A NOTE ON THE PHARMACOLOGY OF RESCINNAMINE AND SERPENTINE

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The pharmacological properties of rescinnamine and serpentine have been studied. Both lower the blood pressure of anaesthetised cats but rescinnamine has a prolonged effect whilst serpentine has only a brief action. Rescinnamine does not antagonise the effects of adrenaline or noradrenaline on the blood pressure of the cat or on the isolated heart, auricles or intestine. Serpentine antagonises vasoconstriction due to adrenaline and noradrenaline in the isolated perfused rat hindquarters but not that due to 5-hydroxytryptamine creatine sulphate, barium chloride or pitressin. Serpentine reversibly antagonises the pressor responses to bilateral carotid occlusion, central vagal stimulation and splanchnic stimulation. Rescinnamine irreversibly antagonises these responses and also the responses from compression of the abdominal aorta and hypoxia, which suggests both alkaloids have an action upon the sympathetic nervous system. Rescinnamine also has some direct depressant effects on cardiac, intestinal and skeletal muscle.

CLINICAL trials of rescinnamine by Smirk and McQueen[1] and by Hershberger, Dennis and Moyer[2] have indicated that there is apparently no important difference between the hypotensive effects of rescinnamine and those of reserpine. It was observed that mental symptoms occurring in patients treated with reserpine were often relieved by changing to rescinnamine without any adverse influence upon the control of the blood pressure. Rescinnamine and serpentine have been reported to have hypotensive properties in animals[3–5], but rescinnamine displays no antagonism to the pressor effects of adrenaline or noradrenaline on the blood pressure of the cat, instead there is a slight enhancement of the pressor response[6]. Rescinnamine inhibits the pressor responses to bilateral carotid occlusion, electrical stimulation of the central end of the cut vagus and the pressor response to hypoxia. On the other hand serpentine does not antagonise the pressor effects of adrenaline or noradrenaline and does not inhibit the response of the isolated guinea pig seminal vesicles to adrenaline[5]. Rises in the blood pressure of the cat following electrical stimulation of the cut central ends of the sciatic nerve or vagus, or following stimulation of the splanchnic nerve, or occlusion of the carotid arteries are either not inhibited, or only inhibited to a minor degree, by serpentine[7].

The information available about the effects of rescinnamine or serpentine on the cat or on isolated tissues and organs, is limited and since both alkaloids are present in some rauwolfia preparations which are used clinically we felt it worthwhile to amplify some of the previous studies.

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Materials and Methods

Perfusion fluids. The composition of these has been described previously[8].

Drugs were dissolved in the appropriate saline solution before use. Rescinnamine was dissolved in dilute acetic acid.

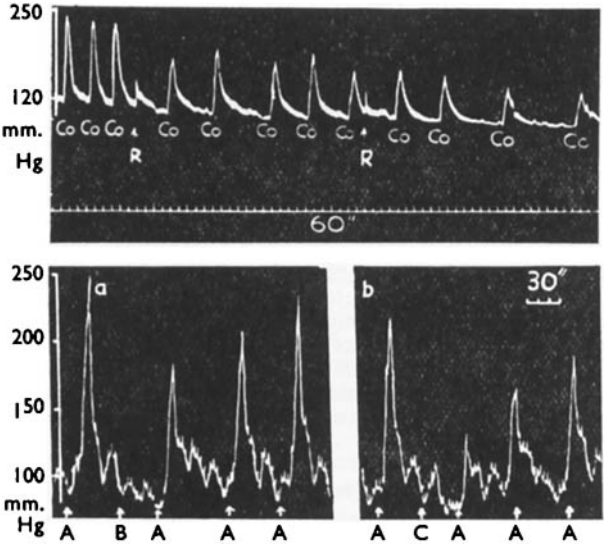

FIG. 1. Influence of rescinnamine and serpentine on the pressor response to bilateral carotid occlusion.
Upper Tracing. Cat, chloralose anaesthesia. Blood pressure record taken from the femoral artery. Drugs administered intravenously. At Co, bilateral carotid occlusion for 30 sec. At R, rescinnamine 0·75 mg./kg.
Lower Tracing. Cat, chloralose anaesthesia. Blood pressure record taken from the femoral artery. Drugs administered intravenously. At A, bilateral carotid occlusion for 25 sec. At B, serpentine 1·0 mg./kg. At C, serpentine 2·0 mg./kg. Record (b) 10 min. after (a).

The following preparations and techniques were used.

In pentobarbitone or chloralose-anaesthetised cats constant pressor responses were obtained to: (*a*) intravenous injection of adrenaline (Ad) or noradrenaline (NA), (*b*) clamping of both common carotid arteries, (*c*) stimulation of the cut central end of the vagus, (*d*) stimulation of the cut central end of the sciatic nerve, (*e*) stimulation of the cut central end of the greater splanchnic nerve, (*f*) compression of the abdominal aorta above the level of the coeliac artery and (*g*) hypoxia by inhalation of a 95 per cent N_2, 5 per cent CO_2 mixture. Nerves were stimulated by square impulses from a Dobbie McInnes stimulator at 5 to 20 volts, frequency of 1000 to 1400 per minute, pulse width 0·5 to 3·0 msec.

A constant hypertension was maintained by intravenous infusion at 1 ml./min. of a solution containing from 50 to 100 μg./ml. of Ad or NA. Depressor responses were obtained by injection of acetylcholine (ACh) or histamine acid phosphate (Hm). Contractions of the nictitating

membrane were obtained in response to electrical stimulation of preganglionic fibres of the cervical sympathetic.

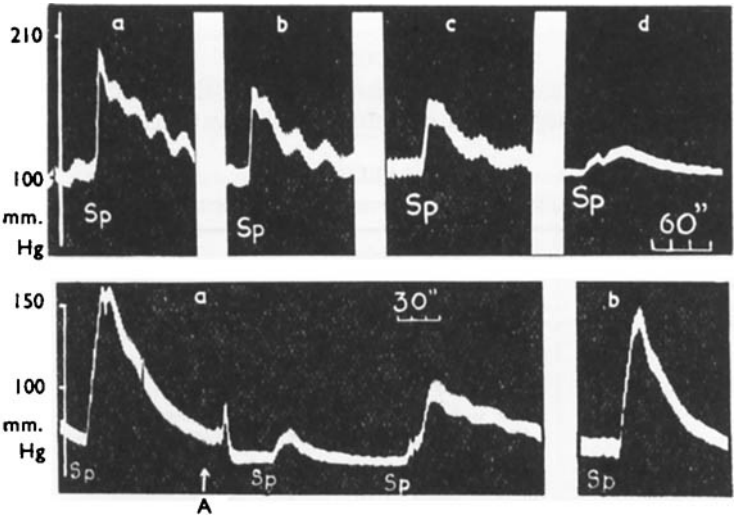

FIG. 2. Influence of rescinnamine and serpentine on the pressor response to stimulation of the splanchnic nerve.

Upper Tracing. Cat, pentobarbitone anaesthesia. Blood pressure record taken from the common carotid artery. Drugs administered intravenously.

At Sp, stimulation of the central end of the greater splanchnic nerve for 15 sec. (square impulses, 10 v., frequency 1,000/min. pulse width, 3 msec.).

(a) before rescinnamine.
(b) 10 min. after 1 mg./kg. rescinnamine.
(c) 50 ,, ,, ,,
(d) 180 ,, ,, ,,

Lower Tracing. Cat, chloralose anaesthesia. Blood pressure record taken from the common carotid artery. Drugs administered intravenously.

At Sp, stimulation of the central end of the greater splanchnic nerve for 30 sec. (square impulses 10 v., frequency 1,200/min. pulse width, 1·5 msec.).

At A, serpentine 1 mg.

Record (b), 20 min. after serpentine.

The frog rectus abdominis muscle was suspended in frog Ringer's solution at room temperature, isolated strips of rabbit duodenum were suspended in oxygenated Locke's solution at 37°, strips of guinea pig ileum in oxygenated Tyrode's solution at 30° and strips of horse carotid arteries in oxygenated Tyrode's solution at 36°. Isolated kitten hearts were perfused by Langendorff's method using oxygenated, double-glucose Locke's solution at 37° and this solution at 29° was used for isolated guinea pig auricles. The isolated rat hindquarters were perfused by oxygenated Locke's solution at room temperature using Gaddum's drop recorder to measure the out-flow.

In experiments with isolated tissues all drug concentrations, unless otherwise mentioned, refer to the final bath concentration in μg./ml. In

experiments on intact cats the doses are expressed as μg. or mg. of drug per kg.

Results. These are presented in Table I.

DISCUSSION

Rescinnamine causes an immediate but short-lived fall in the blood pressure of the anaesthetised cat but our observations do not point to

TABLE I

COMPARISON OF PHARMACOLOGICAL EFFECTS OF RESCINNAMINE AND SERPENTINE

Preparation	Rescinnamine	Serpentine
B.P. Anaesthetised cat	0·5–2 mg. Immediate sharp fall, returning to base line in 10–15 min. No significant change until 3–4 hr. later, when B.P. dropped to 50–80 mm. Hg with bradycardia.	1–2 mg. Immediate short-lived fall.
	0·5–1 mg. No or slight reduction in pressor response to Ad and NA (0·5–2 μg.)	1–2 mg. Antagonism to Ad (1–4 μg.) response more effective than to 1–4 μg. NA.
	0·5–1 mg. No modification of ACh or Hm (1–2 μg.) depressor responses.	0·5–1 mg. As rescinnamine.
	1 mg. Slight reduction in Ad or NA induced hypertension.	1–2 mg. Little or no effect on the hypertension.
	2–4 mg. Irreversibly lowered hypertension to normal in a few minutes.	
Vasopressor reflexes	0·5–1 mg.	1–2 mg.
(i) Bilateral occlusion of common carotid arteries (see Fig. 1)		Pressor effects in (i) reduced and reversible.
(ii) Compression of abdominal aorta	Pressor responses significantly reduced but not completely abolished. Maximum reached after 30–60 min.	(ii) No response.
(iii) Electrical stimulation of greater splanchnic nerve (see Fig. 2)		(iii) Reversible effect.
(iv) Electrical stimulation of central end of cut vagus (see Fig. 3)	Pressor effects abolished in 15–30 min.	(iv) Effects reduced and reversible and of short duration.
(v) Hypnoxia		(v) No response.
(vi) Electrical stimulation of central and of cut sciatic nerve		(vi) Effects reduced and reversible and of short duration.
Nictitating membrane (see Fig. 4)	1–2 mg. No direct stimulant or immediate effect on magnitude of electrically induced contraction, but after 30 min. significant reduction in amplitude with a maximum after 3 hr.	1–2 mg. No direct effect, significant reduction in electrically induced contractions. 3–4 mg. abolished response and also antagonised Ad-induced contractions.
Cardiac muscle	Perfusion of a solution containing 1 μg./ml.	10 μg./ml.
(i) Kitten heart	Irreversible decrease in rate and amplitude gradual in onset. Outflow decreased. Increased rate and amplitude produced by Ad and NA (0·5 μg.) were not altered by 25–50 μg.	Initial stimulation, then decreased in amplitude and rate. Outflow not significantly altered.
(ii) Guinea pig auricles	2–8 μg. Immediate reversible reduction in rate and amplitude. No effect on responses to Ad or NA (0·02 μg.).	1·5–10 μg. Reversible decrease in rate and amplitude. No effect on response to Ad or NA (0·02 μg.). Antagonised depressant effects of ACh 1–2 μg.).

TABLE I—*Continued*

Preparation	Rescinnamine	Serpentine
Vascular smooth muscle (i) Horse carotid artery	10 μg. Little or no direct effect.	10 μg. As rescinnamine.
	2–40 μg. Relaxed the sustained contractions induced by Ad and NA (1–2 μg.), 5 HT (10–50 μg.), ACh (0·02–0·1 μg.) and Hm (1–2 μg.).	10–25 μg. Antagonised stimulant effect of Ad and NA (0·1–2 μg.) and 50–70 μg. antagonised contractions induced by ACh (0·1–0·5 μg.).
(ii) Rat hindquarters	0·1–1 μg. Little or no vasodilatation.	10 μg. Reversible increase in outflow. Antagonism of the vasoconstrictor effects of Ad, NA (0·2–1 μg.) but not to 5-HT (0·01–1·5 μg.), $BaCl_2$ (0·2–1·0 mg.) or pitressin (0·01–0·02 units) see Fig. 5).
Intestinal smooth muscle (i) Guinea pig ileum	1·5–3 μg. In some preparations had a direct stimulant effect which was inhibited by atropine.	1–12·5 μg. No direct effect. Inhibition of contraction induced by 0·2–1·0 μg. of ACh: rapid recovery.
	2–20 μg. Antagonised ACh and Hm (0·04–0·1 μg.) induced contractions. Recovery was complete, but for Hm was prolonged. (see Fig. 6)	
(ii) Rabbit duodenum	No direct effect and no modification of ACh and Ad.	1–10 μg. Slightly stimulated, but 25–100 μg. inhibited peristaltic movement. 2·5–10 μg. antagonised ACh-induced contractions (0·02–0·2 μg.) but no effect on relaxation produced by Ad or NA (0·05–0·2 μg.).
Skeletal muscle Frog rectus	5–50 μg. Direct stimulant effect (Fig. 7). Not influenced by atropine or tubocurarine (5–10 μg.). Antagonised ACh-induced (0·1–0·2 μg.) contractions. This was more marked with prolonged contact (Fig. 7*a*) than with a few minutes contact (Fig. 7*b*).	2–10 μg. Antagonism of ACh (0·25 μg.), nicotine hydrogen tartrate (1·5–2 μg.) and C10 (1–1·5 μg.) induced contractions. Potentiates antagonism of tubocurarine (0·5–1 μg.).

rescinnamine having a definite hypotensive action in the normotensive cat. Rescinnamine does not antagonise the pressor responses to Ad or NA on the blood pressure of the cat nor does it show any marked antagonism to their characteristic effects in isolated tissue preparations. Rescinnamine antagonism to Ad, NA, 5-HT and Hm on isolated strips of artery seems to be non-specific. Gillis and Lewis[9] have shown that reserpine-antagonism to contractions of the guinea pig ileum induced by ACh, Hm, 5-HT or $BaCl_2$ is non-specific in nature and that the effects of reserpine can be antagonised to some extent by certain intermediates of the tricarboxylic acid cycle. It is possible that rescinnamine which is closely allied chemically to reserpine may act in a similar way. Our observations do not support the findings of McQueen and Blackman[10] who have shown rescinnamine to have a vasodilator effect on the isolated innervated and denervated hindquarters of the rat or rabbit.

Rescinnamine antagonises or may reverse the pressor responses to hypoxia and to stimulation of the central end of the cut vagus, whilst pressor responses after bilateral carotid artery occlusion, splanchnic nerve stimulation and compression of the abdominal aorta are considerably reduced. Rescinnamine acts after a latent period and seems to

exert its maximum effect some 30 to 60 minutes after its administration. These reflex pressor responses may have the same mechanism of action, in the liberation of Ad and NA from the endings of adrenergic nerves, the reflex being mediated through the higher centres of the brain. The fact that adrenergic and ganglion blocking agents depress these reflexes supports this view[11]. Antagonism shown to these pressor reflexes indicates that rescinnamine may interfere with sympathetic activity in the central nervous system rather than at the periphery because it shows no antagonism to the peripheral effects of injected Ad and NA. Rescinnamine also

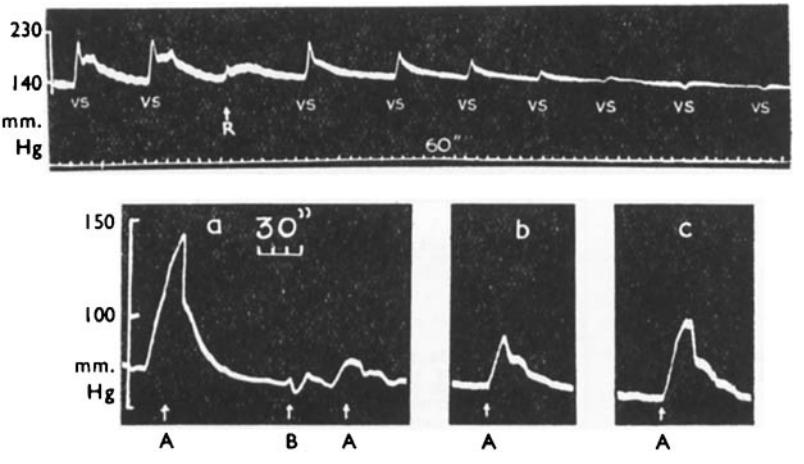

FIG. 3. Effects of rescinnamine and serpentine on the pressor response to stimulation of the cut central end of the vagus.
Upper Record. Cat, pentobarbitone anaesthesia. Blood pressure record taken from the carotid artery. Drugs administered intravenously. At Vs, stimulation of the cut central end of the vagus for 30 sec. (square impulses 15 v., frequency 1,000/min. pulse width 1 msec.). At R, rescinnamine 0·75 mg./kg.
Lower Record. Cat, chloralose anaesthesia. Blood pressure record taken from the carotid artery. Drugs administered intravenously. At A, stimulation of the cut central end of the vagus for 30 sec. (square impulses, 10 v., frequency 1,200/min. pulse width 0·75 msec.). At B, serpentine 1 mg./kg.
Records (b) and (c), 6 and 10 min. after serpentine.

considerably reduces the response of the nictitating membrane to stimulation of preganglionic sympathetic fibres which may be due to its effect on the ganglia. Rescinnamine also has some direct effects on smooth muscle cells; thus it inhibits ACh and Hm induced contractions of the guinea pig ileum and it antagonises the stimulant effects of drugs on artery strips. It also has a depressant effect upon the isolated heart and auricles and antagonises the stimulant effects of ACh on the frog rectus. Like reserpine[12], rescinnamine causes a slow contraction of the frog rectus abdominis muscle, which with reserpine, has been attributed to release of potassium ions. The character of the contraction of the rectus muscle in response to potassium ions is, however, dissimilar to that caused by rescinnamine.

Serpentine has some adrenergic blocking activity. On the blood pressure of the anaesthetised cat serpentine antagonises the response to Ad more than to NA. In higher doses it antagonises the vasoconstriction

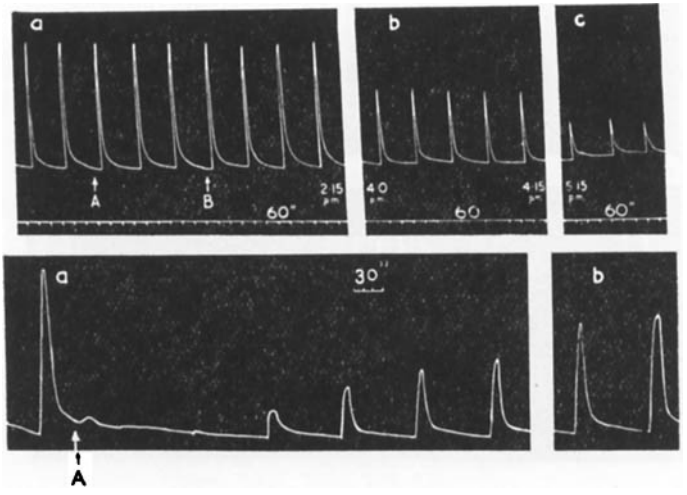

FIG. 4. Effects of rescinnamine and serpentine on the nictitating membrane.
Upper Record. Cat, pentobarbitone anaesthesia. Contractions of the nictitating membrane elicited at intervals of 3 min. by preganglionic stimulation for 30 sec. (square impulses, 10 v., frequency 1,000/min. pulse width 1 msec.). At A, rescinnamine 0·5 mg./kg. intravenously. At B, rescinnamine 2·0 mg./kg. intravenously.
Lower Record. Cat, chloralose anaesthesia. Contractions of the nictitating membrane elicited at intervals of 3 min. by preganglionic stimulation for 15 sec. (square impulses, 20 v., frequency 1,200/min. pulse width 2 msec.). At A, serpentine 2 mg./kg. Record (b), 40 min. after serpentine.

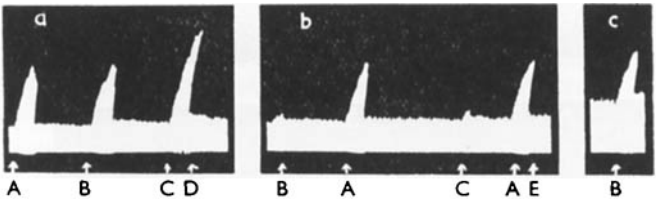

FIG. 5. Isolated rat hindquarters perfused with Locke's solution.
At A, 1·5 μg. of 5-HT. B, 0·01 μg. of Ad. C, 0·015 μg. of Ad. D, perfusion with 10 μg./ml. of serpentine. E, perfusion with Locke's solution.
Record (b), 20 min. after serpentine perfusion.
Record (c), 20 min. after perfusion with Locke's solution.

produced both by Ad and NA on isolated perfused rat hindquarters but it is ineffective against vasoconstriction caused by 5-HT, $BaCl_2$ or pitressin. It also antagonises Ad and NA induced contractions of strips of carotid

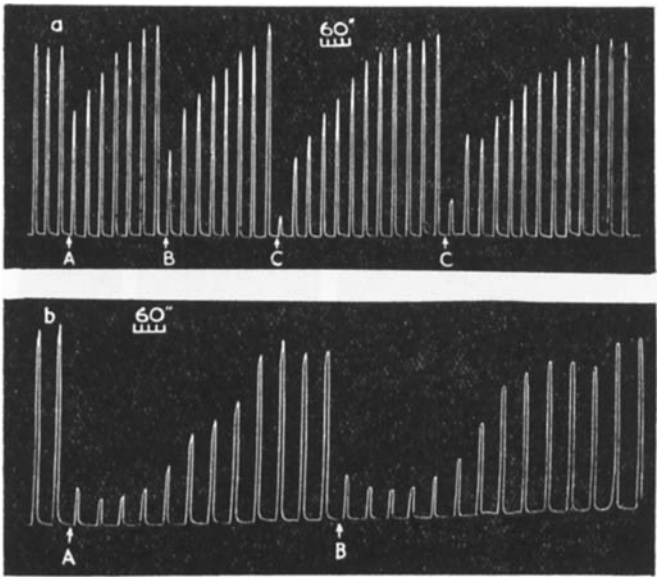

FIG. 6. The effects of rescinnamine on ACh and Hm induced contractions of the guinea pig ileum.

(a) All contractions produced by ACh (0·08 μg./ml.)
At A, rescinnamine 5 μg./ml.
At B, ,, 10 ,,
At C, ,, 20 ,,

(b) All contractions produced by Hm (0·1 μg./ml.).
At A, rescinnamine 8 μg./ml.
At B, ,, 4 ,,

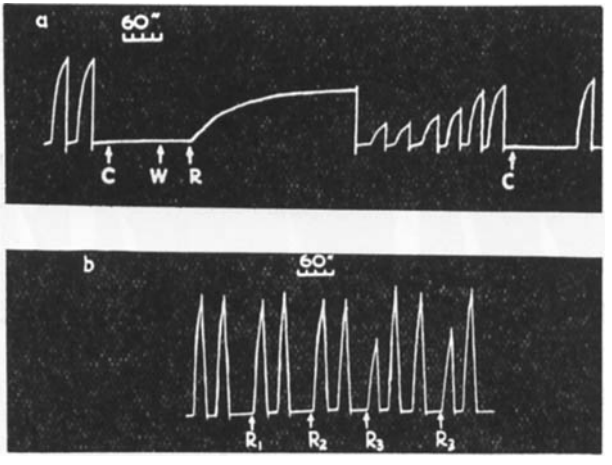

FIG. 7. The effects of rescinnamine on the isolated frog rectus abdominis muscle.

(a) Unlabelled contractions produced by ACh (0·15 μg./ml.)
At C, control solution. At W, wash out. At R, rescinnamine 20 μg./ml. for 20 min.

(b) All contractions produced by ACh (0·10 μg./ml.)
At R_1, rescinnamine 10 μg./ml. for 1 min.
At R_2, ,, 20 ,, ,,
At R_3, ,, 50 ,, ,,

arteries. Serpentine antagonises the vasopressor reflexes due to bilateral carotid occlusion and stimulation of the cut central ends of the vagus, sciatic and splanchnic nerves. Our results differ from those of Bein and Gross[7] who have reported that serpentine does not block these reflexes.

Apart from an initial short-lived fall in blood pressure, rescinnamine acts after a latent period but serpentine acts immediately and its effects wear off completely and rapidly. Serpentine antagonism is reversible but that of rescinnamine is irreversible.

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DISCUSSION

The paper was presented by MR. S. M. KIRPEKAR.

THE CHAIRMAN. In *Rauwolfia serpentina* reserpine was the most important alkaloid, but a great many other alkaloids were also present, including rescinnamine and serpentine. Had rescinnamine or serpentine any properties which suggested that they might replace reserpine in clinical use. Had the Authors satisfied themselves of the purity of their specimens?

DR. G. F. SOMERS (Liverpool). An important aspect of the paper was the differing results from those obtained by Bein and Gross.

MR. C. A. JOHNSON (Nottingham). The Chairman had suggested that reserpine was the main alkaloid of rauwolfia. The other alkaloids were present in much greater proportion, and the presence of reserpine was only recognised many years after such alkaloids as ajmaline and serpentine had been isolated. Did the results obtained on rescinnamine support the contention of clinicians that the hypotensive action of reserpine and rescinnamine were not significantly different, either quantitatively or qualitatively? Both of those alkaloids were closely similar in chemical properties, in contradistinction to serpentine, and both could be hydrolysed to methyl reserpate and a carboxylic acid. Had methyl reserpate an activity similar to that of rescinnamine or reserpine, or was the hypotensive effect reduced by such a hydrolysis? He believed the B.P.C. assay for

total alkaloids of rauwolfia did not extract and determine reserpine. It was the total alkaloids, less these two weakly basic alkaloids, reserpine and rescinnamine, which were determined.

DR. J. W. FAIRBAIRN (London). Was there a quantitative difference in effect between methyl reserpate and reserpine in animals?

DR. W. MITCHELL (London). It seemed surprising if the activity of methyl reserpate had not been determined.

MR. KIRPEKAR replied. Rescinnamine resembled reserpine but serpentine was different. They had taken melting points and had been quite satisfied about the purity of their compounds. It could be concluded that reserpine and rescinnamine had similar qualitative effects as blood pressure reducing agents. Methyl reserpate had been found as a metabolic product of reserpine in the body, but they did not know whether it was active.

MR. LEWIS replied. The drugs probably acted as intact molecules, the theory being that they entered the central nervous system and affected certain receptor sites, altering these in some way. The drug was then rapidly degraded and disappeared, leaving the receptor sites altered.