to any desired level. Of 25 patients who were treated in this way, 23 were well controlled. The 2 exceptions had malignant hypertension and could be controlled satisfactorily only by parenteral hexamethonium.

The presence of a previous coronary occlusion or cerebral vascular accident was an indication not to lower the level too far rather than as an absolute contra-indication, and the success of this approach is borne out by the lack of serious complications. The only coronary occlusion arising during treatment was in a man of 31 who had a borderline malignant hypertension and no previous history of cardiac ischæmia.

The results of combined treatment in the more severe hypertensives have been uniformly satisfactory as far as lowering the blood-pressure and relief of physical signs and symptoms are concerned. It has been very encouraging to see retinal changes recede, hypertensive cardiac failure disappear, and patients' general appearance improve remarkably.

Mental Changes

But it is disturbing to record that there were no less than 4 cases of melancholia, 1 of severe depression, and 1 of severe anxiety state arising in this small group of patients, observed for varying periods of up to two and a half years at the longest. 3 of these patients have had to have electroconvulsive therapy (E.C.T.) and 2 others needed psychiatric treatment. Apart from these, there was 1 patient who had had a previous attack of melancholia and has remained well after a satisfactory response to combined therapy, 1 patient who has suffered from mild depression throughout, with no change in mood on reserpine therapy, 1 patient with a severe anxiety state who has had no change while taking reserpine, and 1 patient who has had mild delusions for years without change on sedative treatment. The rest of the patients have been normal mentally.

It may be of interest to give briefly the history of the cases of depression.

CASE 1.—A woman of 58 with severe hypertension and auricular fibrillation. Following a small cerebral thrombosis, right homonymous hemianopia and frequent attacks of jacksonian epilepsy always culminating in status epilepticus. Well for twelve months with anticonvulsant therapy and oral hexamethonium. Melancholia from the start of therapy, which coincided with the first attack of epilepsy.

CASE 2.—A man of 63 with severe hypertension. On reserpine-pentapyrrolidinium, he was troubled by diarrhœa and hypotensive attacks. Four months after start of therapy, melancholia with delusions necessitating E.C.T. Had an earlier mild depressive episode.

CASE 3.—A woman of 59. Neurotic for a long period. Hypertensive cardiac failure responded very well to combined therapy, but three months after treatment began melancholia with delusions necessitated E.C.T.

CASE 4.—A woman of 75 with hypertensive cardiac failure. Responded to combined therapy but five months after treatment began melancholia with delusions necessitated E.C.T. and has persisted.

CASE 5.—A woman of 65 with mild hypertension for many years, slowly increasing in severity. After four months' combined therapy a severe depression responded to rest in hospital after treatment was abandoned.

It is ominous to note that all 5 of these cases were in the group of 51 patients treated with either reserpine or ganglion-blockers, and that 4 of them had had reserpine. Thus, 4 people out of 44 had melancholia within a period of twelve months. An interesting feature is that these patients were the only ones to complain of depression as distinct from sedation, and this deepened to melancholia when treatment was continued. As far as could be ascertained there were no milder types of depression.

Recently Doyle and Smirk (1955) have remarked on the depressive effects of reserpine, and my own small series seems to bear out their findings. If larger series show that severe depression is as common as it was in my experience, I feel that, excellent though the results of therapy with reserpine may be, the risk of melancholia is too great to permit its use in mild hypertension. If it is used in severe cases a very careful watch must be kept for this side-effect. It may be that the mixed rauwolfia alkaloids will be found to be free from this effect, in which case they may replace reserpine to give an easy, safe, and reliable method of treatment.

Summary

In 133 patients with hypertension, treated as private patients in a general practice over a period of thirty months, there was a group of severe hypertensives who benefited considerably from combined oral reserpine and pentolinium.

No less than 4 patients out of 44 who received reserpine alone or in combination had severe mental depression amounting in 3 cases to melancholia with delusions.

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RESERPINE IN THE TREATMENT OF ANXIOUS AND DEPRESSED PATIENTS

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THE history of *Rauwolfia serpentina* in the treatment of mental illness has been reviewed by Kline (1954) in his account of a clinical trial of reserpine, an active alkaloid extracted from this plant. Kline found this drug to be an effective sedative, and pointed to its possible value in the treatment of patients with anxiety symptoms and obsessive-compulsive drives. Noce et al. (1954) have also reported favourably. We therefore decided on further clinical trials, using ' Serpasil,' a preparation of reserpine.

The dosage was determined, arbitrarily, on the basis of what little is already known. Generally speaking, higher doses have been recommended for mental patients than for hypertensives (Kline 1954).

Case-material and Method

Two groups of patients were treated quite differently.

Group A was made up initially of 67 outpatients. They consisted of all the suitable cases seen at eleven outpatient clinics (controlled by different doctors) during about six weeks. The patients were of either sex, able to live at home and work, and troubled in the main by anxiety and depression for which they had been referred to hospital. They were divided into two subgroups—those receiving the drug (0·5 mg. twice daily), and those receiving dummy tablets identical in appearance and almost indistinguishable in taste. Sealed envelopes containing the coded index of the substance to be prescribed were chosen by a random method and opened for each case by the pharmacist, who alone knew the individual treatment. The medical staff did not know which patients were receiving the drug and which the placebo. The patients were seen weekly in the outpatient department where their mental state was assessed and their pulse-rate and blood-pressure recorded. At the end of the trial period of six weeks (which is above the well-known latency period for reserpine acting as a hypo-

tensive agent) patient and doctor were asked to complete a simple questionnaire. All patients had been told at the commencement of the trial period that they would be receiving a new preparation which it was hoped would help them.

The questionnaire to the doctors was :

A.	Do you consider the patient, compared with his/her condition before treatment,						
	in general to be	much better	better	unchanged	worse	much worse	
B.	in respect of *depression*	much less depressed	less depressed	unchanged	more depressed	much more depressed	N.A.
C.	in respect of *anxiety*	much less anxious	less anxious	unchanged	more anxious	much more anxious	N.A.
D.	in respect of *compulsions/phobias*	much less disturbed	less disturbed	unchanged	more disturbed	much more disturbed	N.A.
E.	in respect of *sleep*	much better	better	unchanged	worse	much worse	N.A.
F.	in respect of *appetite*	much better	better	unchanged	worse	much worse	N.A.

N.A. = not applicable.

The patient was invited merely to answer the first question (A) at the end of the trial period, and also to comment on any reactions he had noticed, whether he attributed them to the substance or not.

Group B consisted of 4 severely disturbed inpatients who were treated with larger doses of the drug. They were middle-aged men (2 of them suicidal) suffering from severe involutional depressive illnesses. All were confidently expected to respond to a three-week course of electroconvulsion therapy (E.C.T.). They were given a three-week course of reserpine by mouth, 3 of them receiving 10 mg. daily and 1 of them 15 mg. daily. At the end of the third week they were given no further treatment for the next seven days, and then, commencing in the fifth week after starting treatment, received E.C.T. twice weekly for three weeks. Pulse and blood-pressure were recorded four-hourly while they were on reserpine, and weight was recorded each week.

Results

Group A

Of the 67 outpatients who started the trial, 13 fell out. Of the 54 patients who completed the trial, 28 had the drug and 26 the inert substance. Table I displays the ratings on item A of the questionnaire made by doctors and patients at the end of the sixth week :

TABLE I—DOCTOR AND PATIENT RATINGS OF GENERAL PROGRESS (FROM ANSWERS TO ITEM A OF QUESTIONNAIRE)

Treatment and rating	Much better	Better	Unchanged	Worse	Much worse
Reserpine :					
Doctor's rating ..	10	8	9	0	1
Patient's rating ..	10	10	8	0	0
Placebo :					
Doctor's rating ..	2	7	16	1	0
Patient's rating ..	3	10	10	3	0

The difference between the groups is significant when doctors' ratings are compared ($\chi^2 = 7{\cdot}15$; d.f. $= 2$; $p = 0{\cdot}03$). The difference is in the same direction when the comparison is between patients' ratings, though it just fails to attain significance at the 5% level of confidence. Hence there seems to be a clear distinction between these two randomised groups of patients in favour of those treated with reserpine.

Of the 13 patients who failed to complete the six weeks' trial, 5 were having placebo and 8 reserpine. It is obvious that the statistical difference tabulated above could be obliterated or rendered insignificant if, to take the extreme case, all the patients on placebo were so " much better " that they discontinued treatment, and all the patients on the drug were so " much worse " that they refused to continue attendance or had to be admitted to hospital. The reasons why these 13 patients discontinued treatment were therefore examined.

Of the 5 patients given placebo, 3 reattended the clinic only once ; 1 of this trio later admitted that he had ceased taking the tablets because he felt they were worsening his condition, but no further information was available about the other 2 patients. The 4th patient had to be admitted to a mental hospital after two weeks because of deterioration in her condition ; the 5th was admitted, three days after commencing placebo, to a general hospital in what was described there as a comatose state which had been attributed to the tablets.

Of the 8 patients having reserpine, 2 discontinued treatment within a week because they declared themselves to be perfectly well and in no need of further treatment. One patient had to leave the country after a week ; another gave up the tablets after one day complaining of ocular and nasal congestion ; another after two days because she preferred amylobarbitone ; another after three days because of general dissatisfaction with the drug. 2 patients were admitted to hospital within two weeks of starting to take the drug.

There is no evidence that the reactions of the 13 patients patients would have upset the tenor of results in table I. The study of their protocols does, however, demonstrate some of the obstacles in the way of even the simplest controlled study on an ambulant neurotic population.

Table II presents the doctor-rated scores on the five individual items of the scale. A difference in favour of the drug-treated patients is apparent for four of the five items, the one exception being sleep. The pattern of

TABLE II—DOCTORS' RATINGS ON INDIVIDUAL SYMPTOMS OF ALL PATIENTS

Treatment	Much better	Better	Unchanged	Worse	Much worse	N.A.
Depression (item B):						
Reserpine ..	4	14	7	1	0	2
Placebo ..	1	6	13	2	0	4
Anxiety (item C):						
Reserpine ..	7	12	8	0	1	0
Placebo ..	1	6	17	1	0	1
Compulsions/phobias (item D):						
Reserpine ..	3	10	6	1	0	8
Placebo ..	0	2	14	0	0	10
Sleep (item E):						
Reserpine ..	4	5	17	1	0	1
Placebo ..	0	8	14	2	0	2
Appetite (item F):						
Reserpine ..	4	10	10	2	0	2
Placebo ..	1	3	16	1	0	5

TABLE III—REACTION TYPES OF ALL PATIENTS

Treatment	Anxiety reaction	Depressive reaction	Schizophrenic reaction	Others
Reserpine ..	17	7	1	3
Placebo ..	13	11	2	..

improvement recorded in the other four is essentially similar, in that a majority of drug-treated patients were recorded as better, whereas the majority of placebo-treated patients recorded themselves as unchanged. The difference, for each item, is highly significant.

Despite the care taken to randomise the subgroups, the possibility that the drug-treated cases had a naturally more favourable prognosis had to be eliminated.

It will be seen from the last column of table II that the numbers of patients in both groups disclaiming the listed symptoms are about equal, which indicates that symptomatically the groups were comparable. On closer analysis it proved equally difficult to distinguish between the subgroup characteristics. The sex-distribution was equal. The average age of the drug-treated group was 37·9 ± 1·62 years, that of the placebo-treated group 40·1 ± 2·03. Table III allocates the two groups into crude reaction types, which are possibly more meaningful than formal diagnostic labels.

Table IV gives the outstanding symptoms of both subgroups. Again there is no indication of major difference.

TABLE IV—OUTSTANDING SYMPTOMS OF ALL PATIENTS

Treatment	Anxiety		Depression		Compulsions and phobias		All other symptoms
	Somatic	Psychological	Somatic	Psychological	Somatic	Psychological	Somatic and psychological
Reserpine ..	10	11	7	17	9	7	11
Placebo ..	9	11	2	15	6	5	8

An attempt was then made to determine how much psychiatric help had previously been sought and received by the patients. Indirect evidence bearing on this point is presented in tables V*a* and V*b*, which show the number of patients with previous inpatient and/or outpatient records, along with any treatment given.

TABLE V*a*—PREVIOUS PSYCHIATRIC HISTORY AMONG ALL PATIENTS

Treatment	Previously inpatients	Previously outpatients	Previously both inpatient and outpatient
Reserpine ..	10	13	5
Placebo	14	15	11

TABLE V*b*—NUMBER AND TYPE OF PREVIOUS TREATMENTS FOR PRESENTING ILLNESS

Treatment	Psychotherapy	E.C.T.	Pharmacotherapy	Social measures	Other forms of treatment
Reserpine	10	1	11	1	5
Placebo ..	13	7	14	3	0

Table VI gives the duration of the outstanding symptoms.

TABLE VI—DURATION OF OUTSTANDING SYMPTOMS AMONG ALL PATIENTS

Treatment	< 1 wk.	< 1 mo.	< 6 mos.	6–11 mos.	1–2 yr.	2–3 yr.	4–5 yr.	6–10 yr.	10 + yr.
Reserpine	1	3	5	3	4	4	1	4	3
Placebo ..	0	1	2	3	3	6	6	3	2

On the basis of all information available, the likely symptomatic responsiveness of each patient before starting treatment was rated by one of us (M. S.) on a three-point scale, from 1, indicating best prognosis, to 3, indicating worst. The ratings are shown in table VII, which suggests only an insignificantly more favourable prognosis for the drug-treated patients as a group.

TABLE VII—RATINGS OF LIKELY RESPONSIVENESS TO TREATMENT (1 MORE FAVOURABLE THAN 2: 2 MORE FAVOURABLE THAN 3)

Treatment	Rating 1	Rating 2	Rating 3
Reserpine	19	7	2
Placebo	13	7	6

Our conclusion, then, was that, in respect of symptoms, diagnosis, and prognosis, no obvious difference could be demonstrated between those patients receiving the drug and those receiving placebo.

A search for distinguishing features among those patients who responded most satisfactorily to the drug proved equally fruitless.

Of the 10 patients so rated by the doctors, 7 fell into the anxiety-reaction type, 2 into the depressive-reaction type, and 1 into neither category. The sex-distribution was equal. The youngest patient was 23, the oldest 54. 4 patients had complained of symptoms for less than one year; 1 had had symptoms for ten years. No one outstanding symptom could be isolated: 6 patients were complaining of obsessional symptoms, 7 of anxiety symptoms, and 4 of depressive symptoms, but the overlap was too considerable for any clear distinction. No patient had been put into prognostic grade 3 (worst prognosis) but 3 of the 10 were in the intermediate grade 2.

Separate mention should be made of the *side-effects* among those patients who completed the six-week trial. These were all attributed by the patients to the substance which they were taking. Among the patients on reserpine, 3 complained of nasal stuffiness, 4 of what was described as "shivering," and 2 of giddiness and dizziness; 1 commented on his large appetite, 1 on increased libido, and 1 of many somatic anxiety symptoms. Of the patients on placebo, 3 complained of fatigue, and 1 felt elated for the first day or two: the more dramatic side-effects displayed by 1 of the patients who did not continue with his tablets have already been mentioned. In no case did the weekly systolic blood-pressure readings fall more than 5 points; but in the outpatient department readings of blood-pressure were taken principally as a precaution and without the care devoted to its recording among the inpatients.

No *toxic effects* were observed in this group.

Group B

All 4 patients were substantially unchanged at the end of the three weeks during which they received reserpine in high dosage, and they remained unchanged until the electroplexy was started. After six convulsions all were much improved, as had been predicted; precautions against suicide were discontinued and all made an uninterrupted recovery.

Though no *toxic effects* were observed, we should mention that in 2 patients outside these groups, receiving more than 10 mg. of reserpine daily, parkinsonism developed (Stead and Wing 1955).

Discussion

The experience gained with the relatively large doses given to group B is of limited value because only 4 patients were treated; but their poor response does suggest that the drug is very unlikely to supersede E.C.T. as the treatment of choice for severe depressive states. The two dramatic cases of reversible parkinsonism indicate a problem to be faced when high doses are prescribed: it is of potentially great pharmacological interest.

In the neurotic outpatients of group A the drug-treated group fared better than the placebo-treated group, over the trial period of six weeks. But the design of the trial, in obviating many of the criticisms usually levelled against findings of this type, allows very little

more to be concluded. The improvement was among the drug-treated patients as a *group*, and no information was obtained about the response to be expected in particular patients. The recent comment of Dodds (Dodds 1955), on the treatment of cancer with hormone preparations, that "it has proved impossible, throughout this work, to forecast whether a given patient is likely to benefit by any course of treatment," illustrates the same situation in another field where much more knowledge has been accumulated.

Against this background there should be considered the instrument employed for the detection of therapeutic response—namely, the rating scale.

Such a scale is valuable when it is necessary to assess subjective responses which are uncorrelated with known and standardised variables. While the standardisation and reliability of these scales is vital for many purposes, it is not essential when group differences, not absolute group values, are the focus of interest. An appreciably large number of doctors contributed to the ratings in both groups, and so increased reliability. Parenthetically, there was no indication that individual doctors failed to complete their forms with due care, for a wide variation among items was provided by each doctor concerned with 2 or more patients.

The validity of this scale cannot be accurately measured. But, item A, the only item to be tackled by patient and doctor, showed an exact agreement between doctor and patient ratings in 34 out of the 54 cases; only 2 of the remaining 20 pairs showed a discordance of more than one point of the scale. Interpretation of the response to treatment in terms of the individual symptoms rated must allow for the "halo effect" of the general improvement in the subjective state of the patient. Some independence of symptomatic response is suggested by two internal observations. First, improvement in items B–F tended to be rated as "better" in contrast to the "much better" recorded of item A (table I). Secondly, the difference between the rated responses to item E (sleep) and those recorded of the other items suggests a more discriminate functioning of the scale.

The side-effects of the drug have all been previously described. The more surprising side-effects of the placebo underline the importance of using controls in such trials and illustrate the pharmacological effects of inert substances, discussed by Wolf and Pinsky (1954).

Summary

Of 67 outpatients, whose main symptoms were anxiety and depression, about half were treated with reserpine and the others with placebo.

Among the 54 patients completing the trial, those treated with reserpine showed more benefit than the others.

Four severely depressed inpatients did not respond to higher doses of the drug, though they later recovered after electroplexy.

Thanks are due to Mr. A. S. C. Ehrenberg, who advised about the statistical design, and to Messrs. Ciba for supplying the 'Serpasil' and dummy tablets.

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"How then, are we to achieve smokelessness in the face of the rigid opposition of the kind experienced recently? This is reminiscent of the fierce unbending criticism which faced those gallant pioneers Simon and Chadwick a hundred years ago when they fought on behalf of the people of this country—including their critics—for clean water and better sanitation. . . . The problem of a filthy atmosphere is as great as any of those that faced Simon and Chadwick in their time. It must not be left in any doubt but that we shall tackle this problem as energetically as they did."—Dr. R. W. ELLIOTT, medical officer of health for Bolton, in his report for 1954.

RETICULOSIS OF THE NERVOUS SYSTEM SIMULATING ACUTE INFECTIVE POLYNEURITIS

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ACUTE infective polyneuritis, with its characteristic pattern of symmetrical peripheral flaccid paralysis of the extremities, slight sensory loss, and bilateral facial weakness, was first described by Guillain, Barré, and Strohl (1916) and later by Holmes (1917) and Bradford et al. (1918). Since then it has received general recognition and, although its ætiology is still unknown, is generally held to be due to a virus infection. The cerebrospinal fluid (C.S.F.) usually shows a characteristic albuminocytological dissociation, with a greatly increased amount of protein. Most patients recover, but death may ensue from rapid ascent of paralysis.

In the case reported here invasion of the nervous system by a reticulum-cell sarcoma caused a similar clinical picture.

Case-report

A housewife, aged 56, had complained for six weeks of increasing weakness in the lower limbs, beginning in the left leg. There had been no previous illnesses of significance. About a week before admission a squint of the right eye and facial weakness had appeared, and she had become so weak that she could neither sit up nor stand.

On examination the patient was obese; there was no evidence of anæmia or of lymphadenopathy; liver and spleen were impalpable; the respiratory and cardiovascular systems were normal; the urine contained no abnormal constituents. The mental state was abnormal; although she was alert and friendly and recognised that she could not walk, her attitude was one of total unconcern and indifference. She did not talk spontaneously, but understood simple questions and could express herself coherently. Attention was hard to sustain; she had difficulty in registration but no gross memory defect for past events, and she was correctly oriented in time and place, and recognised persons. She could not, however, tell her right side from her left. There was no dyspraxia or agnosia. Her sense of smell and visual acuity were difficult to assess, but her optic discs and fundi were normal, and there seemed to be no hemianopia or visual inattention. There were slight right-sided ptosis and paralysis of upward and inward movements of her right eye. She had no nystagmus. Her corneal reflexes were brisk, and light touch and pain were felt over her face. Her jaw muscles contracted strongly. She had bilateral symmetrical facial weakness of peripheral type. Her other cranial nerves were normal. She had little weakness in her upper limbs. She could well maintain the position of her outstretched limbs, and her hand grips were fairly strong. However, some ataxia and terminal intention tremor were evident on performing the finger-nose test. She could not sit up unaided. Her lower limbs were flaccid. Except for slight toe movements and ineffectual efforts to flex the knees against gravity the paralysis was complete. There was no wasting or fasciculation. Her inattention and unconcern made tests difficult to interpret, but painful stimuli were appreciated normally, and there did not seem to be any gross loss of sensibility to light touch. She could detect passive movements of her great toe and finger joints, and deep muscle pain of normal degree could be elicited by squeezing her calves. In her upper limbs the biceps, triceps, and supinator jerks were present. The abdominal reflexes could not be obtained. In the lower limbs the tendon-reflexes were lost. There was no response on stimulating the soles of the feet. Sphincters of bladder and rectum were unaffected. Lumbar puncture produced C.S.F. under normal pressure, and the Queckenstedt