Summary

Five cases of operative removal of splenic aneurysms are reported. In this series there was one death following rupture of an aneurysm, and one recovery after rupture of an aneurysm in a pregnant woman; another patient had a porto-caval shunt. In the three patients with unruptured aneurysms the diagnosis was made by the radiologist before operation, and these patients survived.

I am indebted to Dr. A. B. Hill for the pathology reports; to Dr. E. J. S. Townsend for the radiographs; to Dr. A. Hegarty, who anaesthetized four of these patients; and to my surgical colleagues, Mr. F. J. Milward, under whose care Case 1 was admitted, and Mr. A. McEwan Smith, who referred Case 5.

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CLINICAL TRIAL OF ACEPROMAZINE MALEATE IN CHRONIC SCHIZOPHRENIA

BY

JESSIE F. COLLARD, B.M., B.Ch.

Physician, Hellingly Hospital, Hailsham, Sussex

AND

RONALD MAGGS, M.D., D.P.M.

Consultant Psychiatrist, Hellingly Hospital, Hailsham, Sussex

A new derivative of the phenothiazine group of tranquillizers, acepromazine maleate ("notensil"), was first given a clinical trial in France by Delay and Pichot (1957), who studied its effect in 11 psychoneurotic out-patients and 20 severe psychotics. The use of acepromazine in other kinds of disorders has already been mentioned by Stafford-Clark (1957), and it was understood that our project was only part of the trials planned in this country into the use of acepromazine in different clinical conditions. The largest single clinical group of diseases with behaviour disturbance in a mental hospital remains schizophrenia, and we decided to limit our study to this disease. Our aims were (1) to ascertain whether treatment with acepromazine is of value in chronic schizophrenic patients with behaviour disorders, and (2) to record the incidence of side-effects and toxic effects.

Methods

We defined chronic schizophrenia as an illness characterized by a disorder of emotion and thought, hallucinations, and behaviour disturbances of more than one year's duration. The patients selected numbered 86—42 in the

treatment group and 44 as controls. For various reasons four patients in each group were withdrawn. All had been known to us for at least one year and the diagnosis was agreed upon. Patients with a history of jaundice or evidence of active peptic ulceration were excluded.

Before starting the trial our colleagues agreed to discontinue the use of tranquillizers on schizophrenic patients so that we might observe whether, on withdrawal of these drugs, the patients remained in remission or showed signs of relapse. Those who relapsed were then considered for inclusion in this trial, and if accepted, their clinical, nursing, and psychometric ratings were carried out. Clinical rating was made by one of us (J. F. C.) on the basis of a scale described by Boardman *et al.* (1956), whilst the nursing staff used the rating scale of Baker and Thorpe (1956). Psychometric assessment with a group of tests designed for psychotic behaviour was attempted, but it has not been possible to include these findings in our paper.

Patients were chosen from any ward in the hospital and allocated to treatment or control groups on the basis of Bradford Hill's (1955) prescribed random order chart. This chart was held by the chief pharmacist, who supplied the appropriate substances in identical containers.

The drug, or placebo, was given orally in tablet form at an initial dosage of 50 mg. three times a day. This was increased by 50 mg. a day until a daily total of 300 mg. (given in three equal doses) was reached on the fourth day. We aimed to maintain the dosage at this level for six weeks, although some modifications had to be made when side-effects were encountered. Only those patients who completed a full course of treatment were included in our series.

The clinical and nursing ratings were carried out at weekly intervals during the six weeks of treatment. At the end of this period an approximate clinical assessment of the efficacy of the treatment was made by classification of the subjects into the following groups: (1) improved (to cover all variations between number and severity of symptoms materially less up to a complete remission); (2) not improved; and (3) worse (symptoms aggravated and behaviour more disturbed).

A further statistical assessment of the changes in clinical and behaviour rating scales was made by means of a test on the differences in the ratings before and after treatment.

Distribution of Clinical Types and Comparison of Groups

The 78 patients taking part in the trial were classified according to clinical groups (Table I).

TABLE I

	Control Group	Treatment Group	Total
Simple	11	11	22
Paranoid	10	11	21
Catatonic	13	10	23
Mixed	5	6	11
Hebephrenic	1	—	1
Total	40	38	78
Males	19	20	39
Females	21	18	39

The average age and duration of stay in hospital for each group are shown in Table II.

TABLE II

	Control Group	Treatment Group
Age	44.32 years	48.18 years
Duration of stay	13.29 ..	13.25 ..

As all our subjects had been in hospital for over a year it followed that many of them had previously received some kind of physical treatment. The two groups are compared

in Table III. It is not possible to say whether any of the differences are significant, as the groups are too small for comparison statistically.

TABLE III

Group	E.C.T.	Coma Insulin Treatment	Leptazol	Leucotomy	Tranquil- lizers	Lithium
Control	25	3	1	8	20	2
Treatment	25	2	3	4	4	—

A check was carried out on the distribution of patients ward by ward; this is too parochial to enumerate, but it was established that there were no significant weightings.

Toxic Effects and Side-effects

We did not observe Parkinsonism, jaundice, or dermatitis, but were seriously troubled by the incidence of hypotensive reactions in the treatment group. Of the 42 patients in the treatment group, four (three females and one male) had such severe hypotensive reactions that treatment was discontinued. The fall of blood pressure was considerable even on as small a dose of acepromazine as 10 mg., and in the male patient was associated with a major epileptic fit and depression of corneal reflexes. Of the 44 in the control group, three refused to take tablets and one collapsed as though hypotensive, but there was no loss of consciousness and the blood pressure was not depressed. In these four patients, also, treatment was discontinued.

Clinical Changes

The effects observed, using the criteria mentioned above, are shown in Table IV. An examination of the scales of behaviour and symptom rating showed that an analysis of

TABLE IV

	Treatment Group	Control Group
Worse	5	5
No change	24	34
Improved	9	1

variance represented the most satisfactory method of assessing whether the changes were significant statistically. With this method, allowance was made for the variation between patients. The figures of the summary of the analysis of variance are included in the Appendix.

The assessment showed that with this method there was no significant change in the nurses' rating of behaviour following acepromazine maleate therapy. The clinical rating by the doctor was dealt with in a like manner, and, although this showed that there was some improvement, it did not reach a high level of significance. As described above, a subjective assessment of clinical change was made. To obtain 9 cases of improvement among 38 treated and only 1 case of improvement among 40 not treated is highly significant ($P=0.00556$) (Fisher's exact test).

Discussion

In a study by Wing (1956), the degree of control of the environment has been increased by siting all of the subjects in what is virtually a research ward. We have tackled the problem in a different way by arranging that our patients came from any ward. Thus any environmental weightings were distributed throughout both treatment and control groups, and weighting by individual environmental factors was less likely. Although any purposeful form of activity in mental hospital wards can be of great value, there was no evidence that the special attention given to all of the patients resulted in improvement in the control group.

A direct interpretation of our results has been found difficult, particularly because we have been advised not to

attach too much importance statistically to the findings under "subjective clinical assessment." This leaves us, therefore, to consider the results of changes in both the nurses' and the doctors' ratings. In neither of these was there any evidence of highly significant change, and this finding fits in with our working clinical impression that under the conditions used in this investigation the drug did not produce a dramatic response. It is perhaps important to observe that no worsening of behaviour occurred in our treatment group (the means of the nurses' rating in the first and last weeks are 12.4 and 10.87). The disparity of our findings with those of Delay and Pichot is probably accounted for by the different type of clinical material, although, in view of the recent comments on the use of tranquilizers in schizophrenia, variations in dosage can influence results.

In the Maudsley Bequest Lectures (R.M.P.A., 1957) two methods of administration were put forward. Either the "low-dose" method, in which the drug is given in a dosage of up to 600-800 mg. daily for a period of three to four months, or the "high-dose" method, in which the dosage of up to 2-3 g. is given for only 7 to 14 days. We suggest that, if further investigations with acepromazine are contemplated, either the low-dose method should be continued for a much longer period of time or the high-dose technique should be applied. The French workers used parenteral injections, and, while this method of administration is desirable for uncooperative patients, it is not likely to influence the efficacy of the drug. Fluid medicine for oral use is desirable for psychotic patients where co-operation may be limited, and our study could perhaps be extended on these lines.

Rosenheim (1957) has commented on the problem introduced into any investigation of a drug known to have side-effects or toxic effects. An additional problem for the psychiatrist is that an objective assessment of psychiatric symptoms and signs is fraught with difficulties, and Wing (1956) commented on this and felt that her findings should be interpreted with caution. In our trial we found a new complication arising in that some of the nursing staff regarded the medicine being given to each patient as a challenge to them to find out whether the patient was having the placebo or not. We noticed that this curiosity extended even to the nurses tasting the tablets, and as there was a difference in taste between the placebo and drug it may have influenced their assessment of behaviour. We do not know if this observation has been made before in a clinical trial, but certainly more attention should be paid to the standard of placebos, particularly if the trial is to be "controlled" and statistically assessed. It is impossible to say how much this has influenced our findings, but in designing any controlled investigation we believe it important that this factor should be taken into account.

The occurrence of hypotensive side-reactions in 4 of the 42 patients in the treatment group was most disturbing, particularly as in one of them the changes were observed even on reducing the dosage to 10 mg. The sequence of clinical events in these cases was so dramatic that it could be argued that the observer recognized that the patient was in the treatment group and thus subsequent ratings might have been biased. We did not take this view, although it became necessary for three out of these four to be excluded from the trial as an adequate dosage of acepromazine could not be maintained on account of the hypotensive reaction. In one of our male patients receiving acepromazine the hypotension was associated with a drowsy state of consciousness, in which the corneal and limb reflexes were disturbed. The occurrence subsequently of an epileptic fit suggested that these changes in the reflexes may have been associated with a post-ictal state. It seems, however, that acepromazine, like promazine and chlorpromazine, is able to potentiate epilepsy.

We believe that the findings of our study justify the value of the preliminary trial of a drug before the manufacturers embark upon wholesale advertising and distribution. That

our study concerned only a limited type of schizophrenic illness must be borne in mind when considering its significance.

Summary

A clinical trial is described in the use of acepromazine maleate (notensil) in chronic schizophrenia.

The drug has a limited value.

Side-effects (hypotension and epilepsy) were observed.

The difficulties of making this kind of trial objective are described. The importance of the standard of the placebo is stressed.

We are grateful to Messrs. Bengers for supplying notensil tablets and placebo and for help with the statistical and secretarial facilities. We are grateful also to Mr. R. Bevan, senior psychologist, Hellingly Hospital, and to Mr. P. Slater, of the statistical department of the Institute of Psychiatry, for carrying out a statistical assessment and giving us advice on these matters. In the clinical field we are indebted to many of the staff of Hellingly Hospital, and particularly to our medical superintendent, Dr. David Rice, for having made this study possible.

APPENDIX

Summary of Analysis of Variance (Doctors' Rating Scale—Symptoms)

Source of Variance	Sum of Squares	D.F.	Mean Square Variance
Total variance	1,173.47	151	
Between persons	766.97		
" treatments (treatment/control)	7.17	1	
" sexes	24.17	1	
Sex/treatment interaction	43.00	1	
Residual variance between subjects	692.63		
Variance between trials (first/final)	35.06	1	
Treatment/trial interaction	17.11	1	17.11
Sex/trial interaction	2.95	1	
Sex/treatment/trial interaction	0.90	1	
Residual error	350.48	72	4.868

$$F = \frac{17.11}{4.868} = 3.515. \quad 0.10 > P > 0.05 \text{ on a two-tailed test.}$$

The difference is in the expected direction, that of improvement, but it does not reach a high level of significance.

Summary of Analysis of Variance (Nurses' Rating Scale—Behaviour)

Source of Variance	Sum of Squares	D.F.	Mean Square Variance
Total variance	2,225.26	151	
Between persons	1,831.26		
" sexes	182.48	1	
" treatments	0.94	1	
Sex/treatment interaction	4.95	1	
Residual variance between subjects	1,459.47	72	
Variance between trials	46.42	1	
Treatment/trial interaction	6.74	1	6.74
Sex/trial interaction	1.02	1	
Sex/trial/treatment interaction	0.21	1	
Residual error	339.61	72	4.717

$$F = \frac{6.74}{4.717} = 1.429 \text{ (non-significant).}$$

The assessment showed that, using this method, there was no significant change in the nurses' rating of behaviour following acepromazine therapy.

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DISTURBED RELAXATION OF LIMBS

BY

SIMON BEHRMAN, B.Sc., M.R.C.P.

Neurologist, South-East and North-East Metropolitan Regional Hospital Boards; Physician, Moorfields Eye Hospital

In a few individuals relaxation of limbs in the sitting or recumbent positions, or during sleep, is repeatedly interrupted by a train of motor and sensory disturbances. Though the legs are chiefly affected, occasionally the arms also participate in this disorder. These phenomena can be promptly abolished by suspending relaxation and engaging the affected limbs in active movements, and this latter feature constitutes the chief diagnostic touchstone. According to the nature of the main symptom engendered by relaxation, several groups can be recognized, but certain general features apply to most cases.

General Features

After its onset in early adult life, the disorder persists for many years, during which it remains subject to marked fluctuations without ostensible cause. While the distribution is usually bilateral, occasionally only one limb may be affected. Typically the symptoms supervene after relaxing in an easy-chair in the evenings, when travelling, at the theatre or cinema, or when reading or watching television. The symptoms constantly reappear after a period of untrammelled relaxation of the limbs, a period which varies according to the severity of the case. Only by assuming the erect position or by walking can these symptoms be made to disappear completely for a time. The malady shows a pronounced heredo-familial incidence in an appreciable proportion of cases. Pregnancy and anaemia tend to exert a strong aggravating influence. If the testimony of the patient's spouse is available, one often learns that some twitching and jerking of the legs occurs during sleep. This can be of such frequency and severity as to be very disturbing to the other occupant of the double bed.

Cases fall into the following groups according to the nature of the main symptoms: myoclonus, pain and myoclonus, pain, "sleep-pain," and "restless legs."

Myoclonus Group

A sudden, quick, localized muscle contraction, with or without a movement of the limb, occurs in the legs under the provocative conditions mentioned. The myoclonus is apt to recur in the same situation again and again until the sequence is broken by activity, yet on another occasion a totally different group of muscles may be affected in a similar manner.

Case 1.—A woman aged 39 had for the past 11 years, after relaxing in an easy-chair in the evenings, been subject to sudden recurring muscle twitches, mainly in the left leg—"even in the middle of reading an absorbing book or watching the Mount Everest film." These muscle contractions, which may affect any muscle group of the legs, could be felt and seen; though powerful, they only rarely caused movements of the limbs. Occasionally the resulting jumping of the limb resembled a "knee-jerk." This disorder affected her particularly in bed when about to go off to sleep. Though the jerking "banished sleep," it nevertheless continued to recur at short intervals. She had to remain standing for at least 15 minutes to break the sequence. A shorter period would not suffice, since on returning to bed the muscle twitching reappeared almost at once. She learned to recognize a "non-relaxed sensation"