A CONTROLLED STUDY OF RESERPINE IN THE TREATMENT OF MENTAL ILLNESS*

LUCILE M. WARE** and CURTIS T. PROUT***

THIS paper is a report of the results of an attempt to establish a double blind study of the effects of reserpine (Serpasil)† when this drug was employed in the course of treatment of a series of 50 patients (15 male and 35 female) at the New York Hospital-Westchester Division. This hospital is a voluntary private hospital for the treatment of patients suffering from mental and emotional illness. The patients included in this study had been under treatment at this hospital for varying periods of time and for varying degrees of illness. At some stage of their illness reserpine was used in the course of therapy of each of the 50 patients. Some of these patients had already received electroshock or sub-shock insulin therapy and, in one instance, a lobotomy had been performed (in another institution) prior to the use of reserpine in this series. Following the course of reserpine further adjunctive therapies were employed in some instances. All of the patients in this series also received psychotherapy and the planned program therapies of the hospital.

The 50 patients were selected for treatment without specific regard to the presenting symptomatology, age or diagnosis. Their ages ranged from 15 years to 78 years and the duration of reported symptomatology or mental or emotional illness, prior to but directly related to their hospitalization at the New York Hospital-Westchester Division, ranged from eight days to 19 years.

Anxiety, depression and restlessness were the most frequently recorded symptoms just prior to the initiation of reserpine therapy. In the following order, but with lessening frequency, symptoms of agita-

* Presented by Dr. Prout at the combined meeting of the Section on Neurology and Psychiatry with the New York Neurological Society, at The New York Academy of Medicine, December 13, 1955. Manuscript received December 1955.

From the New York Hospital-Westchester Division, White Plains, New York.

** Assistant Resident Physician.

*** Assistant Medical Director and Clinical Director.

† The product used in this study was Serpasil, generously supplied by the Ciba Pharmaceutical Products, Inc.

tion, insomnia, obsessive-compulsive phenomena, overactivity, impulsiveness, apathy, indifference, negativism and frustration were recorded prior to reserpine medication.

Placebo tablets and intramuscular placebo preparations, which were physically indistinguishable from their equivalent and counterpart dosage, were obtained. The reserpine and reserpine placebos were administered in alternating and identical courses according to a prearranged schedule which included the strength and duration of the course, so that it was by chance only whether a given patient began treatment with the medication or with the placebo. Neither the patients nor the members of the staff, who were in immediate supervisory capacities with the patients, were cognizant of whether the medication itself or the placebo was being administered.

Throughout the course of this experiment all of the 50 patients continued with their regular program of activities except when contraindicated by marked physical side effects of the medication or unrelated physical symptoms. Furthermore, no other adjunctive somatic therapy was prescribed throughout this same period for these patients except for an occasional and temporary use of sedation. Psychotherapy was continued at regular intervals by the physicians in charge of the patients.

Detailed observations were recorded for from three to seven day periods prior to the drug or placebo administration in order to establish a base line for each patient. Recorded observations were then continued throughout the period of drug or placebo administration. These included records of blood pressure, pulse, respiration, temperature, weight and sleep. Prepared nursing records provided a day by day description of behavioral changes and physical complaints. A weekly evaluation, using the Psychiatric Rating Scale of Malamud and Sands* was completed on each patient throughout the study period by the physicians immediately in charge of each of the patients, in addition to the regular hospital record progress notes. Thus detailed records of physiological and psychological changes were obtained and, for comparison and evaluation, each physician was limited to a standard form and the same descriptive terms. Three dosage schedules were arranged:

1. Low dosage (received by 25 patients): An initial intramuscular injection of 3.5 mg. was followed by the daily administration of 1.5 mg. orally for a period of at least three weeks.

* Malamud, W. and Sands, S. L. A revision of the psychiatric rating scale, *Amer. J. Psychiat.* *104*:231-37, 1947-1948.

2. Moderate dosage (received by 13 patients): For the first week, 5 to 10 mg. were given daily and orally.

For the second week 5 mg. orally, daily. Then, for periods with a total average duration of six weeks, 2½ to 5 mg. daily, orally.

3. High dosage (received by 12 patients): Intramuscular injections of 5 mg., twice daily, augmented by an additional 5 mg., intramuscularly, each day, to a maximum dosage of 30 mg.

Oral administration of 15 mg. was then substituted for the intramuscular injections and the dosage gradually reduced to from 5 to 10 mg. daily, which was maintained for periods averaging seven weeks.

The blind technique of administration was considered successful and satisfactory.

The most frequently encountered complaints, due to side effects of the drug, were lassitude, fatigue or drowsiness in varying degrees of intensity. Actually the side effects ranged from a mild headache or flushing of the face to quite severe manifestations which are usually associated with Parkinson's disease, such as mask-like facies, tremors, muscular rigidity, and the typical cogwheel phenomenon. Nasal stuffiness, dry mucous membranes, edema of the face and of the extremities, dizziness, vomiting or diarrhea were observed. Some drop in blood pressure and bradycardia were almost invariable consequences of reserpine medication. Temperature findings were consistently within normal range.

The severity of observed side effects was, in general, in direct ratio to the size of the dosage employed. They were classified as minimal, moderate and marked, to indicate gradations of severity. The side effects observed in the 25 patients on the low dosage schedules were mainly of minimal character with a few presenting moderately severe symptoms. The 13 patients on moderate dosage schedule still presented side effects of minimal severity for the most part but two of the 13 had marked reactions. On the other hand, six of the 12 patients receiving the high dosage presented moderately severe side effects and five had marked reactions.

All of the observed side effects were found to be alleviated and reversible, in a matter of a few hours to a few days, upon reduction or discontinuance of the drug.

In determining the results, this study was so designed that the observed patients' reactions could be rated or classified as improved,

TABLE I—SIDE EFFECTS

Dosage Schedule	*Number of Cases*	*Minimal*	*Moderate*	*Marked*
Low	25	20	5	0
Moderate	13	9	2	2
High	12	1	6	5

markedly improved or unimproved. A further category of sustained improvement was tabulated for those patients who did not relapse upon withdrawal of medication.

These ratings could be established in four categories:

1. General behavior; this included appetite, sleep, appearance, socialization and work ability.

2. Manifestations of anxiety; these were measured by an assessment of feeling, motor activity, responsiveness and aggressiveness.

3. General mood and display of affect.

4. Mental trend and ability to communicate verbally; this included mental content, associations, thought processes, awareness and recollection.

The patient must have been regarded as at least improved or better in each of the afore-mentioned categories to be considered as markedly improved.

The observed results of the various dosage schedules were, surprisingly enough, almost identical in their psychological effects, although the side effects increased proportionately with the higher dosage. Six patients who had been on the high dosage had to be discontinued from the study when they developed severe parkinsonism within four to seven days after the initial dose. One of these patients developed a severe urticarial rash. Within the limits of the periods of observation, no more satisfactory results were obtained in the group treated for a total of six or eight weeks than for those treated for three weeks.

Of the 50 patients in this series, 50 per cent were improved and an additional 16 per cent were markedly improved for a total of 66 per cent improved, or markedly improved, on reserpine as compared with 30 per cent who were improved on placebo. This is a significant difference using the X^2 formula, as the probability was point 5 per cent.

TABLE II—RESULTS ON PLACEBO

Dosage Schedule	*Number of Cases*	*Improved*	*Markedly Improved*	*Unimproved*
Low	25	36%	0	64%
Moderate	13	23%	0	77%
High	12	25%	0	75%
Total	50	30%	0	70%

TABLE III—RESULTS ON RESERPINE (SERPASIL)

Dosage Schedule	*Number of Cases*	*Improved*	*Markedly Improved*	*Unimproved*	*Sustained Improvement*
Low	25	72%	16%	28%	36%
Moderate	13	61%	15%	39%	8%
High	12	58%	17%	42%	8%
Total	50	66%	16%	34%	22%

In 11 patients, or 22 per cent of this series, the improvement was sustained after cessation of medication and they were able to leave the hospital without further adjunctive therapy. Twenty-two, or about 44 per cent of the patients in this series have received electric shock therapy, other drug therapy, and one underwent a lobotomy following their treatment with reserpine.

The results of therapy with reserpine were then investigated in terms of diagnostic reaction types.

Seventeen of the 50 patients were regarded as suffering from some type of schizophrenia. Eleven of these 17 were classified as catatonic, three paranoid, one hebephrenic, and two as simple type. One of the two classified as schizophrenia, simple type, had undergone a lobotomy prior to her admission to this hospital. She failed to show any response to reserpine therapy. Nine of the 11 catatonic patients improved with reserpine and six of these nine sustained their improvement. Two of the three paranoid schizophrenic patients improved with reserpine but failed to maintain the improvement. The one hebephrenic type also improved but did not sustain the improvement. One of the two, diagnosed as simple type, improved and sustained the improvement.

TABLE IV—RESULTS IN SCHIZOPHRENIC GROUP

Type of Schizo.	*Number of Cases*	*Improved on Placebo*	*Sustained Improved on Placebo*	*Improv. on Reserpine (Serpasil)*	*Sustained Improv. on Reserpiue (Serpasil)*
Catatonic	11	3	0	9	6
Paranoid	3	2	0	2	0
Hebephrenic	1	0	0	1	0
Simple	2	0	0	1	1
Total	17	5	0	13	8

The observed improvements, in the schizophrenic group, appeared to be not alone in the area of anxiety, as has been postulated by other authors, but was noticeable in other symptom categories and appeared to be an across-the-board improvement. It was impossible to determine from our study which symptom complaint responded first to the therapeutic effect of the drug. Five of the 17 schizophrenic patients had also improved on placebo medication.

Eight of the 50 patients had been classified as suffering from a manic-depressive illness of circular type. Six of these received reserpine while they were in the depressive phase. There was no significant difference in the response of these six patients to the reserpine than to placebos. Four of the patients showed some improvement in mood while receiving placebos while three responded similarly to reserpine. All of these patients relapsed upon withdrawal of medication except one, and four of the six later required electroshock therapy. The one patient, who did maintain improvement, had shown marked improvement on both placebo and reserpine. The response of the patients in the depressed phase was disappointing and tends to confirm the reports of others that reserpine is not particularly effective in the psychotic depressions. Two of the eight patients were in the manic phase. Both of these revealed marked improvement on reserpine and one maintained the improvement after withdrawal of the medication.

The manic-depressive mixed type and involutional melancholias were grouped together under the classification of agitated depressions. Sixteen of the 50 patients were included in this diagnostic grouping. Eight of the 16 showed improvement while receiving reserpine as

TABLE V—SUMMARY OF RESULTS

Diagnostic Grouping	*Average Age*	*Number of Cases*	*Improved on Placebo*	*Improv. on Reserpine (Serpasil)*	*Sustained Impr.*	*Later EST*
M.D. circ. (depress.)	43	6	4	3	1	4
M.D. circ. (manic)	51	2	1	2	1	0
Agit. Dep.	60	16	3	8	2	13
Psychoneur.	52	5	2	5	0	2
Schizo.	31	17	5	13	7	2
Elderly	73	4	0	2	0	1
Total	47	50	15	33	11	22

compared with three on placebo, and only two maintained the improvement upon withdrawal of the drug. Thirteen of the 16 required electroshock therapy at a later date. The observed improvement noted in those who did respond to reserpine was in the form of a reduction in restlessness, anxiety, and the general behavior improved somewhat as compared to the response to placebos.

Of the five patients considered to belong in the diagnostic grouping of psychoneurosis, all showed some improvement with reserpine and two with placebo. None of these patients maintained the improvement upon withdrawal of the drug and one of the five did considerably better on placebo than on reserpine. This group was prone to marked side effects which they tolerated poorly.

Four patients suffering from senile psychosis or psychosis with arteriosclerosis were classified as the elderly group. The major response in these four lay in that they became easier to manage and less noisy. None revealed any change in trend and again severe side effects were poorly tolerated and made the patients more vulnerable to accidents and stasis problems.

SUMMARY

1. This study suggests that clinical change is not dependent upon the size of the dose of reserpine although the side effects are.

2. The suggested effective therapeutic range lies between 2 and 10 mg. daily.

3. The majority of improvement is observed by the end of the first three weeks following initiation of treatment.

4. It appeared from this study that four weeks seem to be an adequate period in which to ascertain whether reserpine is to be effective.

5. There appeared to be a significant benefit to patients in the schizophrenic group. Those schizophrenic patients who did show marked improvement did so in all four categories.

6. In the manic-depressive circular group some improvement appeared in the manic phase but no benefit was noted in the depressive phase.

7. Only transient benefit was observed in psychoneurotic patients, with a tendency to relapse upon discontinuance of medication.

8. Reserpine appeared to be of some value in the treatment of about one-half of the agitated depressions but only while on the medication.

9. The placebo disguise appeared to have been effective in this study.

10. The side effects of the drug were reversible.

11. Reserpine is not to be regarded as a cure but as another valuable addition to the armamentarium of the psychiatrist in making the patient more amenable to psychotherapy or program therapies.