"hook-up" when the mercury in the thermostat closes the circuit, the coil of the relay will "break" the circuit to the heater.

As the heater consumes 500 watts a considerable spark is generated at the make and break of the relay unless a condenser is connected with the two contact points. A condenser of a suitable size will absorb the spark and prevent the contact points from pitting and sticking.

CONSTANT TEMPERATURE-BATH, SPECIALLY DESIGNED FOR ISOLATED UTERUS EXPERIMENTS, FOR MAINTAINING A CONSTANT TEMPERATURE ABOVE THAT OF THE ROOM.

The details of the construction of an apparatus for isolated uterus experiments and a device similar to the above for automatically maintaining a constant temperature bath for Pituitary Assays was described by the author in a former paper.[1]

RESEARCH PHARMACOLOGICAL LABORATORIES,
SHARP & DOHME, August 8, 1927.

THE COMPARATIVE PHARMACOLOGIC ACTION OF EPHEDRINE AND ADRENALIN.

BY L. W. ROWE.

Although the active alkaloid ephedrine was first isolated in pure form from the Chinese drug *Ma Huang* by Nagai (1) in 1887 and some of its pharmacological properties reported upon by Miura (2) in the same year, it was not until recently that this alkaloid of *Ephedra vulgaris* has attracted attention from the medical profession. Amatsu and Kubota (3) first revived the study of this alkaloid, in 1918, but the widespread publication of Chen and Schmidt (4, 5, 6) and of Chen (7 to 18) in the past two years has been chiefly responsible for the clinical interest. Other pharmacological articles by Japanese and German workers are those by Fujii (19, 20) and Nagel (21).

Chemically the empirical formula of ephedrine (22, 23, 24) is $C_{10}H_{15}ON$, while that of adrenalin is $C_9H_{13}O_3N$, and structurally ephedrine is $C_6H_5CHOH.CH.CH_3.NH.CH_3$ while adrenalin is $C_6H_3(OH)_2CHOH.CH_2.NH.CH_3$.

The first reports of the practical use of this drug in modern therapeutics have been made recently by Miller (25), by Fetterolf and Sponsler (26), and by Rowntree (27). Later clinical reports have been made by Thomas (28), by MacDermott (29), by Miller (30), by Gaarde and Maytum (31), Jansen and Kreitman (32) and by Leopold and Miller (33). There seems to be no doubt about the drug possessing considerable merit.

However, in the preliminary pharmacological and clinical reports the impression is given that this new drug should very largely supplant adrenalin for two main reasons, the first being its prolonged action and the second its action after oral administration. It is the purpose of this paper to report pharmacological experiments comparing the action of these two drugs in various ways with the belief that these tests will show that there may be a definite place in therapeutics for ephedrine but that it will not replace adrenalin.

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[1] "An Improved Apparatus for Testing the Activity of Drugs on the Isolated Uterus" (Second Paper), by Paul S. Pittenger, Proceedings of The Pennsylvania Pharmaceutical Association, 1927, *American Journal of Pharmacy*, Sept. 1927.

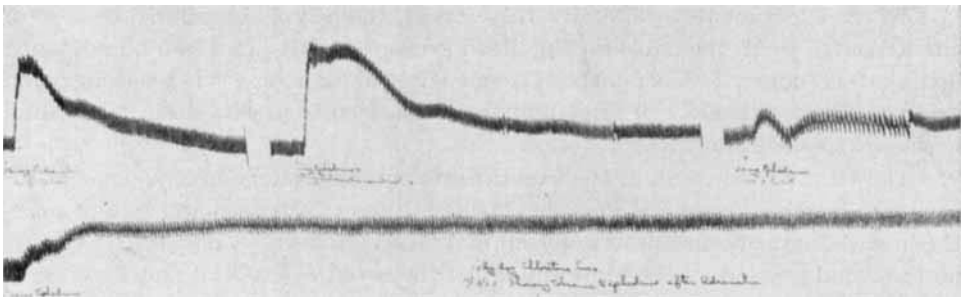
In the experimental work with these drugs, three types of parallel tests were carried out. First, the effect on the blood pressure of large and small doses when given intravenously. Second, the systemic effect of large doses of ephedrine given orally. Third, the effect of large and small doses on the heart itself, when such doses are given intravenously.

Dogs were used in all of the experiments and chloretone administered intraperitoneally was the general anæsthetic since it gives such deep and lasting anæsthesia with a steady and practically normal blood pressure. Comparative effects, on the blood pressure of the same animal, of the two drugs (tested under as nearly similar conditions as possible) may be tabulated very briefly as follows:

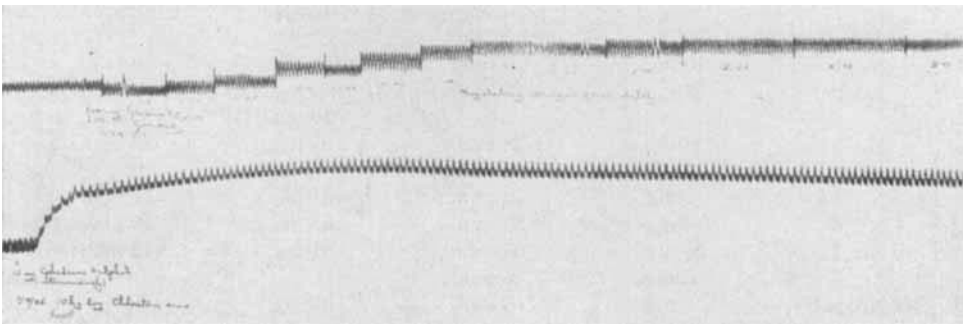
TABLE No. I.

Dog.	Dose of ephedrine.	Maximum rise in pressure.	Dose of adrenalin.	Maximum rise in pressure.
No. 1	10 mg.	10 mm.	.01 mg.	20 mm.
No. 2	50 mg.	19 mm.	.10 mg.	32 mm.
			.50 mg.	50 mm.
No. 3	100 mg.	28 mm.	.01 mg.	32 mm.
No. 4	100 mg.	20 mm.		
No. 5	1 mg.	6 mm.	.01 mg.	17 mm.
No. 6	10 mg.	39 mm.	.01 mg.	19 mm.
No. 7	50 mg.	64 mm.	.01 mg.	15 mm.
	10 mg.	6 mm.		
No. 8	5 mg.	6 mm.	.01 mg.	9 mm.
	100 mg.	22 mm.		
No. 9	10 mg.	9 mm.	.05 mg.	6 mm.
	100 mg.	2 mm.	.10 mg.	22 mm.
No. 10	1 mg.	3 mm.		
	5 mg.	6 mm.	.05 mg.	42 mm.
	100 mg.	31 mm.		
No. 11	100 mg.	16 mm.	.10 mg.	31 mm.
	200 mg.	None (after adrenalin)		
No. 12	100 mg.	19 mm.		
	10 mg.	9 mm.		
No. 13	5 mg.	6 mm.		
No. 14	20 mg.	1 mm.	.02 mg.	40 mm.
			.01 mg.	20 mm.

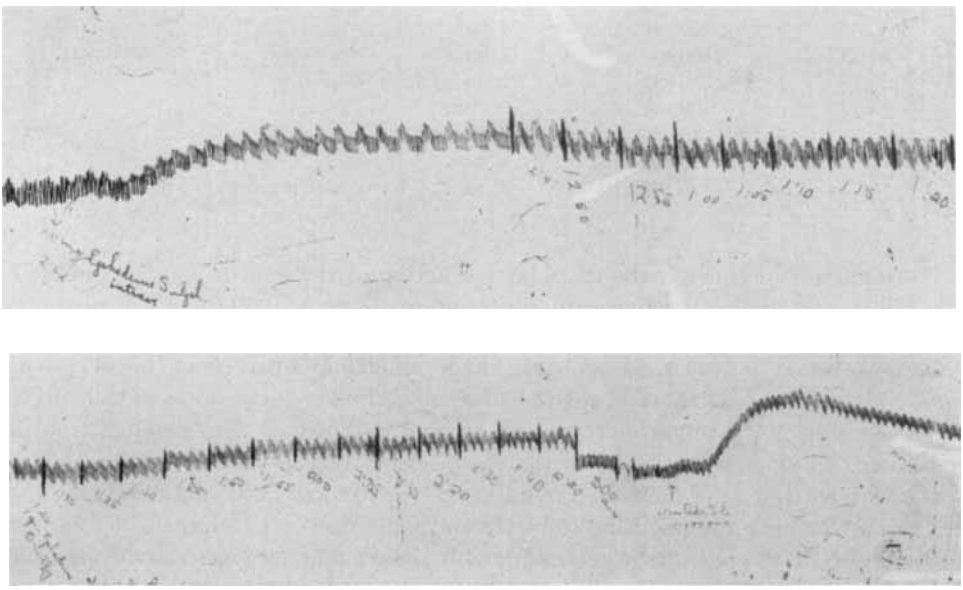
In these experiments the more lasting action of the ephedrine was quite evident, but it was much less powerful, requiring from 100 to 1000 times the adrenalin dosage to produce equivalent effects on the same dog. There was no definite quantitative relation between dosage and effect following intravenous injections of ephedrine sulphate as there is with adrenalin since very large doses of ephedrine failed to bring forth much more rise in pressure oftentimes than resulted from a much smaller dose when given to the same dog. Also in several experiments it was observed that after doses of adrenalin such as .02 mg. or .05 mg. the same dog showed a tolerance to ephedrine sulphate and failed to react to large doses except to a very slight degree. However, adrenalin always reacted vigorously even after large doses of ephedrine. Tracings No. 1, No. 2, and No. 3 show the comparative pressor action from intravenous doses of the two drugs and also the tolerance to ephedrine. Tracings No. 1, No. 2 and No. 3 follow:



Left to right, top row: .02 mg. Adrenalin intrav.; 10 mg. Ephedrine and .01 mg. Adrenalin combined. 20 mg. Ephedrine Sulphate. Tolerance. Lower row: 20 mg. Ephedrine Sulphate intrav.



Upper row: 800 mg. (.8 gm.) Ephedrine Sulphate given orally at 11:10 A.M. Blood pressure taken every 20 min. to 3:00 P.M. Dog came out of anæsthetic slightly. Lower row: 10 mg. Ephedrine intrav. before oral dose.



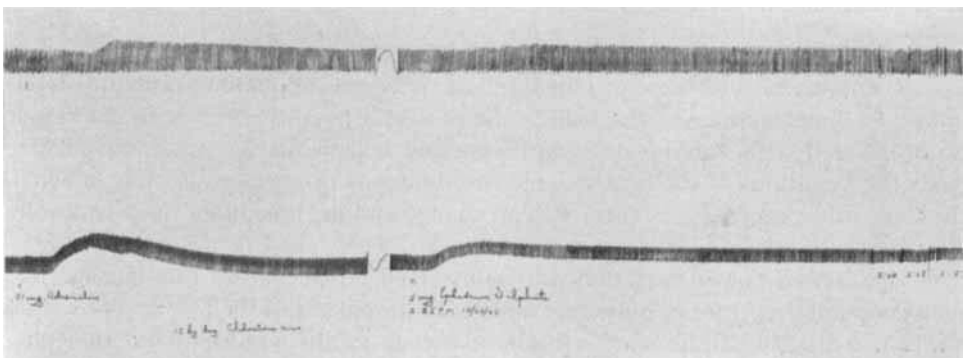
Upper row: 10 mg. Ephedrine Sulphate intrav. Lower row: 1000 mg. (1.0 Gm.) Ephedrine Sulphate given orally, followed by .01 mg. Adrenalin.

EFFECT OF ORAL DOSAGE.

It has been demonstrated in this laboratory that large doses of adrenalin do not produce appreciable systemic reactions in normal animals when such doses are given per stomach. This is due partially to the rapid destruction of the adrenalin in the stomach before it can be absorbed and to the prevention of absorption by the powerful vaso-constrictor action on the vessels of the alimentary tract. The drug can be given in solution sublingually with *definite* therapeutic effect.

From pharmacological and clinical reports the action of ephedrine sulphate, even in moderate oral doses, appeared to be definite and beneficial so that some pharmacological tests were made. Four distinct experiments were conducted upon anæsthetized dogs whose susceptibility to ephedrine was tested by a small dose given intravenously more than an hour before the oral dose.

In the first test a 400-mg. dose was given orally and the blood pressure was



Tracing No. 4.

Above: Direct heart action. Below: .01 mg. Adrenalin HCl intrav. and 5 mg. Ephedrine Sulphate.

raised to a maximum of 7 mm. above normal about one and one-half hours after dosing.

In the second test 1000 mg. (1.0 Gm.) was given orally and the blood pressure was raised to a maximum of 8 mm. within one and one-half hours after dosing. This dog showed a rise of 10 mm. in blood pressure from an intravenous injection of 10 mg. given 2 hours previous to the oral dose. This experiment indicates that the intravenous action is more than 100 times as powerful as the oral effect from the same dose.

In the third experiment a dog was starved for 24 hours and a dose of 500 mg. given orally. Within a period of 2 hours and 10 minutes after dosing, the blood pressure failed to show any rise—in fact, a slight fall in pressure occurred soon after dosing, which may have been due to the dog becoming more completely anæsthetized. At the end of the experiment the dog was killed and an examination showed a small amount of food residues in the stomach so that the period of fasting was not as effective as it should have been. This dog was injected with 10 mg. intravenously about 2 hours before the oral dose and the blood pressure was raised 21 mm.

A fourth dog was starved for 24 hours and then anæsthetized with chloretone. A 10-mg. dose of ephedrine sulphate was given intravenously and caused a maximum rise in pressure of 35 mm., thus showing the marked susceptibility of this dog to the drug. One hour later, when the pressure had returned to normal, an oral dose of 800 mg. was given. The blood pressure was observed for 4 hours and rose 14 mm. within about 2 hours. The higher pressure was partly maintained by the animal beginning to come out of the anæsthetic about 2 hours after dosing. In this experiment the drug was much more than 80 times as powerful when given intravenously as when given orally. Autopsy showed the dog's stomach to be free from food residues. (See Tracings Nos. 2 and 3.)

These experiments show that ephedrine is not absorbed rapidly enough from the stomach to produce a systemic effect upon the blood pressure which is at all comparable to its action intravenously, but that it does act appreciably when given in large doses orally. Apparently specific effects such as the broncho dilator action in asthma may be elicited by smaller oral doses such as 50 mg.

EFFECT ON HEART.

A number of tests were conducted with ephedrine sulphate in order to determine its direct action on the heart. Dogs deeply anæsthetized with chloretone were injected with varying doses intravenously and in the five most satisfactory tests the amplitude of the beat was increased but the rate was not visibly affected. In three other experiments there was no change and in three more there was a decrease in amplitude.

It is a well-known fact that adrenalin given intravenously causes a marked but temporary increase in pulse rate and in the amplitude of the beat. The action of the two drugs upon the heart is similar in increasing the amplitude but the ephedrine does not accelerate the heart even in very large doses to the extent that small doses of adrenalin do. (See Tracing No. 4.)

LOCAL EFFECTS.

The mydriatic action of ephedrine which was first observed by Miura was confirmed by tests on the rabbit's eye. However, 1% to 5% solutions of the drug must be used. Adrenalin has a slight mydriatic action.

When applied locally to mucous membranes the vaso-constrictor action was not more marked from a 5% solution than is caused by a 1 to 2000 solution of adrenalin though it was more lasting. Ephedrine has no local anæsthetic action and because of its weaker vaso-constrictor action is not successfully used with local anæsthetics, while adrenalin is a very useful addition to local anæsthetic solutions that are to be used hypodermically. When tested on the isolated virgin guinea-pig uterus very dilute solutions such as 1 to 100,000 caused a marked but not a maximum contraction of the muscle. The drug may therefore possess some oxytocic action in therapeutics but histamine contracts the isolated uterus very effectively in dilutions of 1 to 20,000,000 and yet it is not valuable clinically.

Neither drug has any appreciable germicidal action.

TOXICITY

Comparative tests were conducted upon white mice, the injections being given intraperitoneally so that absorption would be necessary and yet could be easily

accomplished. The M. L. D. of ephedrine sulphate was found to be about 400 mg. per Kg. body weight (0.4 mg. per Gm.), while that of adrenalin chloride was found to be 8 mg. per Kg (0.008 mg. per Gm.) The ratio of toxic doses by this method is as 50 is to 1 and adrenalin is consequently fifty times as toxic as ephedrine by hypodermic injection. Since adrenalin is fully 100 times as active its factor of safety is consequently twice as great. Orally, both drugs are practically non-toxic as they are not absorbed rapidly enough to produce a toxic action.

SUMMARY.

In this accumulation of the pharmacological data it has been shown that the qualitative action of ephedrine is similar to that of adrenalin in several respects, but that it is much less powerful. The more lasting action of the ephedrine is apparent when given hypodermically in comparatively large doses. The claims of the value of the new drug for oral administration would seem to be somewhat exaggerated, since for a systemic action such as a rise in blood pressure more than 100 times the intravenous dose is required to produce an equivalent effect from an oral dose. Specific effects in abnormal conditions such as the broncho dilator action in asthma can be elicited by oral administration of fairly large doses such as 50 mg. and this action is more lasting than that of adrenalin given hypodermically. However, it is well known that adrenalin is not effective following oral administration.

A tolerance to the action of large doses of ephedrine administered intravenously after moderate doses of adrenalin was exhibited by several dogs, although it did not always occur. The reverse was not observed in my experiments.

Adrenalin was found to be only 50 times as toxic as ephedrine sulphate when injected intraperitoneally into white mice, but it is fully 100 times as potent.

From the pharmacological experiments reported it would seem highly probable that while ephedrine, though much less active relatively, is similar in some respects to adrenalin yet its indications will be more limited and frequently quite distinctive from those of adrenalin.

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THE LIVING BELLADONNA.

(*Continued from p. 836.*)

METABOLISM.

The belladonna, in common with other green plants, receives a small portion of material from the soil in the form of salts dissolved in the water absorbed. The greater portion of the supply, however, comes from the air. This is not the food of the plant, but the raw material—"the makings of food." Before these materials can become food, much work must be expended upon them.

The food prepared by the plant is not immediately used up, the excess over immediate requirements being stored in various parts of the plant for subsequent consumption. The stored food passes through processes of change and digestion associated with a process of assimilation. A constructive process—anabolism, a destructive or breaking down process—catabolism.

The amount of food material taken in by the belladonna plant from the soil is very small. One hundred grains of the green plant will give only about one grain of mineral matter (ash).

When subjected to analytical processes, the belladonna plant has been found to contain the following elements: hydrogen, carbon, nitrogen, oxygen, sulphur, potassium, calcium, phosphorus, chlorine, sodium, magnesium, iron, aluminum, silicon and, in rare instances, copper.

One would not attempt to build up a plant structure from the "humpty-dumpty" array of elements found in belladonna. Each of the several elements noted renders a service to the organism. The activity of the life elements we now know is connected with the forms of electric energy called catalysis.

"The electric action and reaction of the elements according to modern views are the chief phenomena of the internal functions of life, developed in the presence of oxygen by the energy either of the heat of the earth or sun, or both the heat and light of the sun."—Osborn.

It is beyond our ken to understand why, in the interplay of the foregoing elements, at one time there comes a rose and at another time a solanum.