As euphorians and dispellers of the morning headache the amphetamine group of drugs are still the most useful. In a small proportion of cases, probably not more than one in ten, they work like a charm, and yet in others serve no useful purpose. They can be used in combination with barbiturates or aspirin in certain cases.

Malleson (1953) recommends the use of small doses of natural oestrone, ethisterone, and methyltestosterone in cases of premenstrual and menopausal depressions. If one hormone fails to work another is tried, or two are tried alternately. No adequate series has so far been established, but a few most gratifying results have been recorded, and further work on the subject is certainly indicated. There are many drugs on the market which claim to be useful in cases of depression, such as rauwolfia, chlorpromazine hydrochloride, pipradrol hydrochloride, benactyzine, and methyl phenidate hydrochloride, but again none have been given an adequate trial so far in the mild depressions of general practice.

Light work or work devoid of responsibility is to be encouraged, but the patient should not be physically exhausted by his labours, or weighed down by an overactive sense of duty. If work is a burden, it should be abandoned for a while. A change of scenery or company may help those with a mild depression, whereas it is definitely contraindicated in those with the severe type, who need to be kept under constant observation. Very few housewives, who form a big proportion of these cases, ever allow themselves to be put off work altogether.

Summary

The mild endogenous depression accounts for 60% of the cases which occur. The symptoms are usually so mild that the patient is not likely to get past his general practitioner into the hands of a psychiatrist. It is essentially a disease of general practice. The condition is frequently disguised, and is often misdiagnosed either as an anxiety state or as an organic illness. It can also occur as a graft on to established organic disease, and if such a patient is to receive adequate treatment the depression must have due recognition. These disguised forms of endogenous depression are illustrated by typical cases. The severe mental-hospital type of depression, with the classical triad of symptoms, is easy to diagnose. The case of mild depression has to be sought out. Difficulty in thinking, depression, and psychomotor retardation are all evident in an early and modified form. The evolution of such symptoms as suicidal ideas and delusions is observed in the various grades of depression. The mild depression has a distinct "feel" of its own. The patient presents a picture of "injured bewilderment."

Most of these mild cases can be treated at general-practice level. If a suicidal urge emerges, or the patient becomes agitated or deluded, a psychiatrist should be called in. It is as well to pass even a mild uncomplicated case on to a specialist if the depression shows no signs of improvement after three months' observation.

Symptomatic treatment is described, but the most potent weapon in the hands of the general practitioner is a good rapport with his patient. The sympathetic understanding of the doctor goes a long way to tide him over the dreary and painful weeks or months of depression. This is confirmed by the way in which patients with recurrent depression come back as soon as they feel the clouds descending.

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TRIAL OF RESERPINE IN TREATMENT OF SCHIZOPHRENIA

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This is a report on the immediate results of a clinical trial of the use of reserpine in the treatment of 119 cases of schizophrenia. The study covers a period of 18 months. An assessment of the cases was made on December 31, 1955. Only patients whose response to the drug was regarded as decisive by this date were included. The follow-up period ranges from a few weeks to ten months.

Inquiry into the efficacy of a new treatment in psychiatry is notoriously difficult. A controlled investigation satisfactory to statisticians is difficult to obtain, especially with a drug which has marked side-effects. Psychiatric diagnosis is inexact, and descriptive terms may have widely different meanings for different psychiatrists. The natural illness is often fluctuating and subject to remission. Enthusiasm for a new treatment, a new interest in the patient, and a favourable change in the environment can all react markedly on the patient, and influence results.

We have divided our cases into five groups, and the order in which we report on them reflects the history of our attitude to the drug. Thus the first group consists of chronic deteriorated patients who were long since regarded as past any hope of improvement. Results with this group encouraged us to treat a group of cases which had failed to respond satisfactorily to other better-tried methods of treatment. Later, we used the drug as the first line of treatment in cases considered unlikely to respond to these better-known methods. Finally, we report the results in two groups of acute cases in which the immediate prognosis with other methods had been thought likely to be good.

Regime of Treatment

The preparation of reserpine used throughout the trial is marketed under the trade name "serpasil."

When we began to use reserpine it was available only in tablet form, and in group I the dosage varied from 2 to 8 mg. daily by mouth. In the other groups we were guided by Kline's scale of dosage (Kline and Stanley, 1955; Barsa and Kline, 1955), and the following amounts were used: 3 mg. orally daily throughout; 5 mg. intramuscularly on the first evening; and 10 mg. intramuscularly nightly for three to seven weeks, reducing this to 5 mg. on alternate nights for two weeks, and finally 2.5 mg. on alternate nights before discontinuing the injections. If side-effects were troublesome the dosage was reduced earlier. In the most severely and chronically ill the intramuscular dosage was continued as a maintenance dose on every second or third night indefinitely. The giving of the injections at night minimizes absenteeism, due to side-effects, from occupational therapy classes and recreational and social events. Each case must be treated individually, and dosage modified according to the side-effects and the mental

state. Our present tendency is to decrease the dosage rather more slowly than at first, and to keep the patient on an oral maintenance dose for many months after symptoms have disappeared. All discharged patients are encouraged to attend the out-patient department regularly, and, if they live at a distance, to keep under the care of their local doctor and to report to us by letter should untoward symptoms arise. Sometimes a patient who has improved relapses when the drug is reduced, and a return to bigger doses is indicated. A number of patients who subsequently did well showed this tendency to relapse, from the fourth to the seventh week.

The drug was the focal point of the treatment of these patients. They were interviewed at least once weekly and their symptoms elicited. Usually the patient was told directly that he was mentally ill, and simple explanations were given of paranoid ideas, delusions, and hallucinations, with their mode of development. A full programme of occupational therapy, games, work parties in the open, and social events was provided. As soon as possible week-end parole was given.

Effects of the Drug

Often in the first few days, and almost always in the first week, there is evidence of a tranquillizing effect. The patients are more relaxed and sociable, and less preoccupied with their symptoms. Disturbed behaviour is lessened. In some a mild elation replaces confusion and preoccupation. By the end of the first week previously withdrawn or suspicious patients may be anxious to talk to the doctor about themselves and their symptoms. It is often easier to elicit symptoms. Patients who had previously been evasive or secretive about their condition may discuss their abnormal ideas quite freely. Sometimes from then onwards there is a progressive lessening of delusions and hallucinations, with a gain in insight. The patients may for the first time accept explanation and reassurance about the nature of their symptoms. The course varies widely, and, as with other treatments, the most recent symptoms disappear first, and the oldest ones last.

In many patients in the acute schizophrenic group, satisfactory improvement with good insight had been achieved by the 21st day, whereas similar improvement in patients of the chronic group might take 60 days, and occasionally much longer. Sometimes insight appears to be gained as a result of patient and persistent explanation; in others there may be a sudden change for the better, symptoms subside, and patients appear to gain insight overnight, almost as if some crisis had been passed. Several chronic patients said spontaneously that they had suddenly realized for the first time that they were mentally ill. One patient who had written scores of paranoid abusive letters, complaining about his alleged illegal detention, over years, wrote a letter in the third month of treatment saying that he had just realized that he was ill, that what had been done was in his best interests, and that he would like to change his status to that of a voluntary patient for the remainder of his treatment. The patient, a paranoid schizophrenic of seven years' duration, has achieved a very good remission, and has been symptom-free for more than nine months.

A highly intelligent woman with a three-years schizophrenic history was convinced of the reality of her "voice," and admitted it without reserve. After a month's treatment she flushed angrily when it was suggested that the voice was a hallucination, and com-

plained in a letter to her husband that the doctors suggested she was "mental." She had then achieved sufficient insight to wish to avoid discussion of her symptom. A month later she could discuss her symptom objectively, admit that it was a product of her illness, expressed pleasure at the fact that it sometimes went away altogether, and inquire anxiously when it was likely to go away permanently.

A number of patients expressed fear that their "voices" would come back again when they stopped taking reserpine, and for this reason were loath to give up taking it.

Side-effects

In the first few days of treatment flushing, tremor, nasal stuffiness, and drowsiness occur. Sometimes there is dizziness and vomiting. In a few patients short periods of elation occur, but more often there are periods of tension and depression. These may coincide with the drowsiness which tends to come on from one to three hours after an intramuscular dose of the drug. After about seven to nine days restlessness appears, and within a few days, in varying degrees, the other side-effects—pains in the calves and forearms, pains in the lumbar region and neck, loss of natural mobility of the face and arms with increase of salivation—appear. These latter may progress to a well-developed picture of Parkinsonism.

Rigidity may be so marked that spoon-feeding is required within two weeks of the beginning of treatment. Often sleep is disturbed, and early waking may be a troublesome feature, even in patients who are not depressed. A curious combination of drowsiness and restlessness appears. Drowsiness makes the patient want to lie down on his bed, while the restlessness impels him to pace up and down the ward. Those of a phlegmatic temperament bear it grimly, while the more volatile clamour for attention and relief. Nasal stuffiness may result in nose-bleeding, and we have seen sinus infections in two cases. Breathlessness and, rarely, a sensation of smothering may occur. Rarely, too, a patient may feel weak to a degree he interprets as "paralysis." Frequency of micturition and nocturnal incontinence are fairly common. Delay in initiating micturition, subjective impairment of accommodation, and unexplained oedema of the face and ankles have been noted. We have had no difficulty from postural hypotension. If for any reason electroplexy is given, adequate relaxants and preliminary atropine are necessary. Otherwise excessive salivation and possibly nose-bleeding might cause difficulty in maintaining the airway. We have, however, had no worry from any of these.

One patient, after discharge from hospital on a daily dosage of 2 mg. orally, had an attack which may have been epileptic. This is our only experience of that complication, which is described by Barsa and Kline (1955). We have given reserpine to several epileptics, not included in this series, without any increase in their attacks.

One patient, not in this series, died while on reserpine. She was suffering from schizophrenia and thyrotoxicosis. The cause of death was a thyroid crisis, which may have been precipitated by a maxillary sinusitis due to reserpine.

Appetite is often increased, and some patients get up in the middle of the night to appease their hunger. When side-effects become marked, reduction in appetite and difficulty in swallowing may lead to loss of weight. In a few cases diarrhoea has occurred.

Provided explanation and encouragement are given, the side-effects present no great problem in the average case. An antazoline-naphazoline nitrate ("antistin-privine") nebulizer is useful when nasal symptoms are severe; too great restlessness is usually relieved by one of the short-acting barbiturates or chlorpromazine hydrochloride ("largactil"). Tincture of belladonna is a help in lessening the salivation of Parkinsonism. All the side-effects lessen if the dose is reduced. Indeed, these side-effects, although

troublesome, appear to have their value; they create a bond between the patient and his fellows; they provide a topic of conversation, and many seem almost relieved to complain of physical rather than mental symptoms. In some cases they seem to distract the patient from preoccupation with his fantasies and delusions. Patients turn to the doctor to ask for relief of their physical symptoms, and sometimes this is the beginning of a more satisfactory doctor-patient relationship.

Barsa and Kline (1955) have described a turbulent phase of variable duration following on a sedative phase in the first week. In this, they state, the patients become more deluded, hallucinated, and disturbed. We have not been able to confirm this observation. In our experience the turbulent phase, except in the rare patient, is one of physical disturbance rather than mental turbulence. It is due to the side-effects of the drug—in particular, restlessness—rather than any increase in the psychotic process. In a few patients who appeared to have a low tolerance for tension the physical restlessness led to impulsive behaviour, such as breaking cups or a window. These few patients described sensations of something about to snap in their heads.

Trouble from side-effects varies widely, but is generally more pronounced in patients with neurotic or psychopathic personality traits. Some leucotomized patients seemed to be very tolerant of the side-effects of the drug.

Depression

The most serious complication of the treatment is the development of severe depression. This has been noted by physicians treating hypertension with—by our standards—small doses of the drug (Freis, 1954; Doyle and Smirk, 1955; Smirk and McQueen, 1955). Transient depression may come on a few hours after an injection, but in most cases it passes off again. In our experience, persistent deep depression has developed as early as the 27th day and as late as five months after treatment has started. A number of those who developed depression after a long period on the drug did so when the dose had been substantially reduced—sometimes when an oral dosage only was being given.

The picture is usually characteristic of the endogenous type of depression—early wakening, a sense of hopelessness, often a sense of guilt, with suicidal preoccupation. Although there is a retardation and deep dejection, the patient is usually able to express his thoughts, and admits to thoughts of suicide. Sometimes there is a fear of giving way to a suicidal impulse rather than a desire to be dead.

When depression occurs we feel that reserpine should be discontinued and sedatives given for relief of tension and insomnia. In a few cases symptoms have subsided within a week or two; in others a course of electroplexy has been given with success. A few patients proved resistant and required several courses of electroplexy before the depression finally cleared up.

Two of our patients in this series made determined suicidal attempts after discharge from hospital and while on maintenance dosage of 2 mg. daily. Fortunately neither suffered serious injury. Both were depressed, but neither showed any return of the schizophrenic symptoms for which the treatment had been given originally. It may be significant that the pre-psychotic personality make-up of both these patients showed definite evidence of immaturity and instability. The attempt was an impulsive desire to be rid of an intolerable feeling of tension and depression; it was not premeditated, nor was it the result of delusional thinking or in response to a hallucination.

It seems probable that the risk of suicide in this reserpine-induced depression is greatest in personalities with a poor tolerance for tension. *It must be emphasized that this is a very serious complication of the treatment. It is quite unsafe to prescribe the drug unless the patient can be seen regularly by a doctor aware of the dangers involved.* Some out-patients may require admission to hospital.

Group 1. Chronic Deteriorated Schizophrenics

Our first group of cases were chosen from a small ward of chronic deteriorated patients who had been in hospital for many years. Twenty-two patients were included (11 male and 11 female). Their average age was 45 years and their average stay in hospital 13.5 years. The shortest stay was one year, but in her case there was evidence that she had been ill for ten years. The patients were chosen because of one or more undesirable features in their behaviour, such as resistiveness, aggressiveness, noisiness, or destructiveness. Only with three could one establish contact or make conversation. Some were having maintenance electroplexy to control their disturbed behaviour. Some had been on chlorpromazine hydrochloride, and in all cases the usual sedative drugs had been tried over the years.

Regime.—Reserpine was given orally in dosage of 2–8 mg. daily for an average period of 75 days. The initial dosage was 2 mg., but if there was no beneficial effect this was increased. Following this, control tablets were substituted without the knowledge of the medical staff—with the exception of the physician in charge of the clinical trial. The control tablets were given for an average period of 45 days, when reserpine was resumed in all the patients and dosage adjusted within the limits of 2–8 mg. to obtain the best response. Otherwise the routine of the patients was unchanged, except that any fresh interest in occupational therapy or social events was encouraged.

Side-effects were comparatively mild. Increased appetite and weight gain were frequent. Twelve of these very chronic patients improved on the drug, a few strikingly. Ten of them relapsed on controls, and two of these failed to regain improvement on a second course of reserpine. Most of those who improved did so in the first two weeks of treatment. A sedative effect, sometimes with drowsiness, was noted, beginning most usually from the second to the seventh day. Those in whom drowsiness was well marked did best.

These figures give an indication of the results, but cannot really convey the general improvement of the group in morale, in hygiene, in the standard of occupational therapy, and in the general happiness of both patients and staff in this section of the hospital.

There is general agreement in the published literature that reserpine is of value as a sedative in some patients of this type (Kline, 1954; Glynn, 1955; Noce *et al.*, 1955).

Group 2. Chronic Treated Schizophrenics

For the intensive treatment we chose first a group of patients whose illness was more recent than that of Group 1 but none the less chronic. None was ill for less than two years; the average duration of symptoms was 7.5 years (range 2–29 years). The average age was 35.5 years (range 18–52 years). In every case one or more of the physical methods of treatment had been tried and had failed to produce a sustained remission. The average duration of reserpine treatment was 193 days (range 53–470 days).

TABLE I.—*Treatments Previously Given to the 38 Patients (23 Male, 15 Female) in Group 2*

Previous treatment	No. of Cases
E.C.T.	37
Insulin	27
Leucotomy	19
Intravenous acetylcholine	12
Leucotomy was planned for 9 patients if reserpine failed to produce remission.	

Table I shows the treatment previously given to the 38 patients in this group. In none had a sustained remission been produced. Leucotomy was projected in nine cases because of the continued failure to respond to treatment. All patients were classifiable as chronic hospital invalids or likely to fall into this class if projected leucotomy did not produce a remission. Twenty patients presented serious nursing problems because, under the influence of their delusions or their "voices," they became aggressive or negativistic.

All but four of these cases had been under our own observation in hospital for at least a year, many for much longer periods. Of the four patients treated in other hospitals, one had been leucotomized and three had had insulin and electroplexy combined. These patients were known intimately by the staff of the hospital, and every effort had previously been made, without success, to achieve a sustained remission. Thus this group of patients could act as their own controls. In none of these cases was the diagnosis in any doubt—all showed active schizophrenic process symptoms. Seventeen of the patients admitted to auditory hallucinations when reserpine treatment started; 31 were deluded, without insight; 24 had ideas of reference or influence; 22 showed marked affective blunting or incongruity.

In assessing results we tried to make our criteria as objective as possible. A clinical impression that the patient had improved was not regarded as valid unless it could be shown that specific psychotic symptoms had disappeared. The term "recovered" was deliberately avoided, in view of the short-term nature of the results. We classified the results into three groups: much improved, improved, and no improvement. These terms are defined in the legend below Table II.

Of the 17 patients who were hearing voices when the treatment started, 11 lost their hallucinations, but in two they returned. Of the 24 who had clear-cut ideas of reference or influence, 11 lost them. Of the 31 who had frank delusions, 15 lost them or showed considerable diminution in delusional ideas. Ten gained fairly good or good insight.

This group was a most instructive one because the case material was so well known to us, the symptomatology so clear-cut, and, since no other physical method of treatment was used once reserpine therapy started, improvement when it occurred could be attributed with reasonable certainty to the drug. The statistical details of this group are given in Tables II, III, and IV. One patient became depressed.

TABLE II.—Response of Patients in Group 2

	Much Improved	Improved	No Improvement	Total
Whole group	17	10	11*	38
Leucotomy	7	6	6	19
Insulin—E.C.T.—Leucotomy —projected "leucotomy"	4	6	3	13
	7	2	—	9

* Includes one case of depression.

Much improved—Free of all psychotic symptoms—that is, delusions, hallucinations, ideas of reference or influence, thought disorder, affective incongruity, or marked blunting; some insight.

Improved—Better, but with some residual symptoms, chiefly emotional flattening or incongruity.

TABLE III.—Response of Patients in Group 2 Related to Age at Time of Treatment

Age	Much Improved	Improved	No Improvement	Total
30 and under ..	6	6	4	16
31–40 ..	9	4	3	16
41 plus ..	2	—	4*	6

Average age, 35.5 years. Range, 18–52 years.

* Includes one case of depression.

TABLE IV.—Response of Patients in Group 2 Related to Duration of Symptoms

Duration of Illness	Much Improved	Improved	No Improvement	Total
Less than 5 years	5	4	2	11
5–10 years ..	11	6	4	21
More than 10 years	1	—	5*	6

Average age, 7.5 years. Range, 2–29 years.

* Includes one case of depression.

Group 3. Chronic Untreated Schizophrenia of Insidious Onset

The third group of cases also could act to some extent as their own controls. The group consisted of recent admissions who were regarded as unsuitable for insulin treatment

by reason of long history, insidious onset, or lack of florid features. It comprised 17 patients (14 male, 3 female), 16 of whom had never been in hospital before, and none had been ill for less than two years. One had been in hospital for 22 years but had never been treated by any of the physical methods because permission was refused by relatives.

In this group the average age was 29.4 years, ranging from 17 to 56 years. The length of illness ranged from 2 to 22 years, with an average of 6 years.

Five of the group had been given electroplexy since admission to hospital. In such chronic cases this was not given in the hope of any long-term benefit, but in order to obtain initial sedation or co-operation. Five patients had auditory hallucinations and nine had persecutory delusions. Nine showed apathy, withdrawal, lack of initiative, and marked affective blunting. Six cases might be termed "simple schizophrenia."

The dosage and general regime was the same as in Group 2, and the criteria used in assessing results were also the same. Nine patients were regarded as much improved and six as improved. Twelve have been discharged, and nine are known to be back at work. Details are given in Table V.

TABLE V.—Response of Patients in Group 3

	Much Improved	Improved	Not Improved	Total
Whole group ..	9	6	2*	17

"Much improved" and "improved" as defined in Table II.

* Includes one case of depression.

The results here are in some respects more unexpected than those in group 2, because the symptomatology was less florid, the pre-morbid personalities were less good, and the onset was more insidious. Although none had been thoroughly treated by the physical therapies, they had all been rated as unlikely to respond to these methods when reviewed by the staff at case conferences.

Group 4. Acute Schizo-affective Psychosis

The fourth group in this series were diagnosed as suffering from schizo-affective psychosis. It consisted of 21 patients (7 male, 14 female) who presented predominantly manic (7 cases) or depressive (14 cases) features. In addition, all cases showed some schizophrenic features such as auditory hallucinations or paranoid delusions. Seven depressed and five manic patients had had previous psychotic episodes. They had achieved a good remission of their symptoms, either with electroplexy (7) or electroplexy combined with insulin coma therapy (5). All but one had been treated in St. Patrick's Hospital. All the patients in this group were thought to have a good prognosis for the present episode. With two exceptions, patients were given reserpine because the expected remission did not follow one or more courses of electroplexy—the patient either did not improve or relapsed within a few weeks of treatment. All had been ill for less than one year. The average age was 39 years (range 18–61 years).

The two patients who went straight on reserpine therapy were recent admissions, but both had had previous episodes, one having achieved a remission following electroplexy and insulin, and the other having achieved a remission on reserpine given a year previously in an American hospital. Both these patients improved with reserpine alone, and they are both out of hospital and back at their work.

Because the illnesses reported in this group were of much shorter duration, a more rigid standard of assessment was used. The term "recovered" was again discarded, in view of the lack of follow-up period. Cases were classified as much improved only if free of all psychotic symptoms and if their pre-psychotic personality had been restored as judged by clinical observation. Cases regarded as improved were

better but had some residual symptoms or personality defects. The results are shown in Table VI.

TABLE VI.—Response of Patients in Group 4

	Much Improved	Improved	Not Improved (All Depressed)	Total
Depressed ..	5	1	8	14
Manic ..	5	1	1	7

Much improved=Free of all psychotic symptoms; pre-psychotic personality restored.

Improved=Better, but with some residual symptoms.

It is instructive to note that the incidence of depression was much higher in this group. This observation, if confirmed in larger series, would seem to indicate that this serious complication may occur chiefly, if not entirely, in those constitutionally predisposed to endogenous depression.

Group 5. Acute Schizophrenia

The last group under review consisted of 21 acute schizophrenics (5 male, 16 female). All had a history of under one year. Patients with marked manic or depressive features, and who might thus be regarded as suffering from a schizo-affective psychosis, were excluded. All showed active process symptoms. All had been ill for less than one year. Average age was 30 years (range 19–52 years).

In general the immediate prognosis in this group was regarded as very good. Six of the group had suffered from previous schizophrenic episodes (one or more). Five of them had remitted following insulin coma therapy, and one following electroplexy. Five other patients had recently completed full courses of insulin coma therapy without sustained improvement. In two cases a course of insulin treatment had been stopped—one because of hypersensitivity to insulin, and one because of her violent behaviour during sopor. Three were not given insulin because of a history of pulmonary tuberculosis, and one because she was considered too old. The remaining five patients were given reserpine as a first choice.

All patients in this group had been given a course of electroplexy on admission to hospital to control acute symptoms. They were given reserpine only when clear-cut schizophrenic symptoms persisted after electroplexy.

TABLE VII.—Response of Patients in Group 5

Much Improved	Improved	Not Improved	Depressed	Total
18	3	—	—	21

"Much improved" and "improved" as for Table VI.

The results were assessed by the same criteria as in group 4 and are shown in Table VII. The average duration of treatment in this group was 80 days. On the completion of treatment, 18 of the 21 patients were regarded as much improved and 3 as improved. Twenty of these patients have been discharged from hospital, and 15 are known to be back at their former occupations.

Since December 31, 1955, when the table was drawn up, two patients placed in the much improved group have been readmitted—one was brought back by her relatives in a state of deep depression, the other was noted to be rather depressed on a routine follow-up visit and was readmitted for observation. There has been no return of schizophrenic symptoms in either case.

Discussion

The results we have had are encouraging and justify the continued use of the treatment. Not only have some schizophrenics with all the characteristics associated with chronicity lost their process symptoms, but in many cases they have gained a surprising degree of insight.

A woman civil servant aged 35 was referred for inefficiency and absenteeism in 1952. She had the delusion that she was hypnotized by a strange man whom she had met some years previously, and his voice dominated her life. In 1952 a full course of insulin coma therapy (60 comas) made her less withdrawn and more sociable. She never lost her hallucination or gained insight. She has been seen by one of us (J.N.P.M.) periodically as an out-patient since then, but the picture has remained unchanged. In October, 1955, she was given a last chance by her employers and told that if she was late or absent again she would be dismissed from the service. She was re-admitted to hospital and started on intensive reserpine therapy. After 10 weeks she spontaneously said in a shamefaced way—"Whether it is a good thing or not, at last I believe you when you say I am mentally ill." "Thank goodness the voice goes away sometimes—do you think I can get rid of it altogether?"

In this type of case the drug does not merely act as a sedative. Sometimes the psychotic process remits after reserpine therapy. Such a remission of symptoms occurred in a convincing number of cases. It occurred to patients, such as those in group 2, who had resisted other standard treatments, and in a regime unchanged except for the addition of the drug. We can offer no explanation of how this remission is achieved, but we would suggest that the drug has a central effect on schizophrenic patients. These become less influenced by their delusions and hallucinations. Fresh delusions and hallucinations cease to form. They can view their symptoms more objectively, and psychotherapy can play a part in bringing them into true perspective. They are more able to take interest in their surroundings, and active rehabilitation therapy is more likely to be successful.

Enthusiasm for a treatment in psychiatry always has a favourable influence on the patient. This factor plays much less a part when one has been dealing with psychotics, as we have in this study. Lavish enthusiasm and a placebo could not have produced the changes, often striking, which are reflected in our results. This is particularly true of patients in group 2 who were resistant to all other forms of treatment. The fact that this drug will in some patients produce a typical endogenous depression indicates that it has an action on some centre of fundamental importance in the development of mental illness. The associated effects on the pulse, blood pressure, and pupil, with the production of Parkinsonism, suggest that this may be in the region of the hypothalamus and basal ganglia. Experimental work tends to confirm this (Plummer *et al.*, 1954; Winsor, 1954).

A most impressive feature of the use of the drug is the quality of the remission. Insight into their morbid ideas, friendliness towards staff and fellow-patients, and a healthy interest in occupational and social activities is a usual rather than exceptional result of the treatment. This insight is reflected in the readiness with which patients agree to report for follow-up talks after leaving hospital. Appointments have been kept punctiliously, even though in some cases it meant a long journey by train or car. Liberal parole was granted as soon as improvement began and when side-effects permitted, and only a few have not returned to hospital.

Besides using the drug in the intensive way described in this series, we have given smaller oral dosage to a number of chronic schizophrenics. We are not reporting in a detailed way on these cases here. A number of well-preserved chronic hospital patients, as well as a number of ex-patients who attend our out-patient department for general advice and supervision, have benefited greatly by small doses of the drug—for example, from 1–4 mg. daily. A few have improved dramatically. Some have been able to remain out of hospital when otherwise admission seemed inevitable.

Another problem for the future, therefore, is to decide whether or not the large doses prescribed by Kline and Stanley (1955) and Barsa and Kline (1955), and followed in this work, are necessary. Our present impression is that where an active progressive schizophrenic process is present the intensive dosage may be necessary. It seems, too, that length of history may be an important factor in deciding both the length and the intensity of the treatment required.

For example, the average length of treatment in the acute group was 80 days, whereas in the chronic treated group it was 195 days.

Apart from the treatment of schizophrenia, we have used reserpine in a number of other psychiatric conditions. In general the results have not been so dramatic. Patients with endogenous depression are not improved (and may be made worse). We noted in the early stages of this trial (before we became aware of the danger of depression as a side-effect) that some patients who were restless, unsettled, and discontented after a course of electroplexy did become more settled on 1-3 mg. daily. It seems wiser, however, *never* to use the drug in cases of endogenous depression or in those with a past history of depression. Cases of anxiety neurosis were given the drug mainly by mouth on an out-patient basis. Rarely do they get any immediate subjective relief of their symptoms, and many are put off by the side-effects, such as nasal stuffiness or drowsiness, and stop the drug. Patients with chronic anxiety states who are underweight seem most helped by the drug. They may put on weight, and this is accompanied by a feeling of well-being and reduction in tension rather similar to the improvement one gets with modified insulin. Classical cases of anorexia nervosa appear to respond very well to the drug. Seven patients who showed the characteristic mixture of hysterical and obsessional traits in their personalities, with anorexia, amenorrhoea, emaciation, and restlessness, lost their symptoms and put on weight. Details of this group will be published elsewhere.

Apart from the statistical results given in the tables and mentioned in the text, the introduction of reserpine treatment has greatly changed the character of the hospital. Negativistic or impulsive behaviour has been much diminished, and the general morale of the wards has been correspondingly improved. Maintenance electroplexy is now seldom used.

Although patients do not like the treatment because of the irritating side-effects and the numerous injections involved, little difficulty is experienced in encouraging them to carry on with it. It does not arouse the fear and antagonism sometimes evoked by electroplexy and insulin treatment.

The restlessness induced by reserpine must be helped not only by sedation but by organized activity. Many more patients than formerly are well enough to take an active part in occupational, recreational, and social therapy. Classes of all kinds have had to be greatly increased. Physical training classes, relaxation classes, and organized games are particularly helpful in combating reserpine-induced restlessness. In the same way, outdoor work parties, digging, cutting grass, sawing logs, etc., are beneficial and mostly welcome activities, except where the patient is heavily under the influence of the drug.

With awakening insight, patients are in particular need of psychotherapeutic interviews, and the work of the medical staff in this respect has been greatly increased by the treatment. The fact that memory is not disturbed makes explanation and reassurance more rewarding as well as more necessary. Although we have not used group therapy in any formal way, it seems probable that, in future, only by this means can the medical staff cope adequately with the patient's needs.

It must be stressed that the results given here are the immediate results. Few cases have been in a state of remission for more than six months. We have satisfied ourselves that the drug can favourably influence a schizophrenic process, at least temporarily. Only a long-term follow-up can decide the drug's eventual place in the treatment of schizophrenia.

Summary

Reserpine given orally may benefit deteriorated chronic hospitalized schizophrenics with troublesome symptoms.

Chronic schizophrenics who have failed to achieve a sustained remission following E.C.T., insulin coma, or leucotomy may improve remarkably with intensive reserpine therapy. As a result of our experience we have made it a rule that no schizophrenic should be leucotomized without first having prolonged trial on reserpine.

Patients with schizophrenia of insidious onset but without florid symptoms or gross personality deterioration may respond favourably to intensive reserpine therapy. It is probably necessary to continue on an oral maintenance dose for a prolonged period.

Immediate results of reserpine therapy in acute schizophrenics are impressive. Observation over a prolonged period alone can determine whether in these early cases it is a better therapeutic agent than insulin coma therapy.

Severe depression of the endogenous type with characteristic early morning waking and suicidal preoccupation is the most serious complication of the treatment. The incidence of this complication was greatest in the schizo-affective type of psychosis. A past history of endogenous depression is a contraindication to the use of the drug.

Some chronic schizophrenics improve on oral dosage only. Intensive and prolonged treatment seems necessary in most cases of progressive schizophrenia.

Some patients with chronic anxiety states, especially if underweight, may benefit from oral reserpine. The results in most cases are not so dramatic as in schizophrenia.

Most patients on reserpine eat better and put on weight. Cases of anorexia nervosa may improve rapidly on the drug.

The extensive use of reserpine alters the character of a psychiatric unit considerably. Negativistic, aggressive behaviour is greatly diminished. Patients can enjoy more freedom and take a more active part in the hospital routine. It places an increased demand on hospital staff for individual psychotherapy.

We are indebted to Ciba Laboratories Ltd. for liberal supplies of reserpine in the form of "serpasil" and for supplies of "antistin-privine."

ADDENDUM

A follow-up of the 109 cases described above was undertaken from November 1, 1956. About half of these patients were interviewed either by one of us or by other members of the medical staff of St. Patrick's Hospital. Information about the remainder was obtained by letter from the patients, their relatives, or their family doctor. The results for groups 1 to 5 are shown in Tables Ia, IIa, IIIa, and IVa. The assessment criteria are the same as in the main paper.

TABLE Ia.—*Response of Patients of Group 2—Chronic Treated Schizophrenia*

Much Improved	Improved	No Improvement or Relapsed	Untraced	Total
16*	2	19	1	38

* One relapsed and was given a second course of reserpine.

TABLE IIa.—*Response of Patients of Group 3—Chronic Untreated Schizophrenia of Insidious Onset*

Much Improved	Improved	No Improvement or Relapsed	Untraced	Total
9	4*	2	2	17

* Three relapsed and were given a second course of reserpine.

TABLE IIIa.—*Response of Patients in Group 4—Schizo-affective Psychosis*

Case Type	Much Improved	Improved	No Improvement or Relapsed	Untraced	Total
Depressed ..	2	0	11	1	14
Manic ..	5*	0	2	—	7

* One relapsed and was given a second course of reserpine.

TABLE IVa.—*Response of Patients of Group 5—Acute Schizophrenia*

Much Improved	Improved	Relapsed	Untraced	Total
15*	2*	4	—	21

* One relapsed and was given a further course of reserpine.

It will be seen that the results confirm in a general way the trends of the initial assessment and encourage us to continue trial of this method of treatment.

A further year's experience suggests that smaller doses may give similar results with less distressing side-effects. At present an intramuscular dosage of 10 mg. daily is the exception rather than the rule. Our usual maximum dosage is 3 mg. orally and 5 mg. intramuscularly daily.

We hope to publish a further paper on a larger series with a detailed analysis of the factors influencing good or bad response, the relapse rate, and the incidence of depression.

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IDIOPATHIC OR HYPERCATABOLIC HYPOPROTEINAEMIA

CASE EXAMINED BY ¹³¹I-LABELLED ALBUMIN

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Hypoproteinaemia is not an uncommon clinical finding, and is nearly always caused by an external loss of protein—for example, proteinuria, skin disease, bleeding—or a reduced protein synthesis (hepatic or intestinal disease, starvation, etc.).

In a few exceptional cases such low serum protein has been entirely inexplicable—idiopathic. A critical review of the literature shows that the reported cases which can be designated idiopathic hypoproteinaemia do not amount to more than 25.^{1 2 4 6-18 21 22} Despite this small number of cases the syndrome appears to be well defined.

The main sign of this disease is oedema formation caused by and varying with the hypoproteinaemia, which (nearly) always affects the albumin and globulin fractions equally. In most instances the disease has persisted for months and often for years. Practically all the reported cases of idiopathic hypoproteinaemia have been particularly well studied. In addition to the low serum

protein some of them have exhibited eosinophilia (4 out of 10 cases so examined) and several have been allergic, but all other tests have failed to show abnormalities.

Attempts at raising the serum protein level by oral administration of protein in large amounts have proved ineffective, although a highly positive nitrogen balance may be obtained thereby.⁷

Most authors have merely concluded that in idiopathic hypoproteinaemia protein synthesis is impaired. It has been suggested that this reduced protein synthesis is due to hepatic disease, but what kind of hepatic disease is not quite clear, as no patient with genuine idiopathic hypoproteinaemia has shown other signs of hepatic involvement.

The Degradation Theory

As no external loss of protein can be demonstrated and as there is no obvious cause why the production of protein should be reduced, the reason for the low serum protein might theoretically be imagined to be an internal loss—an increased degradation of protein.

Only a few authors have dwelt on this idea. As early as 1935, however Cope and Goadby⁷ stated: "The possibility that unduly rapid breakdown of plasma protein was occurring could not be excluded, but was considered to be improbable."

In recent years, however, reports on four patients with idiopathic hypoproteinaemia indicate that in these patients there has been a question of increased breakdown of protein. In 1949 Albright, Bartter, and Forbes¹ (1 patient) and in 1955 Hennemann and Albright¹¹ (2 patients) studied the fate of intravenously administered albumin. These extremely difficult and painstaking investigations will not be described in detail here: suffice it to mention that during the experiment the patients received 52 g. of serum albumin intravenously every day for more than two weeks.

The results of these balance experiments unequivocally showed that, compared with normal persons, the patients retained only a small proportion of the administered albumin during the experimental period, whereas an excessive amount must have been burned or converted into protoplasm. These authors conclude¹ that "the disorder in albumin metabolism was not a decreased rate of synthesis, but an increased rate of destruction."

Kinsell *et al.*¹⁴ studied the fate of intravenously administered ³⁵S-labelled methionine in some patients, including one with idiopathic hypoproteinaemia. This study also failed to show any signs of reduced plasma protein synthesis—rather the opposite. The rate at which ³⁵S disappeared from plasma protein by far exceeded that in normal people. Similarly, the urinary excretion of ³⁵S was increased compared with normal persons. Kinsell *et al.* sum up that "the basic defect is one of hypercatabolism."

Against the studies of Albright *et al.* it may be objected that intravenous administration of 50 g. of albumin daily for 16 days is rather an unphysiological procedure, and against the technique of Kinsell *et al.* that it may be difficult to assess the results of experiments with labelled amino-acids because of the possibility of their re-utilization. As patients with idiopathic hypoproteinaemia present special possibilities of elucidating the largely unknown mechanism which regulates serum proteins, it seemed to us of great interest to study the serum protein turnover, using directly labelled