A CLINICAL TRIAL OF STEMETIL (PROCHLORPERAZINE)

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INTRODUCTION

PHENOTHIAZINE derivatives have been widely employed in the management of schizophrenia over the past few years. Possibly the most commonly used has been chlorpromazine under its trade name "Largactil".

The compound under investigation is a new phenothiazine derivative incorporating a piperazine ring in the side chain. This preparation, prochlorperazine, is marketed under the trade name of "Stemetil".

In laboratory tests this agent does not show in such close parallelism the relationship between the anti-emetic and central sedative effects of the earlier phenothiazine derivatives such as chlorpromazine. The anti-emetic effects have been studied experimentally and, recently, clinically by Smithy and Homburger (1957), the results confirming its greater anti-emetic potency compared with chlorpromazine. In view of this property prochlorperazine has been studied in cases of Ménière's syndrome and in migraine.

Ducrot and Koetschet (1956) found that Stemetil was 5–10 times less active than chlorpromazine in impairing the performance of the reflex in mice concerned with regaining their balance after being suspended from a horizontal wire.

Experimentally, it has been found to produce in rats, in a dosage of 10 mg./kg. subcutaneously, a cataleptiform state with immobility, some rigidity, and a condition resembling flexibilitas cerea. These animals can be moulded into abnormal postures which are sustained for a considerable time. (It will be seen later that comparable states have been observed in two of our patients.) Troublesome though this complication was, it was never prolonged and it cleared up rapidly.

Broussolle and Dubor (1956) investigated its action in mental disorder. The provisional results of their trial at the end of 4 months indicated that prochlorperazine is active in smaller doses than chlorpromazine. The side-effects described were those of Parkinsonism and atypical involuntary movements.

MATERIAL AND METHOD

The patients studied in this trial consisted of 50 male schizophrenics, ranging in age from 21 to 58 years.

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The following table gives details of the clinical diagnosis, average duration of illness and treatments employed prior to the trial.

Diagnosis	No.	Average Duration of Illness in Years	E.C.T.	Insulin	Leu-cotomy	Chlor-promazine
Simple hebephrenic	20	12	16	7	2	19
Catatonic	15	9	15	10	3	14
Paranoid	15	11	11	6	—	14

As will be seen, the average duration of illness, overall, was about 11 years. Most of the patients were of the type to be found in the chronic wards of any mental hospital. Prior to the trial most of them were unemployable, liable to impulsive behaviour, and generally careless of their appearance. They were withdrawn and aloof, and took little part in the social activities of the hospital. In most of them hallucinations and delusions were prominent. Even when given parole few of them would use it. E.C.T., and deep insulin therapy had produced transient improvement only, and leucotomy had failed. Chlorpromazine in the dosage used had produced better results without, however, removing all the troublesome features.

All but 3 of the patients had had chlorpromazine with an average dose of 75 mg. t.i.d., and their response to the drug was known and charted.

The present trial could therefore be considered as a comparative study of the effects of prochlorperazine against the known effects of chlorpromazine.

Two weeks prior to the administration of prochlorperazine, chlorpromazine therapy was discontinued.

During this period, the behaviour of the patients deteriorated rapidly, thereby proving the value of chlorpromazine in certain types of chronic psychosis. The patients were probably at their worst when prochlorperazine was introduced. Each patient received 25 mg. t.i.d. of the drug orally with the exception of two acute catatonic schizophrenics who were given it intramuscularly because they were unco-operative.

Prior to treatment, routine blood counts, liver function tests (i.e. thymol turbidity and flocculation and Van den Bergh), urine analysis, basal blood pressure, body temperature and weight were noted. During the trial, pulse and temperature were recorded twice daily, blood pressure daily for the first week, and thereafter on the 2nd, 3rd, 6th, 9th, and 12th week.

The E.S.R., W.B.C., and liver function tests were repeated at similar intervals.

The weight was recorded at weekly intervals.

The nursing staff was requested to note any specific side-effects. All the patients were granted parole as soon as their condition permitted, and were encouraged to take part in occupational therapy and other social activities.

The progress or otherwise of the patients was assessed in two ways:

1. *By the Nursing Staff*

A behaviour rating chart was used similar to that described by Baker and Thorpe (1956), the principle being that the more abnormal the behaviour the greater the scoring.

The nursing staff marked each patient's behaviour daily from Monday to Friday.

The individual scores thus obtained were totalled each day and the average rating per day for the whole group was thereby ascertained.

Every week the total for each of the 12 factors of behaviour (A to N, Baker and Thorpe) was calculated, and these weekly readings were charted. The charts which follow later will make this clear.

2. *Assessment by One of Us (H.B.M.)*

During the trial all clinical observations were made by the same observer in order to standardize the assessment.

Results

Within 5 weeks of treatment, the patients showed improvement comparable to that obtained with chlorpromazine, i.e. the average daily behaviour rating, which rose rapidly following the withdrawal of chlorpromazine, returned to what it had been under chlorpromazine therapy but on an average dose of 25 mg. t.i.d. of prochlorperazine, that is one-third of the chlorpromazine dosage. The patients continued to improve beyond this stage, and maximum benefit was attained by the 10th week of treatment by which time the average daily rating had fallen to half of what it had been, without any change in dosage.

Analysing the individual factors we found the most marked changes in tidiness, personal hygiene, ability and willingness to work without supervision, and facility of verbal expression. Patients who had hitherto been withdrawn, asocial, and monosyllabic, became friendly and co-operative. They began to enjoy their work and their leisure. During the first month of treatment, many patients showed marked motor restlessness and, indeed, many complained of this spontaneously, a complaint never encountered during chlorpromazine therapy. This restlessness, troublesome though it may be subjectively, has in our opinion the merit of activating the hitherto inert patients. It is merely a phase which passes into more purposeful activity and more normal affect.

Hallucinations and delusions tend, in successful cases, to go into the background or disappear altogether.

The graphs on the following pages will show clearly the results of improvement in diagrammatic form.

The overall results of this trial are very encouraging. It has to be borne in mind that the prognosis for the patients selected was bad. The most disappointing results were seen in paranoid schizophrenics. On the face of it, this would seem surprising, as the worst results with any treatment are practically always seen in simple schizophrenics and hebephrenics.

We think there are two reasons for this: firstly, many of the chronic paranoid schizophrenics in this hospital had been successfully treated, and discharged after intensive chlorpromazine therapy and those in our group were the treatment-resistant paranoids.

Secondly, prochlorperazine seems to increase drive and affect in simple schizophrenics and hebephrenics, whereas chlorpromazine does not appear to have this effect.

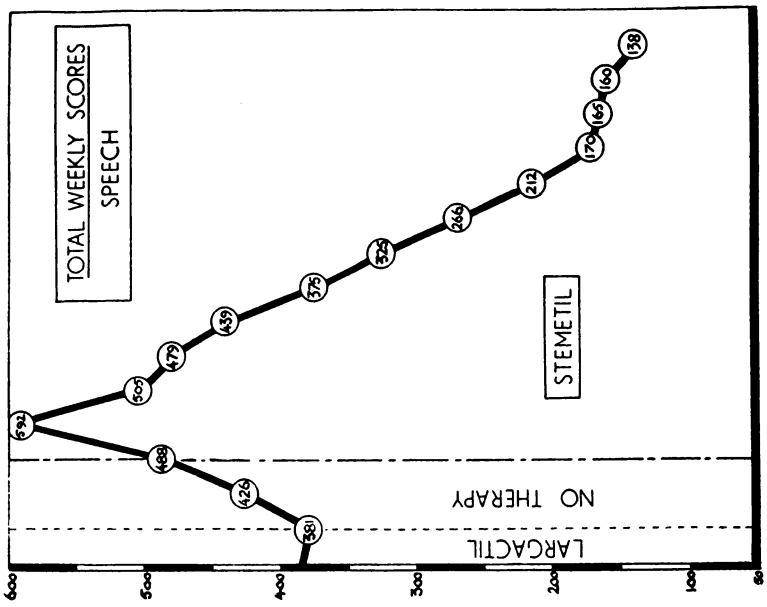

FIG. 2.

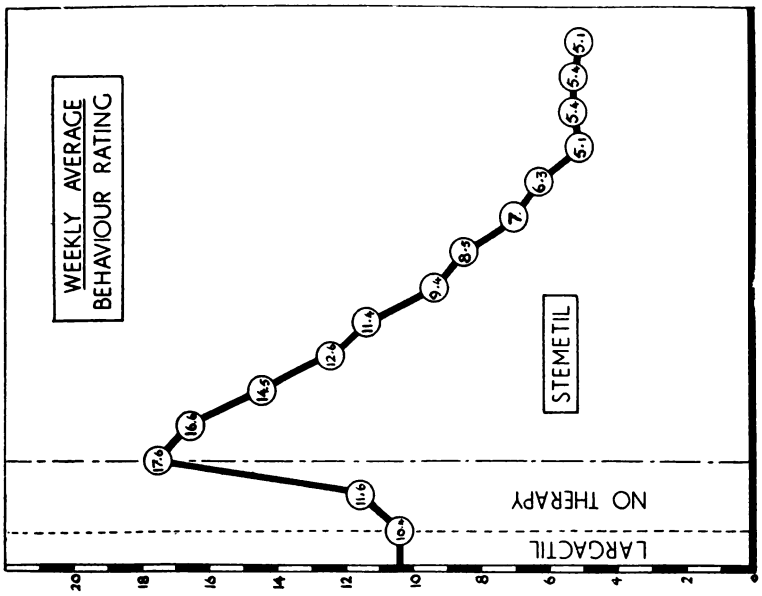

FIG. 1.

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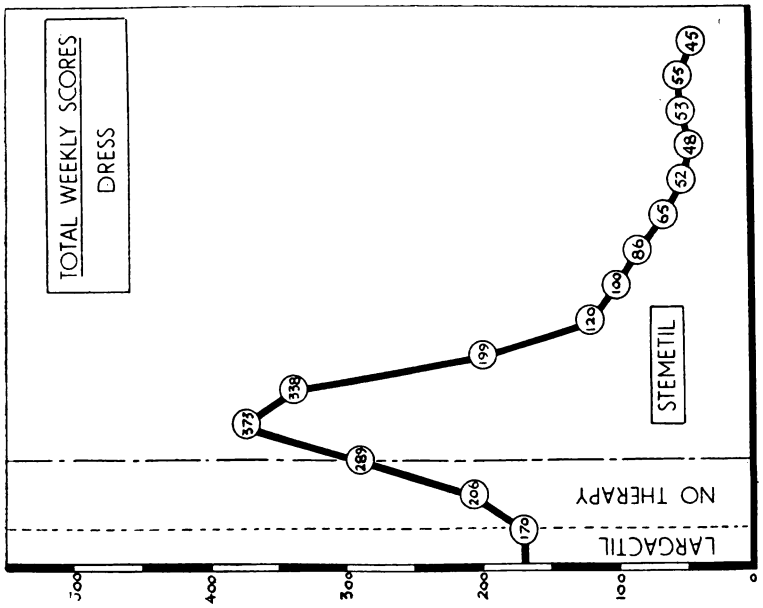

FIG. 4.

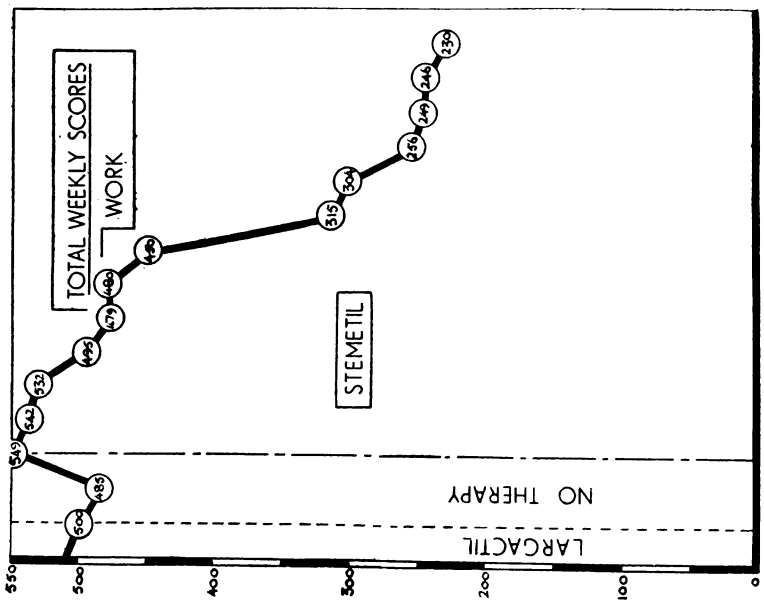

FIG. 3.

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The following case will illustrate this:

E.K., aged 34, a married man who had been a bank clerk. One sister is a chronic schizophrenic in our hospital.

Onset of present illness in 1949. He became increasingly flattened in affect, showed thought-blocking and was manneristic, untidy, and unable to work regularly. He was frequently aggressive towards his wife and children. There was no evidence of delusions or hallucinations. He received E.C.T., deep insulin, and prolonged courses of chlorpromazine and reserpine but with transient improvement only.

Five weeks after introduction of prochlorperazine he showed normal interest and affect. He was no longer manneristic or aggressive. Two months later he was well enough to go to a Rehabilitation Centre where he stayed for 8 weeks. He is now living a normal life, and works regularly in partnership with his father in the grocery trade. He attends our Out-patient Clinic periodically and has so far shown no sign of relapse. He is taking 50 mg. of prochlorperazine t.i.d. His wife reports that he is as well as he was prior to the onset of his illness in 1949.

Table of Results

Diagnosis	No.	Discharged	Much Improved	Improved	No Improvement
Simple hebephrenic	20	5	3	8	4
Catatonic	15	5	5	4	1
Paranoid	15	3	3	5	4

Side-Effects and Complication

No blood dyscrasias were observed. None of the patients in this series developed jaundice. (A female patient, not in this series, developed jaundice which cleared up on withdrawal of the drug.) Ten patients in this series showed abnormal liver function on tests while under chlorpromazine therapy. Withdrawal of chlorpromazine resulted in a return to normal liver function. Under prochlorperazine their liver function tests remained normal as did those of all other patients in this series. No abnormalities were revealed by urine analysis or blood sedimentation rate. None of the patients showed photosensitization. In the early stages, all patients complained of dryness of the mouth, nasal stuffiness and some also of excessive thirst. Where the serum sodium and potassium were checked they were found to be normal. Two severe hypotensive attacks occurred within 30 minutes of oral administration of 25 mg. of the drug. Both these attacks took place within the first few days of treatment, and responded rapidly to rest; they did not necessitate withdrawal of the drug.

Five patients showed varying degrees of extrapyramidal disturbance, viz. mask-like face, cog-wheel rigidity, difficulty in walking and tremor. Temporary discontinuation of the drug abolished these side-effects. When prochlorperazine was combined with the administration of 25 mg. Phenergan t.i.d., the extrapyramidal signs did not recur. As mentioned earlier, two of our cases, both catatonics, produced a syndrome reminiscent of the cataleptiform state seen in rats. One patient after 60 mg. of prochlorperazine i.m., in divided dosage, began to exhibit involuntary movements of a post-encephalitic type. There was posturing, flexibilitas cerea and opisthotonos. Strangely, these involuntary movements could be controlled by command. He also showed dilatation of the pupils, reddening of the conjunctivae, epiphora, and oculogyric crises. There was tachycardia and raised blood pressure. His tongue protruded and became progressively swollen. Treatment was discontinued at this stage, and within two days all side-effects cleared up. When treatment was resumed with smaller doses no adverse effects appeared.

SUMMARY

A new therapeutic agent prochlorperazine ("Stemetil") was administered to 50 chronic male schizophrenics. The results were most encouraging, especially in the group of simple and hebephrenic schizophrenics. Affect and drive returned in the majority of those patients in whom chlorpromazine had failed. The drug is active in lower dosage than chlorpromazine, as was noted by Broussolle and Dubor (1956). Although drowsiness was not infrequently present early in the treatment it did not persist, and the patients were much more alert than chlorpromazine-treated patients. Serious side-effects were absent with the exception of the rather alarming extrapyramidal syndrome mentioned above. However, if the drug is introduced in small dosage, e.g. 10 mg. t.i.d., and gradually increased to the optimum, these side-effects are minimal and respond rapidly when prochlorperazine is combined with Phenergan 25 mg. t.i.d.

ACKNOWLEDGMENTS

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REFERENCES

1. BAKER, A. A., and THORPE, J. G., "Deteriorated Psychotic Patients—their Treatment and its Assessment", *J. Ment. Sci.*, 1956, **102**, 780–789.
2. BROUSSOLLE, P., and DUBOR, P., "Preliminary Appraisal of the Clinical Effects of a New Neuroleptic", *Congr. Alién. Neurol.*, Bordeaux, 1956.
3. DUCROT, R., and KOETSCHET, P., "Anti-emetic Properties of a New Phenothiazine Derivative 3-Chloro-10-(3-N-methyl-piperazinylpropyl)-phenothiazine (6140 R.P.)", *Int. Physiol. Congr.*, Brussels, 1956.
4. SMITHY, G., and HOMBURGER, F., "Prochlorperazine for the Treatment of Nausea and Vomiting in Patients with Advanced Cancer and other Chronic Diseases", *New Eng. J. Med.*, 1957, **256**, 27.