USE OF RESERPINE AND RAUWOLFIA IN PSYCHONEUROSES

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In the following investigation the effect of reserpine and rauwolfia was studied in 75 psychoneurotic patients, of whom 30 had anxiety states, 25 reactive depressions, 3 hysteria, 6 obsessive compulsive neurosis, and 11 personality disorders.

Interest in the use of reserpine and of rauwolfia preparations in psychiatric disorders was aroused after reading a paper by Hakim (1953). Previously, in 1950, after publication of a paper by Vakil (1949), Wilkins and Judson (1953) introduced rauwolfia into the United States for the treatment of hypertension. It was subsequently demonstrated that reserpine, one of fourteen substances isolated from the crude alkaloidal extracts of *Rauwolfia serpentina*, was unique in its sedative action on the central nervous system and appeared to be the chief active principle of rauwolfia. Schlittler *et al.* (1954) in their work on the chemistry of rauwolfia showed reserpine to have the empirical formula $C_{33}H_{40}O_9N_2$, and have proposed a formula with six methoxyl groups and an amino-acid which they named reserpic acid. Wilkins, and others, have confirmed that rauwolfia is a hypotensive agent of modest potency, with a definite sedative action, most beneficial in relieving the "neurotic" symptoms of hypertensive patients with tachycardia. Nasal congestion, a gain in weight, and increased bowel motility were observed, and in larger doses diarrhoea, nightmares, or a state of agitated depression could be produced, relieved by reducing the dosage. Serious side-effects were noticeably absent over prolonged periods of administration.

Kline (1954) designed an experiment to evaluate the sedative action of rauwolfia in psychiatric disorders after Hakim presented his paper on the cure of schizophrenia. The majority (all but 5.6%) of 411 patients treated were diagnosed as schizophrenic. A sedative action, not equally effective in all cases, was described. On the basis of a small number of additional cases it was suggested there was evidence "that rauwolfia will reduce anxiety and obsessive-compulsive drives, and will overcome excessive inhibition and reticence." In the trial to be reported below particular note was taken of these conditions.

Noce *et al.* (1954), in a preliminary report, described the use of reserpine in 74 mentally ill patients in disturbed wards, patients with the worst prognosis, and 15 mentally retarded patients. The report is extremely enthusiastic, attributing improvement in 80% of patients to the use of the drug.

Freis (1954) reported five cases of depression in hypertensive patients treated for long periods with reserpine, varying from 1 to 2 mg. daily in four cases and 0.25 mg. a day in one case. Winsor (1954), writing on the human pharmacology of reserpine, thought the site of action was, in part at least, the subcortical regions of the brain, possibly the hypothalamus, as shown by the blocking of the inspiratory and pain reflexes after large

doses. Noce *et al.* considered the action on the hypothalamus, "the seat of emotional behaviour," a rational basis for trial in the mentally ill.

It was decided to investigate the effect of the active alkaloid reserpine ("serpasil") and an alkaloidal extract ("rauwiloid") in cases of psychoneurosis.

The Trial

The patients were assessed in two separate groups, and in each group an attempt was made to control the results.

In group A, patients received the active drug or a placebo, each made up in identical tablet form, in alternate courses lasting a month each. The therapist himself remained ignorant of which preparation the patient was receiving, since the tablets were dispensed by the pharmacist, and the key to the allocation was not disclosed until after all results were assessed. If a patient reported no effect whatsoever at the end of two months treatment was stopped. In all other cases treatment was continued for four months and in a few doubtful cases for six months. One month was regarded as the minimum period of administration of the drug or placebo, because of reports of a delay in the action of these drugs.

In group B, patients acted as their own controls—that is, the negative results of previous pharmacological and psychotherapeutic treatment over a long period were considered to provide an adequate baseline for assessment of any beneficial results obtained by the administration of the active drug itself. No suggestion was made about the effect of the drug. The duration of treatment varied between two and six months. It was intended that any patient in this group showing improvement should subsequently be given the placebo, but this proved impracticable in most cases. Criticism of this method of "clinical control" is discussed below.

As the majority of the 75 patients in this study were out-patients they were all treated by the oral route to obtain conformity of results. Sixty-seven patients received reserpine in a dosage of 0.25 mg. thrice daily initially, rising to 0.5 mg. thrice daily where this could be tolerated without side-effects. This scheme of dosage followed that suggested by Kline for the treatment of neuroses. Seventeen patients received rauwolfia in a dosage of 2 mg. twice daily, and of these nine patients subsequently received reserpine, thus raising the total number of cases in the results to 84.

Results

In the accompanying table the patients are classified according to the predominant symptom and an assessment of

	Free Floating Anxiety, i.e., Tension	Anxiety with Somatic Dysfunction	Phobic States	Conversion Hysteria	Obsessive Compulsive Disorders	Depression	Personality Disorder with "Excessive Inhibition"	Total
Group A								
Reserpine:								
Much improved	—	—	—	—	—	—	—	—
Somewhat im-	—	—	—	—	—	—	—	—
proved	7	—	2	1	1	4	6	21
No relief	—	—	—	—	—	—	—	—
Rauwolfia:								
Much improved	—	—	—	—	—	—	—	—
Somewhat im-	—	—	—	—	—	—	—	—
proved	4	—	2	—	—	1	2	9
No relief	—	—	—	—	—	—	—	—
Group B								
Reserpine:								
Much improved	1	—	—	—	—	—	—	1
Somewhat im-	1	1	1	—	1	1	—	5
proved	6	1	3	1	4	21	4	40
No relief	—	—	—	—	—	—	—	—
Rauwolfia:								
Much improved	—	—	—	—	—	—	—	—
Somewhat im-	—	—	—	—	—	—	—	—
proved	2	1	—	1	—	2	2	8
No relief	—	—	—	—	—	—	—	—

their response to the drug is made on the following basis: "Much improved" is limited to relief sufficiently pronounced to allow discharge of the patient on a maintenance dose of the drug. "Somewhat improved" indicates obvious benefit of some symptoms with continuation of others. "No relief" included temporary or slight relief.

It will be seen that only 6 out of 67 patients showed any improvement on reserpine, while none of 17 patients showed improvement on rauwolfia.

In group A, three patients felt equally improved on active drug and placebo, and were obviously discounted. Four patients felt improved while taking the placebo. One patient felt worse during a month on placebo; another felt worse on active drug and placebo. None of the patients in this group felt improved while taking only active drug.

In group B, one patient was "much improved" and five were "somewhat improved." Four of these patients were diagnosed as having anxiety states, of whom two were suffering from tension, one from somatic dysfunction (skin disorder), and one from phobias; one patient suffered from an obsessive compulsive neurosis; and the sixth suffered from reactive depression. Three of these patients suffered from hypertension. Thirteen patients treated with reserpine showed temporary improvement only ("no relief").

Complications.—Foote (1955) observed three cases of oedema of the legs, including one with oedema of the face, in 32 psychotics receiving 4 mg. of reserpine daily. Richman and Tyhurst (1955) report the appearance of extrapyramidal signs and symptoms in 12 out of 19 patients receiving 3–13 mg. of reserpine intravenously and 0.5–5 mg. orally. The occurrence of depression reported by Freis has already been mentioned. In our series seven patients complained of nasal stuffiness, four of unpleasant or excessive dreaming, two of conjunctival irritation, three of looseness of the bowels at the beginning of treatment, and four of slight drowsiness. Four patients observed a gain in weight. The complications recorded with larger doses were not seen in our series.

Discussion

In view of the enthusiastic reports quoted, the result of this work was disappointing, using as we did the dosage suggested by Kline for neuroses. Much larger doses have been used with psychotic patients. A number of useful points do arise, however, as a guide to the possible value of these drugs in selected cases. Eight hypertensive patients in the 75 treated provided three out of the six improved cases; they showed a reduction of tension and irritability, and a reduction of blood pressure in two. Apart from a reduction of anxiety in the other three improved cases no other common factor was established. It was observed that side-effects were more often encountered among the improved than the unimproved cases, indicating a possible sensitivity to the drug.

In group A, of the 21 patients treated with reserpine, none improved; but in group B, of 40 treated with reserpine six improved. These results suggest a possible discrepancy in the methods of assessment.

The patients who felt equally improved on both the active drug and the placebo, or on the placebo alone, had experienced either a change in circumstances or were unduly suggestible, as were so obviously the one or two patients who complained of side-effects whilst receiving the placebo. This supports the contention that controlled experiments are desirable in any investigation involving the use of new drugs if their value is to be accurately assessed.

A number of inadequate personalities were treated, mainly in the chronically anxious, depressive, hypochondriacal, and self-conscious groups. Not one of these patients showed any real benefit. Tonge (1955) found equally unrewarding the treatment of a group termed "neurasthenic psychopaths." The inclusion of these patients in this study may account to some extent for our disappointing results.

Where a neurosis occurs in the setting of a good basic personality, individual psychotherapy must remain the treat-

ment of choice. A few patients spontaneously expressed the opinion that amylobarbitone had helped them more effectively in the past. In the presence of tension, chlorpromazine may be found useful (Garmany *et al.*, 1954).

The suggestion of Kline that rauwolfia reduces obsessive-compulsive drives and overcomes excessive inhibition and reticence has not been confirmed. Anxiety in association with hypertension, however, is apparently reduced with reserpine.

Summary

An investigation of the effects of rauwolfia and reserpine upon 75 psychoneurotics failed to confirm the results claimed in a number of psychiatric disorders. The need for adequate control in such investigations is stressed.

Six patients benefited, of whom three were hypertensive. Side-effects were infrequent and slight in nature.

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JAUNDICE IN RELATION TO CHLORPROMAZINE THERAPY

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The occurrence of jaundice in relation to chlorpromazine therapy is becoming well known. We report four further cases of this complication encountered during a relatively small experience with the drug. We have also obtained information by questionnaire of the occurrence of this complication in the experience of other physicians, and present certain facts and inferences.

We have given chlorpromazine to 26 patients (8 males, 18 females) for the prevention and treatment of nausea and vomiting. Their ages ranged from 8 to 65 (mean 45). The conditions treated included radiation sickness, pregnancy sickness, uraemia, cerebral tumour, "cyclical" vomiting, and therapy with morphine, diamorphine, pethidine, mustine hydrochloride, oestrogens, and digitalis. The usual dose of chlorpromazine was 25 mg. thrice daily and the duration of treatment one week. The largest daily dose was 100 mg. and the greatest duration of treatment 14 days. Jaundice developed in three of these patients.