ORAL PREPARATIONS OF RAUWOLFIA SERPENTINA IN TREATMENT OF ESSENTIAL HYPERTENSION

BY

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The older Indian literature records the liberal use over several centuries of preparations of the roots of *Rauwolfia* species, and particularly *Rauwolfia serpentina*, for the treatment of dysentery, snakebites, and fever (? malaria). In more recent times these preparations have been used in India as sedatives and also for insomnia and insanity. By the end of the seventeenth century this use of rauwolfia root as a sedative had apparently reached Europe. The genus *Rauwolfia* belongs to the Apocynaceae and contains some 40 to 50 species, but *R. serpentina*, a large twining shrub found in India and Malaya, appears to be the main member used for these purposes, and it is therefore this plant whose roots were credited with all these most desirable qualities.

Preparations of these roots of *R. serpentina* were found to have definite hypotensive properties when tried in animals (Chopra *et al.*, 1933) in addition to producing hypnotic and sedative effects. This hypotensive action on the blood pressure has apparently been confirmed in varying degree in hypertensive patients (Vakil, 1940, 1949; Bhatia, 1942; Wilkins and Judson, 1953; Ford *et al.*, 1953; Arnold and Bock, 1953; Klausgraber, 1953; Joiner and Kauntze, 1954).

The hypotensive and hypnotic action of preparations of *R. serpentina* root would appear to reside in the content of alkaloids, of which some 15 have so far been isolated, two of the most active of these being rescinnamine and reserpine, ester alkaloids chemically related to yohimbine, differing only in the acid moiety (trimethoxycinnamic and trimethoxybenzoic acid). Reserpine makes up about 0.1% of crude preparations, and would seem in man to be more likely to cause drowsiness and diarrhoea than rescinnamine. In dogs it has only half the hypotensive potency (Cronheim and Toekes, 1955), but there is a marked variation in relative activity of these alkaloids in different animal species. There would also appear to be at least one other, as yet unidentified, highly active alkaloid in the crude extract.

Since, experimentally, rauwolfia does not interfere with transmission at the autonomic ganglia and in therapeutic dosage is neither adrenolytic nor sympatholytic, it has been suggested that the hypothalamus is the site of its activity, but this has not been proved.

Our past experience when using recommended hypotensive agents given by mouth for the treatment of essential hypertension had been most unsatisfactory. When rauwolfia became available two years ago it was therefore decided that a carefully controlled trial was essential. A prolonged period of observation by observers, if possible unchanged during the trial, of a suitable series of hypertensive patients in need of treatment, using each patient as his own control, would, it was felt, be most likely to yield results of any value at this stage of our knowledge of the treatment of hypertension.

This paper is a report to date of such a trial with a group of 39 severely hypertensive patients (38 of whom had essential hypertension) treated for a minimum period of six months and a maximum period of 20 months with rauwolfia (" rauwiloid ").

Type of Hypertensive Subjects Participating and Nature of Drugs Used

The trial was confined entirely to out-patients who were fully ambulatory. So far as was practicable every patient was seen at least once every two weeks, but many were seen far more often, though in some cases these intervals had to be increased. When ill-health caused a patient to take to bed or be admitted to hospital, he or she was immediately excluded from the trial from that date, the information then available being used, however, in arriving at our conclusion.

Every patient observed had a minimum diastolic pressure when attending the out-patient department of never less than 130 mm. Hg (see Table). No patient was used in this particular trial who had been known to us for less than six months, and some had been under our observation for several years, a few having participated in our early trials with the oral administration of methonium compounds (Locket *et al.*, 1951, 1952).

All the patients (except one) were suffering primarily, so far as could be judged clinically, from essential hypertension, and none came into the category of labile hypertensives. So far as possible, all cases of severe renal insufficiency from any cause, or any cause of hypertension other than essential hypertension, were excluded. Renal insufficiency developing during the trial did not exclude the patient.

The 39 patients (see Table) consisted of 31 females, average age 55 (range 34–72) and 8 males, average age 47 (range 37–64).

Each patient on attending the out-patient department was given a number by which he was identified to the dispensary during the trial, the numbers being consecutive. According to the number of the patient, using a chart of random numbers, the pharmacist, Mr. Williams, prescribed either control tablets or active drug. At some time later during the course of the trial the patient was changed from active drug to control tablets, or vice versa. At no time were any of the clinicians or patients concerned in the trial informed whether the participant was receiving dummy (control) tablets or active drug.

In the first ten months of the trial the active preparation used was total root extract (1,000 mg. daily). Since then (January, 1954) we have used total active alkaloids (8 mg. daily). We began this trial with the oral preparations known as rauwiloid, and these have been used consistently. However, when the trial was well under way we included some patients receiving other varieties of rauwolfia, with little apparent difference. Sixteen consecutive patients in addition received 8–10 mg. of *Veratrum viride* extract (" veriloid ") daily, during their entire observation period—that is, both with control tablets and with active rauwolfia.

In some patients, owing to the persistence of certain symptoms (later proved to be due to the drug), it was thought advisable to reduce the dose to 500 mg. of total rauwolfia extract, or 4 mg. of total active alkaloids, and occasionally even to stop this medication entirely. The clinician nevertheless, though suspecting that he was in these cases giving active drug, did not know this for certain until the final analysis.

Since we could detect little difference in hypotensive effect between 500 and 1,000 mg. of total root extract or between 4 and 8 mg. of total active alkaloids (nor between total extract and total alkaloids), the results of both alkaloids and total extract are considered together.

Method of Classification of Data

In assessing these results the initial observations were confined entirely to the level of the blood pressure, using

Certain Important Features of Cases Treated; Drugs Used in Treatment, and Results of Treatment on Height of Blood Pressure

Case No.	Sex and Age	Average Blood Pressure and Range During 3 Months Without Treatment Before Start of Trial		Papilloedema + = Present − = Absent	Albuminuria + = Present − = Absent ± = Occas. present	Period Under Observation in this Trial (Months)	Associated Cardio-vascular Renal Disease	Drugs Received	Result on Height of Blood Pressure of Treatment with Rauwolfia
		Systolic (mm.Hg)	Diastolic (mm.Hg)						
1	F 57	260 245–300+	160 150–210	+	+	20	L.V.F.	RE RA	S No response also +pentolinium +apresoline
2	F 56	260+ 230–280	145 135–150	−	+	8	A. of E.	RE	S
3	M 56	250 220–270	160 150–170	+	+	11	L.V.F.	RE RA	S
4	F 34	210 190–230	135 130–145	−	−	7	—	RE	O
5	F 53	210 180–220	135 130–140	−	+	18	L.V.F.	RE RA	A
6	F 57	250 240–260	145 140–150	−	−	19	A. of E.	RE RA	A
7	M 61	260 230–290	145 135–160	−	+	20	Int. C.	RE RA	G
8	F 56	260 230–280	150 140–160	+	+	20	Ret. haem.; Cere. thr.	RE	A
9	M 58	220 200–240	135 130–140	−	−	20	Ret. art. thr.	RE	A
10	F 52	275 260–300	135 130–140	−	−	6	—	RE	O
11	F 44	270 240–300+	150 145–160	−	−	20	—	RE	A
12	F 52	250 220–260	150 140–160	+	+	20	—	RE	O
13	F 50	260+ 245–300+	150 140–160	+	+	17	—	RE V	O
14	F 55	250 230–270	135 130–150	−	+	17	A. of E.	RE V	G
15	M 54	230 200–260	135 130–160	−	+	17	Cerbb. thromb.	RE V	G
16	F 72	260 200–280	140 135–165	−	−	7	Senile dementia	V	A Only patient to show a fall in B.P. without receiving rauwolfia
17	M 64	220 200–230	140 130–150	−	−	15	—	RE V	O
18	F 52	200 180–220	135 130–140	−	±	16	Mitral stenosis	RE V	O
19	F 58	260+ 240–300+	155 140–160	−	+	16	L.V.F.	RE RA V	O
20	F 41	260 150–280	170 150–180	+	+	7	Cereb. thromb.	RE V	O Received active drug during entire period until death
21	F 63	270 260–300	135 130–140	−	−	14	A. of E.	RE V	A
22	F 42	290+ 280–300+	165 140–185	+	+	18	Cereb. thromb.	RE RA V	O No response either with apresoline and pentolinium+rauwolfia+veriloid
23	F 61	230 200–240	140 130–145	−	−	6	—	V	O
24	F 55	270 240–300+	145 130–170	−	+	13	A. of E.	RE RA V	A
25	F 62	235 220–240	135 130–145	−	−	12	A. of E.	RE RA V	A
26	F 40	245 230–300	150 140–175	+	+	6	Cereb. thromb.	V	O
27	F 48	210 190–220	140 130–150	−	+	8	—	RE V	O No response with apresoline added. Had chronic nephritis and died whilst on active drug
28	M 50	195 190–210	135 130–140	−	−	10	—	RA V	A
29	F 64	260 150–300	140 135–165	−	+	8	Ret. art. thromb.	RA	S+mephenesin daily and sodium amytal nightly
30	F 46	260 250–290	140 135–160	−	+	14	L.V.F. A. of E.	RA	O
31	M 47	230 210–250	140 135–165	−	−	10	—	RA	G
32	F 56	260+ 260–300+	160 150–170	−	+	7	L.V.F.	RE RA	A
33	M 37	250 200–230	160 150–180	+	+	8	—	—	O Also receiving massive oral doses of pentolinium and apresoline
34	F 42	230 200–250	135 130–140	−	−	7	—	—	O Bilateral sympathectomy between control period and trial, with no effect
35	F 55	210 200–240	140 130–150	−	−	9	—	RA	A
36	F 64	260 230–290	140 135–145	−	+	6	—	RA	S
37	F 56	210 200–240	130 130–135	−	−	6	A. of E.	RA	S
38	F 56	230 270–210	140 130–160	−	−	6	—	RA	O
39	F 54	250 270–240	135 130–160	+	±	6	Ret. art. thromb.	RA	S

The upper figure in columns 3 and 4 records the average untreated blood-pressure level, and the lower two figures the range.
L.V.F. = Left ventricular failure. A. of E. = Angina of effort. Int. C. = Intracranial catastrophe, ? Cerebral thrombosis. RE = Rauwolfia total root extract. RA = Rauwolfia total active alkaloids. V = *Veratrum viride* extract. O = No hypotensive action. S = Slight—i.e., fall 10–20 mm. Hg. A = Appreciable—i.e., fall more than 20 mm. Hg. G = Good—i.e., fall to below 100 mm. Hg diastolic and in excess of 30 mm. Hg.

this to divide the patients into several separate categories. We then attempted to observe the relationship, if any, between these blood-pressure categories, the patient's symptoms, and any objective findings. In this trial, laboratory and other investigations were those essential for the diagnosis, observation of progress, and treatment of any case of hypertension of this degree of severity.

We were mainly concerned with the level of the diastolic pressure, since there is far less spontaneous variation in the diastolic level than in the systolic in these hypertensives. Also, the future expectation of trouble for these patients depends upon the height of the diastolic pressure.

All readings were obtained with the patient sitting. In every case where these showed a fall or rise in excess of 10 mm. Hg. from earlier pre-trial readings, they were checked on both arms by more than one observer.

The patients were divided into four groups according to the recorded fall of diastolic blood pressure. These were : O = no fall ; S = slight consistent fall—that is, 10–20 mm. Hg ; A = appreciable fall, greater than 20 mm. but not falling below the level of 100 mm. Hg ; and G = fall to a level consistently below 100 mm. Hg, and the fall was therefore always in excess of 30 mm. Hg (see Figs.).

Results

Of the 39 patients, 16 showed no consistent fall in diastolic blood pressure, 7 a slight fall, 12 an appreciable fall, and 4 a fall to below 100 mm. Hg. Of the 16 patients with no consistent fall in blood pressure, 4 had during the entire trial received either the control tablets alone or with extract of *Veratrum viride*, but never an active rauwolfia preparation. In the other 23 cases (except for one case in group A receiving extract of *V. viride* only) the fall in blood pressure occurred only whilst the patient was receiving the active rauwolfia preparation. When the patient was transferred to the control tablets the blood pressure, after a brief interval, began gradually to rise (see Figs.), and, similarly, transfer to active tablets resulted in a fall. Of 34 patients receiving active rauwolfia tablets at some period during this trial, 22 (67%) showed a fall in blood pressure of varying degree (slight in 21%, appreciable in 34%, and good—that is, to below 100 mm. Hg—in 12%) whilst actually taking the active preparation and not when on the control.

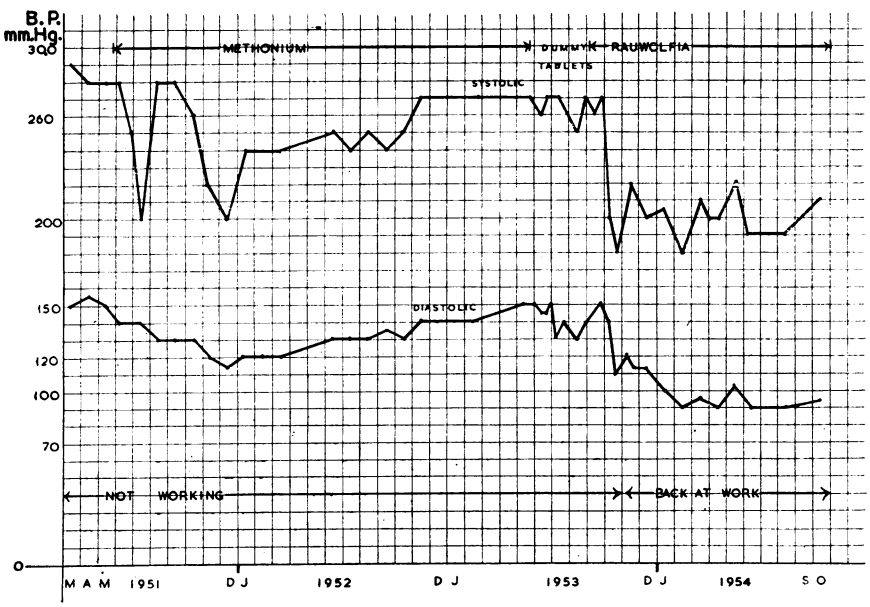

FIG. 1.—Graph of Case 7.

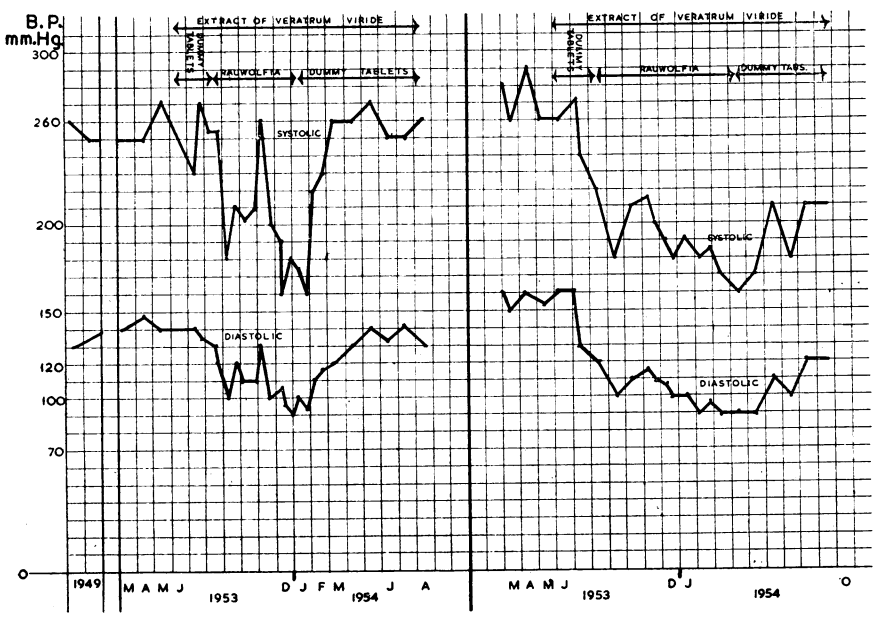

FIG. 2.—Graphs of Cases 14 and 15.

The combination of *V. viride* extract and rauwolfia gave 6 patients out of 13 who showed a hypotensive effect, as against 16 patients who showed a fall in blood pressure out of 21 receiving rauwolfia without additional *V. viride* extract. Nevertheless, the only patient in the trial who showed an appreciable fall in blood pressure without rauwolfia was actually receiving *V. viride* extract, and two of the four patients (see Fig. 2, Cases 14 and 15) in whom the diastolic blood pressure fell to below 100 mm. Hg were receiving both rauwolfia and extract of *V. viride*. It will be seen that the fall in blood pressure in Case 15 antedated the use of rauwolfia slightly, and with cessation of active drug rose slowly to a lower level than the control. This most satisfactory result, too, may be partly due to the *V. viride* extract.

The average age of patients who failed to respond to rauwolfia was 50 (range 34–64), whereas the average age of all patients who responded was 56 (range 44–64). Of the eight males, seven received rauwolfia and six (average age 55.2 years) showed a hypotensive effect (S, 1 ; A, 2 ; G, 3). Three of the seven males were receiving *V. viride* extract with the rauwolfia. Of the 31 females, 27 received rauwolfia, and of these 15 (average age 56.6 years) showed a hypotensive effect (S, 6 ; A, 9 ; G, 1). Of these 27, 10 were receiving extract of *V. viride*. The average age of the 11 females who did not respond to rauwolfia was 48.3 years.

Albuminuria in varying degree was present in 50% of patients in each of the four categories, but of 10 patients showing papilloedema 6 were in group O, 3 in group S, and only 1 in group A.

There were 8 patients who at the beginning of this trial were complaining of angina of effort—1 each in groups O and G, 2 in group S, and 4 in group A.

Four deaths occurred during the trial. One patient aged 48 who died of uraemia due to chronic nephritis (the only nephritic in the series) failed to show any hypotensive response and was actually receiving active drug at the time of her death. Two other deaths occurred in women aged 41 and 40, from cerebral haemorrhage, and one of these was receiving the active drug at the time of death. The fourth patient, a man aged 56, died of a dissecting aneurysm whilst receiving the control tablets.

In no case did we find a precipitate fall in blood pressure associated with circulatory symptoms due to hypotension which is said to occur due to " hypersensitivity " to the drug, and no patient developed postural hypotension.

In every case in which the patient responded to the drug there was a delay in the onset of the hypotensive effect, usually of 7 to 14 days, but occasionally as long as four weeks elapsed before the fall in blood pressure began. In about half the patients several further weeks on active drug were necessary before the diastolic blood pressure reached its lowest level (see Figs.). Stopping the active drug resulted in a gradual rise of blood pressure level in every case (see Cases 14 and 15, Fig. 2), but again, though in most patients one to two weeks elapsed before the blood pressure reached its previous height, in three patients (two receiving *V. viride* extract) it took at least six to eight weeks for this to happen.

Side-effects

Side-effects were seldom severe enough to necessitate cessation of treatment, though they occurred in more patients than we had been led to believe from reading the published clinical results (Klausgraber, 1953 ; Meilman, 1953a, 1953b ; Vida, 1952). Many patients, while complaining, for example, of diarrhoea, would nevertheless state that they felt better than ever before.

Though within the limits of our trial there was little difference in the hypotensive effects using 4 or 8 mg. of total alkaloids, or alternatively 500 or 1,000 mg. of crude extract, we noticed an appreciably higher incidence of undesirable side-effects with the larger doses. Side-effects, nevertheless, occur at all therapeutic dosage levels.

Depression was complained of by 5 patients (15%), and in fact one patient who had been receiving the active drug for nine weeks with no effect on her blood pressure was admitted to hospital as a case of attempted suicide from coal-gas poisoning. Nine patients (26%) complained of one or more of the following, though rarely in any severe degree—namely, fatigue, lack of energy, drowsiness and muzziness, loss of interest, loss of libido (one male), feeling " strung up inside," and vague general malaise. These symptoms did not bear any relation to the hypotensive effect of the drug, occurring relatively as often in those who failed to respond as in those who responded adequately.

Three patients complained of flashing lights in their field of vision, and in one of these patients this was followed by a period of amaurosis lasting two or three minutes. Another patient had several brief episodes of amaurosis lasting less than a minute. In all four patients eventual transfer to the control tablet produced complete relief of these visual phenomena.

A complaint of buzzing or fullness in the head was made by five patients (15%). Nasal congestion was complained of by five patients (15%), but response to an antihistamine occurred in only two of them.

Three patients complained of nausea and vomiting (one of these was also receiving *V. viride*). Diarrhoea occurred in eight patients (24%), necessitating cessation of treatment in two and halving of the dose of drug in two.

In four cases the side-effects were severe enough for it to be necessary to discontinue the drug (two patients with depression and two with diarrhoea). One patient in fact felt so depressed at work, which he had previously enjoyed, that he wished to change his job. Within two weeks of stopping the drug he was happy and contented again. A fifth patient, admitted as a case of attempted suicide, had the drug discontinued.

Increase in weight and in appetite occurred three times as often in the group when on the active drug, and two patients gained over 1 stone (6.4 kg.) in weight during five months on the drug. On the other hand, one patient who gained over 1 stone (6.4 kg) in eight months never received any rauwolfia during this period.

Conclusions and Summary

In a carefully controlled series of 39 severe cases of hypertension (38 with esssential hypertension and 1 with nephritic hypertension) treated for 6 to 20 months with rauwolfia preparations, we found a definite consistent fall in blood pressure in 67% of cases when actually receiving active preparations of *R. serpentina*. In most cases there was a proportionate fall in both systolic and diastolic blood pressure, but in several the fall in the diastolic appeared to be relatively greater than in the systolic. The fall was slight (10–20 mm. Hg diastolic) in 21% but appreciable or marked in 46% (greater than 20 mm. Hg diastolic), and in four patients the diastolic blood presure fell to below 100 mm. Hg. Within the limits of dosage set by this trial, and contrary to some other published work (Meilman, 1953a, 1953b ; Wilkins and Judson, 1953), these results did not appear to be appreciably contributed to by the continued simultaneous administration of oral preparations of *V. viride* extract in 13 cases, by hydrazinophthalazine in three cases, or by pentapyrrolidinium bitartrate in two cases. The use of *V. viride* extract seemed, however, to delay the rise of blood pressure, on stopping the rauwolfia. There was suggestive evidence to indicate that the better response occurred in males, and in the older hypertensive patients with arteriosclerotic manifestations, rather than the younger patients, and also that the presence of papilloedema usually meant that those patients would not respond to this drug, or only slightly.

All patients with angina of effort found it necessary to continue to use nitroglycerin, even though in one case the blood pressure dropped to normal figures. There was certainly no worsening of the pain in either its severity or its frequency, but there did not appear to be any real alleviation either.

The presence of albuminuria in varying degree did not significantly affect the hypotensive response.

There was no evidence in this series to suggest that only the mild, labile, or relatively symptomless cases respond. Quite severe cases (as judged by the blood-pressure level), symptomatically incapacitated, frequently responded better than the symptomless and often less severely hypertensive patients. Many symptoms responded well to treatment, but in a way more closely allied to reassurance than to actual specific drugs.

The cessation or amelioration of complaints of headache (but not the severe occipital headache often made worse by reclining), palpitations, precordial discomfort (frequently occurring at rest and not resembling angina of effort), vertigo, and tinnitus occurred in 80% of patients with and without active drug, and appeared to be related to the interest shown in their illness rather than the actual fall in blood pressure. Subjective symptomatic relief and objective improvement in blood-pressure levels did not show the close parallel that might be expected.

It was also our impression that, contrary to the usually accepted belief, once the patient was aware that he had

a "raised blood-pressure" repeated visits to hospital and blood-pressure measurements reassured him quite considerably.

We were not particularly impressed by the sedative or so-called "tranquillizing" action of the drug when given in the doses used by us.

From our experience in this clinical trial we felt that this was by far the most effective and useful orally administered agent for reducing blood-pressure which we have yet used. In our opinion this substance is fully worthy of a trial in every case of essential hypertension in which treatment is thought to be necessary. The severe cases, which always need treatment, are as likely to respond as the mild.

I am grateful for the constant help I received from my house-physicians and registrars, Mr. Williams, the hospital pharmacist, and the staff of the dispensary, as well as from Sister Wills and the nursing staff of the out-patient department of Oldchurch Hospital, while making these observations. This work would, however, never have been possible had it not been for the willing and active co-operation of all the hypertensive patients who have participated. I wish to thank Mr. J. A. Lumley and Riker Laboratories Ltd. for providing an adequate supply of rauwolfia extract and, later, total active alkaloids, control tablets, and *Veratrum viride* extract which enabled this work to be carried out. Finally, I am indebted to Dr. W. S. M. Grieve for many discussions and criticisms, and to my secretary, Mrs. E. D. Price, for her patience and excellent secretarial assistance.

REFERENCES

Arnold, O. H., and Bock, K. D. (1953). *Dtsch. med. Wschr.*, **78**, 565, 879.
Bhatia, B. B. (1942). *J. Indian med. Ass.*, **11**, 262.
Chopra, R. N., Gupta, J. C., and Mukherjee, B. (1933). *Indian J. med. Res.*, **21**, 261.
Cronheim, G., and Toekes, I. M. (1955). *J. Pharmacol.* In press.
Ford, R. V., Livesay, W. R., Miller, S. I., and Moyer, J. H. (1953). *Med. Rec. (Houston)*, **47**, 608.
Joiner, C., and Kauntze, R. (1954). *Lancet*, **1**, 1097.
Klausgraber, F. (1953). *Mod. Med. (Minn.)*, **21**, 174.
Locket, S., Swann, P. G., and Grieve, W. S. M. (1951). *British Medical Journal*, **1**, 778.
—— —— —— and Player, H. P. (1952). Ibid., **1**, 254
Meilman, E. (1953a). *New Engl. J. Med.*, **248**, 894.
—— (1953b). Ibid., **248**, 936.
Vakil, R. J. (1940). *Med. Bull. (Bombay)*, **8**, 495.
—— (1949). *Brit. Heart J.*, **11**, 350.
Vida, F. (1952). *Medizinische*, p. 1157.
Wilkins, R. W., and Judson, W. E. (1953). *New Engl. J. Med.*, **284**, 48.

RESERPINE IN HYPERTENSION

BY

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Reserpine ("serpasil") is a colourless, crystalline, ester-alkaloid derived from the roots of *Rauwolfia serpentina*, crude and unstandardized preparations of which have been used in the treatment of hypertension for the past 20 years or so. It has a melting-point of 266 to 270° C., and its empirical formula, $C_{33}H_{40}O_9N_2$, contains a pentacyclic nucleus.

It is claimed that reserpine is a single entity and does not produce any of the undesired effects of the unknown alkaloids of the whole root, but possesses only its sedative and antihypertensive actions. The fall in blood pressure is characterized by a gradual beginning and a prolonged duration, and occurs in about two-thirds of all cases of essential hypertension, and may occur in renal hypertension and hypertension associated with hyperthyroidism. The desired effect is obtained even in severe cases and in cases of hypertension which have remained at a fixed level for a considerable time.

The fall of blood pressure is sustained, so that sharp fluctuations do not occur, and the effect may not disappear for several weeks after the drug has been discontinued. Experiments in anaesthetized cats show that the hypotensive effect cannot be increased beyond a certain point despite the increase in dosage. This is taken to suggest that the drug acts mainly by protecting from abnormal tensive stimuli the autonomic nerve centres which regulate blood pressure. Postural hypotension has not been observed.

The fall in blood pressure is always associated with slowing of the pulse rate and, in some patients, with improved cardiac output. The depth of respiration is somewhat increased, but the rate remains more or less unaltered. Intestinal motility is increased in dogs but not in monkeys or rats. Diarrhoea may occur in human beings.

Reserpine produces a pronounced central sedative effect in cats, rabbits, and dogs. The animals remain quiet and sleep unless disturbed. The sedative effect is not a narcotic effect, and no electroencephalographic changes have been recorded in rats. It also does not protect against convulsant drugs. In man the lethargy is easily counteracted by caffeine or dextro-amphetamine sulphate in small doses. It occurs generally in the earlier stages of administration of larger doses, but even then it usually abates with time. Lower maintenance doses are well tolerated. In most patients there is subjective improvement associated with a sense of well-being.

The minimum lethal dose in rabbits and rats is about 10 mg. per kg., whereas its pharmacological effects are noticeable with doses of 1 μg. per kg. daily for five days. Thus the drug in recommended dosage (see below) has a wide margin of safety. In rabbits the prolonged administration of 0.1 mg. per kg. daily for 12 days or on alternative days for 24 days did not produce any changes in the heart, spleen, liver, kidneys, adrenals, stomach, or intestines. Side-effects in human beings with recommended dosage are mild and tolerable. They consist of nasal congestion—which is relieved by local vasoconstrictors—nausea, anorexia, more frequent or looser stools, headache, dizziness, heaviness of legs, and urticaria, which is relieved by antihistamines.

The initial therapeutic dose is 0.25 mg. three or four times daily, and is continued till the blood pressure falls. This occurs after a latent period, and the cause of delayed action is not known. Massive doses as used in acute experiments are not recommended. Subsequently the daily maintenance dosage may be 0.1 to 1 mg. Patients do not develop tolerance, and withdrawal symptoms do not occur. The drug is not habit-forming and there are no known contraindications to its use.

Literature

Recent clinical reports substantiate the above claims to varying extent. Löffler *et al.* (1953), using reserpine in doses varying from 0.75 to 1.5 mg. a day on 51 hypertensive patients, found that its hypotensive effect was insignificant in 27 and the blood pressure actually was higher than before in 6. In 14 the lowered pressure lasted only 12 days in spite of continued dosage, and in only 4 was the lower pressure sustained throughout the period of observation in hospital. Increase of dosage above 1.5 mg. a day did not increase the hypotensive activity, but it increased the incidence and severity of side-effects: 17 felt fatigued, 11 were depressed, 8 complained of heaviness of the limbs, 5 saw flickers in front of the eyes, 2 had bradycardia, 2 became mentally excited, 1 complained of dryness of the mouth, and 1 had miosis.

Vakil (1953) treated 25 cases with 0.5 mg. twice a day after meals for four weeks followed by a similar two-weeks course after an interval of a fortnight. After four weeks' treatment the systolic pressure dropped by 25 to 68 mm. Hg