustration, after the intravenous administration of epinephrine 0.05 mg. the cardiac standstill was prevented by the development of a

1 Barger, G., and Dale, H. H., *J. Physiol.*, 1910, **41**, 19.

2 Nathanson, M. H., *Arch. Int. Med.*, 1934, **54**, 111.

ventricular rhythm with a rate of 60. A similar reaction was evoked by the intravenous injection of 100 mg. of ephedrine, giving an approximate ratio of ephedrine to epinephrine of 1:2000. Table I shows the comparative activities of a group of these substances as determined by this method.

TABLE I.

Comparative Activities of Sympathomimetic Amines on Cardiac Standstill.

Drug	Structural Formula	Approximate Ratio of Activity to l-epinephrine
l-epinephrine		1:1
d-epinephrine		1:20
[illegible]		1:10
Synthetic Substance		1:40
Synthetic Substance		1:40
Neosynephrin hydrochloride		1:100
Synephrin tartrate		1:400
Tyramine		1:1,200
Hordenine		1:6,000
Ephedrine		1:1,500 - 1:2,000
Phenylethanolamine		1:8,000
Catechol		Ineffective

The compounds were in the following forms: l-epinephrine, [illegible] amino 3,4 dihydroxy propylbenzene and the first-mentioned "Synthetic Substance" as hydrochlorides; d-epinephrine as the bitartrate; tyramine and hordenine, ephedrine and phenylethanolamine as the sulphates.

From a therapeutic standpoint there are clinical conditions in which it is highly desirable to have a substance available which possesses the property of preventing cardiac standstill and which is sufficiently stable to be active on oral administration and capable of producing a prolonged effect. Such a substance is especially ap-

plicable in the prevention of the ventricular standstill of heart block and the cardiac arrest which occurs in individuals with a hypersensitive carotid sinus reflex.[3] Ephedrine was the only substance available in the previous study which was effective when administered by mouth. The hydroxyamines as illustrated by the synephrins and tyramine were definitely more active but failed to show any effect on oral administration in large doses. Ephedrine possesses 2 features which limit its therapeutic value, (1) the comparative weakness of its action (ratio to epinephrine 1:2000 by this method) and (2) when administered in adequate dosage, unpleasant side effects due to stimulation of the central nervous system.

In chemical structure, parahydroxyphenylisopropylamine stands between ephedrine and epinephrine (Fig. 1). Alles[4] has shown

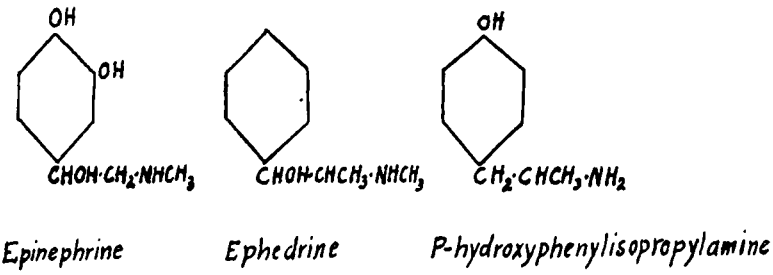

FIG. 1.

Chemical structure of epinephrine, ephedrine, and parahydroxyphenylisopropylamine.

that this substance has a more intense pressor activity than phenylisopropylamine, a compound closely related to ephedrine. In contrast to the hydroxy-amines previously studied, this substance is effective when administered by mouth. In a patient with a hypersensitive carotid sinus reflex, oral administration of the drug prevented the cardiac arrest.[5] In the present study, parahydroxyphenylisopropylamine hydrobromide* was administered to 8 individuals in whom a cardiac arrest could be consistently induced by pressure over the right carotid sinus. In each case the following procedure was carried out. A control electrocardiogram was made showing the induced cardiac arrest. A single dose of the drug was then administered by mouth which consisted in 6 instances of 60 mg. and in 2 cases of 40 mg. Electrocardiograms were then taken at intervals

[3] Weiss, S., and Baker, J. P., *Medicine*, 1933, **12**, 297.

[4] Alles, G. A., *J. Pharmacol. and Exp. Therap.*, 1933, **47**, 339.

[5] Prinzmetal, M., Personal communication.

* The parahydroxyphenylisopropylamine hydrobromide was supplied by the Smith, Kline and French Laboratories.

of 15 minutes and the pressure on the carotid sinus repeated. The cardiac standstill was abolished in every instance. In 5 individuals the standstill was eliminated due to the development of a new pacemaker in the ventricles, in 2 cases the sinus node retained its activity and in one instance beats from a supraventricular focus alternated with ectopic beats of ventricular origin. The effect was noted consistently within 30 minutes after the administration of the drug and the duration varied from one to 3 hours. In 3 subjects the experiment was repeated after an interval of several days to a week, using 100 mg. of ephedrine sulphate. In each instance ephedrine produced qualitatively the same effect as the parahydroxyphenylisopropylamine but the reaction was definitely less intense. The parahydroxyphenylisopropylamine produced a reaction which was earlier in onset and of longer duration. This is illustrated by Figs. 2 and 3. The qualitative similarity of the reaction is indicated in the electrocardiograms by the identical contour of the complexes which followed the administration of the 2 substances. Of particular in-

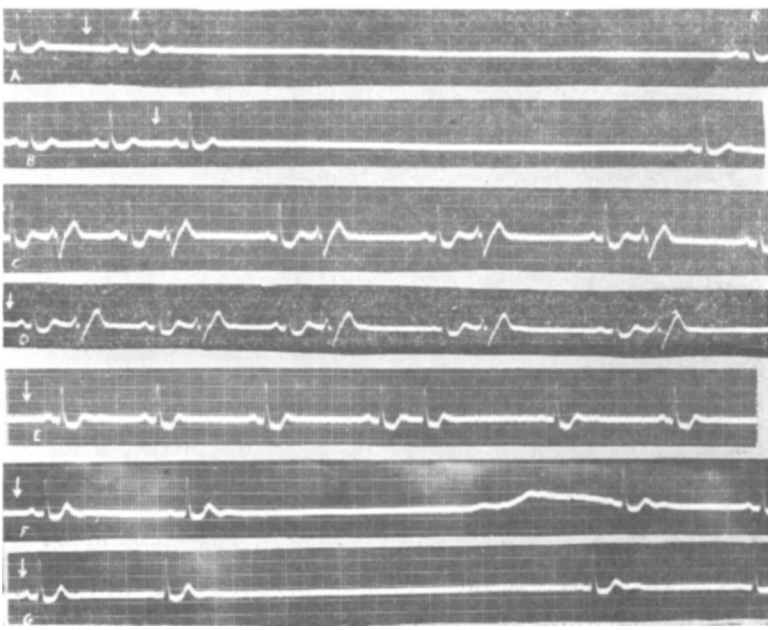

FIG. 2.

(Patient G. S.) Strip A shows cardiac standstill of 7.2 seconds induced by pressure on the right carotid sinus (arrow). Lower strips taken at 15-minute intervals following the oral administration of 60 mg. of parahydroxyphenylisopropylamine hydrobromide. Strips C and D show the standstill prevented by the development of beats of auricular and ventricular origin. In strip E the beats are all supraventricular in origin.

terest was the fact that no symptoms referable to stimulation of the central nervous system were noted. Symptoms of nervousness, tremor, apprehension and sweating were looked for but were not observed in any instance. A moderately severe headache occurred in one case apparently due to the rise in blood pressure.

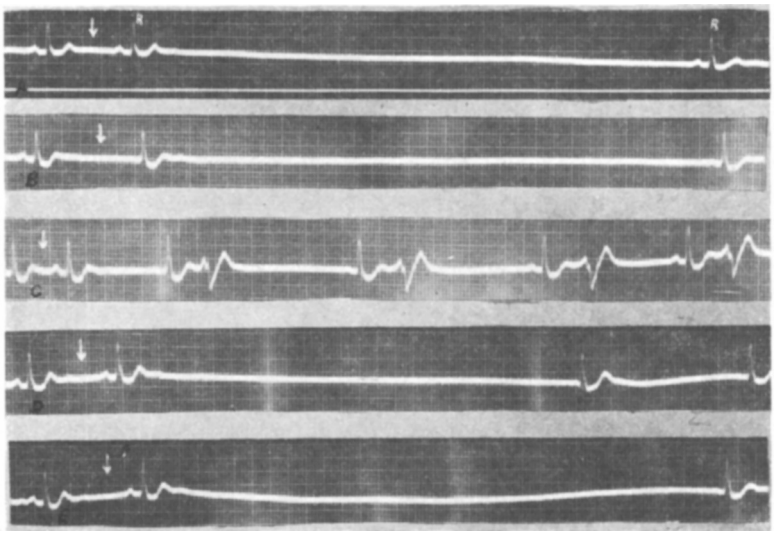

FIG. 3.

(Patient G. S.) Strip A shows a cardiac standstill of 7 seconds induced by pressure on the right carotid sinus (arrow). Strip B taken 30 minutes after the oral administration of 100 mg. of ephedrine sulphate. The cardiac standstill can still be induced. Strip C taken 45 minutes after the drug shows the standstill prevented by the development of beats of auricular origin alternating with beats of ventricular origin. D and E taken at 60 and 75 minutes after the drug show the disappearance of the effect. Compare with Fig. 2 and note that the response to the ephedrine is qualitatively similar but distinctly less intense.

Conclusions. 1. Parahydroxyphenylisopropylamine, when administered by mouth, is effective in the prevention of cardiac arrest. 2. This substance is more active than ephedrine on induced cardiac arrest. 3. When administered in a dosage effective in preventing cardiac standstill, parahydroxyphenylisopropylamine does not produce a central nervous stimulation with resultant unpleasant side effects.