# A CONTROLLED TRIAL OF THIOPROPAZATE DIHYDROCHLORIDE (DARTALAN), CHLORPROMAZINE AND OCCUPATIONAL THERAPY IN CHRONIC SCHIZOPHRENICS

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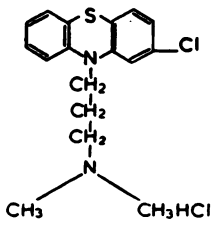
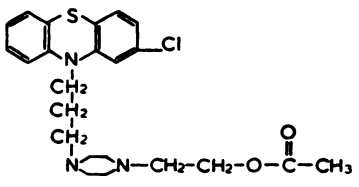
SINCE the introduction of chlorpromazine for the treatment of mental illnesses a number of other tranquillizing drugs, belonging to the phenothiazine group, have come into use. Experience has shown that the first of a new kind of drug is not necessarily the best and it is important that "variations on a theme" should be properly tested.

In 1956 Cusic, Hamilton and Lourie synthesized thiopropazate dihydrochloride (Dartalan) in the Chicago Laboratories of G. D. Searle & Co. Ltd. As can be seen, this drug has a close structural relationship to chlorpromazine.

Chlorpromazine




Thiopropazate




After extensive tests in animals and later in human subjects, thiopropazate was considered to exert tranquillizing effects comparable to those of chlorpromazine. Furthermore, it was found that these effects were produced in considerably lower doses with minimal unpleasant side-effects and a marked absence of toxic reactions. It was studied particularly in relation to toxic effects on the liver and so far no cases of liver damage resulting from its use have been reported. In fact, thiopropazate had been administered to patients who had previously developed jaundice from chlorpromazine, without further ill effects.



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A trial of thiopropazate dihydrochloride was made by Edisen and Samuels (1958) on a heterogeneous group of 104 patients with emotional disorders. A double-blind technique was employed with the patients serving as their own controls. Doses of thiopropazate varied from 10 to 120 mg. daily. The patients were assessed for 12 symptoms on a 5-point scale, and improvement was rated in four degrees: Worse, unchanged, slight and definite improvement. An overall estimate was also made. The majority of the patients were schizophrenics and they reported that of 62 chronic schizophrenics treated, 30 showed a definite improvement and of 19 acute schizophrenics, 11 showed definite improvement, particularly in defect of association, depersonalization and anxiety, delusions, withdrawn sociability, flattened affect and anorexia, as compared with those having placebo. Statistical tests were significant at levels ·01 and ·05 probability.

A number of unpublished observations indicated that thiopropazate might be useful in agitated states associated with cerebral arteriosclerosis. It was effective in cases of catatonic and paranoid schizophrenia, where, in addition to amelioration of mood, there was reported to be improvement in social behaviour and aptitude for work. Other workers reported improvement of hallucinations, delusions and inappropriate affect in chronic schizophrenics, and diminution of psychomotor activity.

It appears to be agreed so far that thiopropazate is three to five times more potent than chlorpromazine and the acute toxic dose is one and a half to four times that for chlorpromazine. Unpublished observations indicate that the therapeutic oral dose range is small, the action of the drug rapid and the full therapeutic effect achieved within one week.

## The Present Trial

Many difficulties appear in the evaluation of the effects of a drug on chronic mental patients, especially schizophrenics. It is generally agreed that such patients benefit to a marked degree from changes in environment, increased occupational activity and the promotion of social interaction, Bickford (1955), Merry (1956). Account must therefore be taken of the social and psychological effects produced by the trial itself (Mitchell, 1956). The patients who receive a placebo in order to serve as a control group, themselves benefit from the changed atmosphere of the ward, and this tends to obscure the effects of the drug on the treated group. There is no easy solution to this problem.

Instead of trying to eliminate the effects of environmental influences, it is possible to change the viewpoint of the trial and to attack the problem from the opposite direction. The trial could be designed to determine the effects of a drug combined with occupational and social therapy. Since it is now recognized that tranquillizers have no fundamental effect on the underlying pathology of schizophrenia, it is likely that their greatest value may lie in potentiating the effects of intensive social therapy. In this enquiry, an attempt has been made to tackle this problem, as well as to test the direct value of drug treatment.

## Population

The investigation was made on 54 chronic male schizophrenics (average age 38 years), all of whom had been resident in the hospital for a continuous period of not less than two years (average duration of residence in hospital 8·6 years). They were all liable to be overactive and aggressive from time to time. All of them had been referred to the Occupational Therapy department at some time but had not been able to continue to attend because they were too

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difficult to control. As a group, they were typical of the patients to be found in a refractory or semi-refractory ward of a mental hospital. Nearly all of them had had courses of E.C.T., over half of them had received insulin coma treatment, and all had had courses of tranquillizer drugs. All drug treatment was discontinued for one month before the first assessment in the trial.

The trial was designed in the form of a $2 \times 3$ factorial experiment. The patients were randomly allotted to 6 groups of 9 patients each. Three groups were randomly selected to attend Occupational Therapy (O.T.). They attended the O.T. department on five afternoons a week for 2 hours and were offered a choice of activities varying from simple repetitive tasks to complex, intricate work requiring planning, patience and skill. The patients were encouraged to persist in their chosen tasks or attempt ones requiring more skill, but where necessary they were advised on the activity most suited to their abilities. Each of these three groups was randomly coupled with another group, and the names of the patients in the three pairs of groups given to the hospital pharmacist. He randomly selected one pair of groups to receive chlorpromazine, 300 mg. daily; another group to receive thiopropazate 30 mg. daily, and the third pair of groups to receive placebo tablets. Since two drugs were being administered, it was necessary to have two sets of placebo tablets. One of the groups in the pair receiving placebos had five patients given the placebo tablets matching chlorpromazine and four patients given the placebo tablets matching thiopropazate. The other group of nine patients received the placebo tablets with the numbers reversed. Thus from the point of view of the patients, nurses, and physicians, there were 27 patients receiving one kind of tablet and 27 receiving the other kind, but only the pharmacist knew which of the patients were receiving active and which inert tablets. All the tablets were sugar-coated and the placebo tablets were indistinguishable from the active drugs.

## Assessment

The patients were assessed on Behaviour in the ward by the charge nurses, and on Symptoms by the physicians. Before the trial began, the physicians practised rating patients comparable with those who were to be included in the trial. Each patient was seen at an interview by two physicians, one of whom conducted the interview and the other asked any supplementary questions he considered necessary. The ratings were made independently and then compared. The results were discussed in order to clarify interpretation and to eliminate differences in standards of rating. The charge nurses also made practice assessments on patients not included in the trial, and these were discussed with the physicians. Their ratings were based on the patients' behaviour during the previous week.

All the patients on the trial were then assessed by the physicians at such double interviews, and the ratings summed to give a measure of the patient's condition. The drug trial was then started, and two weeks later the assessments were repeated. They were again repeated 6 weeks later, i.e. 8 weeks after the start of the trial. It was arranged at the second and third assessment, that the patients were not interviewed by the physician in direct charge of them. The difference between the ratings made at the first and second interviews measured the change in the patient's condition after two weeks, and the difference between the ratings at the first and third interviews measured the change in 8 weeks.

As there were two day shifts, there were two charge nurses to each ward. These charge nurses made independent ratings of the behaviour of the patients

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in the week preceding the start of the trial, again after two weeks and again after another 6 weeks. The forms on which the ratings were made were collected as soon as they were filled in. The ratings of the two charge nurses were summed to give an assessment of the patient's condition, and changes were measured by subtraction, as described above.

The nurses used a specially designed rating scale for behaviour in the ward, consisting of eight items. This scale is very simple compared with many well-known behaviour rating scales. We consider that a balance has to be struck between the loss of information in a short and simple scale, and the many errors of a long and elaborate one.

The physicians used a scale which was based on a modification of the relevant items in the scale of Lorr (1953). These modifications were made because of difficulties found in interpretation of certain items. Each item was scored from 0–3, for increasing intensity of symptoms. There is no doubt that the use of the scale requires not only practice in the scale, but also experience in interviewing chronic schizophrenic patients. Much patience is needed to persuade withdrawn schizophrenics to talk, and the interviews cannot be hurried. Important information sometimes appeared only towards the end of the interview, for which reason, a set time for the interview is unsatisfactory. It was found convenient to have some knowledge of the patient's history, symptoms and behaviour, in order to have suitable starting points for the interview.

## Results

### 1. *Nurses' Ratings of Behaviour in the Ward*

There is no great difficulty in studying the results of this trial as it affected the behaviour of the patients in the ward. Each nurse rated the patient on eight variables, at the beginning of the trial, after two weeks and again after another six weeks. The nurses' ratings were summed to give a total rating. The difference between the totals at the start of the trial and after two weeks measured the improvement during the first two weeks; and the difference between the first and third ratings measured the improvement over eight weeks (Table I, p. 44). There were six groups of nine patients and the total improvement for each group is given in the appropriate cell of the table.

At the end of two weeks, the patients receiving thiopropazate had a mean improvement of 3·2 points, those receiving placebo had improved by 1·6 points, whereas those receiving chlorpromazine had worsened by 0·6 points. The differences between these figures were statistically significant. The results support the claim that the effects of thiopropazate are manifest in a short period of time.

Occupational therapy also showed its effects quickly. The patients who received O.T. improved 2·7 points, whereas those who did not improved by only 0·1 points. The difference between these two means was significant. It is necessary to point out, however, that O.T. is not possible under "double-blind" conditions, for manifestly *all* the patients knew who was receiving O.T., i.e. those receiving it and those not so privileged, as well as the nurses. It is therefore quite proper to argue that the improvement recorded is merely an expression of the bias of the nurses. The point will be considered again.

At the end of eight weeks, the differences between the mean scores of improvement of the patients on drugs was still significant. Thiopropazate maintained its lead with a mean improvement of 4·6 points, compared with chlorpromazine 1·1 points and placebo 1·0 points. The results of O.T. changed.

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TABLE I

*Improvement in Ward Behaviour*

| | Chlor-promazine | Thio-propazate | Placebo | Total |
|---|---|---|---|---|
| **After 2 Weeks** | | | | |
| Occupational therapy .. | 2 | 39 | 33 | 74 |
| No occupational therapy .. | −13 | 19 | −3 | 3 |
| Total .. .. .. | −11 | 58 | 30 | 77 |
| Sum of squares = 1,054 | | | | |
| **After 8 Weeks** | | | | |
| Occupational therapy .. | 4 | 44 | 35 | 83 |
| No occupational therapy .. | 15 | 39 | −17 | 37 |
| Total .. .. .. | 19 | 83 | 18 | 120 |
| Sum of squares = 1,397 | | | | |

(Each cell gives the total points of improvement for 9 patients)

Analysis of Variance (2 Weeks)

| Source | d.f. | 54 × SS | 54 × MS | F | P |
|---|---|---|---|---|---|
| Drugs .. .. .. | 2 | 7,226 | 3,613 | 4·56 | < ·05 |
| Occupational therapy .. | 1 | 5,041 | 5,041 | 6·37 | < ·05 |
| Interaction .. .. .. | 2 | 722 | 361 | <1 | N.S. |
| Error .. .. .. | 48 | 37,998 | 792 | | |
| Total .. .. .. | 53 | 50,987 | | | |

Analysis of Variance (8 Weeks)

| Source | d.f. | 54 × SS | 54 × MS | F | P |
|---|---|---|---|---|---|
| Drugs .. .. .. | 2 | 8,322 | 4,161 | 4·52 | < ·05 |
| Occupational therapy .. | 1 | 2,116 | 2,116 | 2·30 | N.S. |
| Interaction .. .. .. | 2 | 6,434 | 3,217 | 3·50 | < ·05 |
| Error .. .. .. | 48 | 44,166 | 920 | | |
| Total .. .. .. | 53 | 61,038 | | | |

Those receiving it had a mean improvement of 3·1 points, and those who did not 1·2 points. The difference between these means was not significant statistically.

If the improvement in the O.T. patients is merely a record of the bias of the nurses, it becomes difficult to explain why this bias should have diminished to statistical non-significance by 8 weeks. It is very likely that the patients given O.T. do improve in their general behaviour, and that this improvement appears quite rapidly; hence the result at the end of two weeks. Little further improvement occurs in them, but it can be seen that further improvement has occurred in those not receiving O.T. and it could be suggested that this is the result of the improvement in the general "atmosphere", a sort of "social contagion" of improvement. This is plausible in the light of clinical experience, and has the support of the work by Robin (1957). Detailed examination of the results shows that another interpretation can be made, for it will be observed that the patients receiving neither drugs nor O.T. have in fact worsened, changing from a mean of −0·3 to a mean of −1·9. Most of the improvement is to be found in those patients on chlorpromazine only, who have improved from a mean score of −1·4 at 2 weeks to 1·7 at 8 weeks, supplemented by the further improvement of those on thiopropazate from 2·1 points to 4·3 points. Thus, the patients not receiving O.T. show a continued improvement with the drugs.

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At the end of 8 weeks, the disappearance of the main effect of O.T. is accompanied by the appearance of an interaction between drugs and O.T. Of the patients receiving placebo, those on O.T. improved by a mean of 3·9 points, those without O.T. worsening by 1·9 points. For those on thiopropazate, the changes were 4·9 and 4·3 points respectively, and for those on chlorpromazine, 0·4 and 1·7 respectively. It would therefore appear that the drugs tend to inhibit the effects of the O.T., this effect being more prominent with chlorpromazine than with thiopropazate. The presence of such an interaction makes any conclusions about main effects insecure, e.g. that chlorpromazine is no better than placebo, but the number of cases is insufficient for reliable comparisons to be made between individual combinations of treatments.

2. *Physicians' Ratings of Symptoms*

The improvement scores for the Symptoms were obtained in the same way as those for behaviour in the ward, but the analysis and interpretation of the results were anything but simple. For various reasons (see Appendix), the symptoms were divided into two groups P and N, which were considered

TABLE II

*Improvement in P Group of Symptoms*

After 2 Weeks

| | Chlor-promazine | Thio-propazate | Placebo | Total |
|---|---|---|---|---|
| Occupational therapy .. | 69 | 55 | 45 | 169 |
| No occupational therapy .. | 19 | 74 | 127 | 220 |
| Total .. .. .. | 88 | 129 | 172 | 389 |

Sum of squares = 7,869

After 8 Weeks

| | Chlor-promazine | Thio-propazate | Placebo | Total |
|---|---|---|---|---|
| Occupational therapy .. | 80 | 40 | 46 | 166 |
| No occupational therapy .. | 58 | 112 | 123 | 293 |
| Total .. .. .. | 138 | 152 | 169 | 459 |

Sum of squares = 8,431

(Each cell gives the total points of improvement for 9 patients)

Analysis of Variance (2 Weeks)

| Source .. .. .. | d.f. | 54 × SS | 54 × MS | F | P |
|---|---|---|---|---|---|
| Drugs .. .. .. | 2 | 10,586 | 5,293 | 1·08 | N.S. |
| Occupational therapy .. | 1 | 2,601 | 2,601 | <1 | N.S. |
| Interaction .. .. .. | 2 | 26,154 | 13,077 | 2·68 | N.S. |
| Error .. .. .. | 48 | 234,264 | 4,880 | | |
| Total .. .. .. | 53 | 273,605 | | | |

Analysis of Variance (8 Weeks)

| Source .. .. .. | d.f. | 54 × SS | 54 × MS | F | P |
|---|---|---|---|---|---|
| Drugs .. .. .. | 2 | 1,446 | 723 | <1 | N.S. |
| Occupational therapy .. | 1 | 16,129 | 16,129 | 3·72 | <·05 |
| Interaction .. .. .. | 2 | 18,662 | 9,331 | 2·15 | N.S. |
| Error .. .. .. | 48 | 208,356 | 4,341 | | |
| Total .. .. .. | 53 | 244,593 | | | |

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TABLE III

*Improvement in N Group of Symptoms*

| | After 2 Weeks | | | |
|---|---|---|---|---|
| | Chlor-promazine | Thio-propazate | Placebo | Total |
| Occupational therapy .. | 57 | 15 | 89 | 161 |
| No occupational therapy .. | 15 | −18 | 24 | 21 |
| Total .. .. .. | 72 | −3 | 113 | 182 |

Sum of squares=4,096

| | After 8 Weeks | | | |
|---|---|---|---|---|
| | Chlor-promazine | Thio-propazate | Placebo | Total |
| Occupational therapy .. | 22 | 17 | 48 | 87 |
| No occupational therapy .. | 10 | 5 | 25 | 40 |
| Total .. .. .. | 32 | 22 | 73 | 127 |

Sum of squares=3,761

(Each cell gives the total points of improvement for 9 patients)

Analysis of Variance (2 Weeks)

| Source | d.f. | 54×SS | 54×MS | F | P |
|---|---|---|---|---|---|
| Drugs .. .. .. | 2 | 20,762 | 10,381 | 3·41 | <·05 |
| Occupational therapy .. | 1 | 19,600 | 19,600 | 6·44 | <·05 |
| Interaction .. .. .. | 2 | 1,634 | 817 | <1 | N.S. |
| Error .. .. .. | 48 | 146,064 | 3,043 | | |
| Total .. .. .. | 53 | 188,060 | | | |

Analysis of Variance (8 Weeks)

| Source | d.f. | 54×SS | 54×MS | F | P |
|---|---|---|---|---|---|
| Drugs .. .. .. | 2 | 4,382 | 2,191 | <1 | N.S. |
| Occupational therapy .. | 1 | 2,209 | 2,209 | <1 | N.S. |
| Interaction .. .. .. | 2 | 242 | 121 | <1 | N.S. |
| Error .. .. .. | 48 | 180,132 | 3,753 | | |
| Total .. .. .. | 53 | 186,965 | | | |

separately. The N group consists of the expression of various delusions, together with evidence for hostility; and the P group consists of disturbances of speech and thought, disturbances of posture and mannerisms, disturbed affect, including apathy, and finally, objective evidence for hallucinations based on the patient's behaviour rather than on his statements. The P group of symptoms describes the withdrawn uncommunicative patient, with whom an interview is a continuous struggle to make contact and to elicit some response. Such patients are not "out of contact" with their environment, but their response to it has undergone a qualitative change from the normal. The patient who shows the N group of symptoms responds to the interview in normal fashion, answering questions more or less freely, and giving vent to his delusions.

There was a general tendency for all symptoms to diminish at successive interviews. For the P group, at the end of 8 weeks the only significant difference

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was between those patients on O.T., who improved by a mean of 6·1 points, and the rest, who improved by a mean of 10·9 points. The same but smaller trend was found at 2 weeks, and it is of interest that the patients on O.T. showed the same score at 2 and 8 weeks, the change being due to the continued improvement in the patients not on O.T. Although no other differences were significant, at both the second and third assessments the patients receiving placebo improved most, and those receiving chlorpromazine improved least.

Turning to the N group of symptoms, we found the reverse effect, for here at 2 weeks the patients on O.T. showed a mean improvement of 6·0 points, compared with the 0·8 points of improvement shown by the rest, and this difference was statistically significant. The drug effects were also statistically significant, with the patients on drugs doing worse than those on placebo; the results were an improvement of 2·7 points for those receiving chlorpromazine, a worsening of 0·1 points for those on thiopropazate, compared with an improvement of 4·2 points for the patients receiving placebo. At the end of 8 weeks, the same trends were visible, but all the differences had diminished below statistical significance. The general conclusion was that for the N group of symptoms, all the patients in the trial were recorded as having shown an improvement, but that neither drugs nor O.T. had made any significant difference in the end, although in the first two weeks the patients on O.T. had made a temporary spurt ahead of the others.

The results for all symptoms can be found by adding the results for the P symptoms to those of the N symptoms. Since O.T. and the two drugs show opposite effects for the two groups, when these are added, they cancel out, and the nett effect is that there are no significant differences due to drugs or O.T. either at 2 or at 8 weeks*.

TABLE IV

*Decrease in Scores on Bipolar Factor*

After 2 Weeks

| | Chlor-promazine | Thio-propazate | Placebo | Total |
|---|---|---|---|---|
| Occupational therapy .. | 12 | 40 | −44 | 8 |
| No occupational therapy .. | 4 | 92 | 103 | 199 |
| Total .. .. .. | 16 | 132 | 59 | 207 |

Sum of squares=7,083

After 8 Weeks

| | Chlor-promazine | Thio-propazate | Placebo | Total |
|---|---|---|---|---|
| Occupational therapy .. | 58 | 23 | −2 | 79 |
| No occupational therapy .. | 48 | 107 | 98 | 253 |
| Total .. .. .. | 106 | 130 | 96 | 332 |

Sum of squares=8,496
(Each cell gives the total change for 9 patients)

* The sum of squares for the total symptoms is 17,447 at 2 weeks and 15,888 at 8 weeks. The analysis of variance can be calculated from this plus the information available in Tables II and III.

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TABLE IV—*continued*

Analysis of Variance (2 Weeks)

| Source | d.f. | 54×SS | 54×MS | F | P |
|---|---|---|---|---|---|
| Drugs | 2 | 20,634 | 10,317 | 2·01 | N.S. |
| Occupational therapy | 1 | 36,481 | 36,481 | 7·12 | <·01 |
| Interaction | 2 | 36,650 | 18,325 | 3·58 | <·05 |
| Error | 48 | 245,868 | 5,122 | | |
| Total | 53 | 339,633 | | | |

Analysis of Variance (8 Weeks)

| Source | d.f. | 54×SS | 54×MS | F | P |
|---|---|---|---|---|---|
| Drugs | 2 | 1,832 | 916 | <1 | N.S. |
| Occupational therapy | 1 | 30,276 | 30,276 | 4·92 | <·05 |
| Interaction | 2 | 21,192 | 10,596 | 1·72 | N.S. |
| Error | 48 | 295,260 | 6,151 | | |
| Total | 53 | 348,560 | | | |

## DISCUSSION

The ratings described above are based on measurements of individual items in the scales, and therefore a good deal of information is available on qualitative changes in the patients, not necessarily related to "improvement". These have been omitted from the above account of results, in order to avoid obscuring the aim of the investigation, which was primarily concerned with the effects of treatments in improving the patients' illness. These qualitative changes are dealt with below, together with their theoretical background.

It is now generally agreed that the phenothiazine compounds alter the behaviour of chronic schizophrenic patients, but have little or no effect on the underlying pathological process. The results of this investigation are in agreement with this opinion, the drug effects being significant on behaviour in the ward but not significant on Symptoms at interview. The former merit close scrutiny. The most striking result, in a sense, is the absence of any significant difference between the effect of chlorpromazine and placebo. It cannot be argued that the method of assessment of behaviour was incapable of showing any improvement, because the thiopropazate showed a significant one, and so did the O.T.

It is possible that the length of the trial was insufficient. However, favourable results with chlorpromazine were reported by Seager (1955) in a controlled trial lasting only 4 weeks. Elkes and Elkes (1954) reported that the effects of chlorpromazine were manifested in 3–6 weeks. These are but two examples. It may be that the dose of chlorpromazine was insufficient, but Seager gave only up to 225 mg. daily. Vaughan and Leiberman (1955) reported favourable results in a controlled trial, using 150–200 mg. daily, and Elkes and Elkes used only 150 mg. daily, and reported improvement.

The literature on chlorpromazine is immense, but the number of controlled trials on chronic schizophrenics is relatively small, and of this number some report negative results, e.g. Hall and Dunlap (1955), Mitchell (1956), Little (1958), Fleming and Currie (1958), Walsh, Walton and Black (1959). The present findings of no improvement in symptoms following the administration of chlorpromazine is therefore not an isolated one. Nevertheless, the presence of marked inhibitory interaction between this drug and O.T. makes conclusions about the general effect insecure.

The upshot of our work with the scale used is that we are not satisfied

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that the interview is an adequate method for obtaining full information about the symptoms of chronic schizophrenic patients. Also we believe that ratings on ward behaviour are by themselves insufficient for making an assessment of the patient's condition, i.e. the state of his illness.

The interaction between drug and O.T. on behaviour is one of peculiar interest. Grygier and Waters (1958) found that patients on an energetic re-socialization programme improved more when given chlorpromazine than when given placebo. The improvement was slight but statistically significant. The present results are that the drugs inhibited the effects of O.T. but this became manifest only after several weeks. It is true that none of the patients of Grygier and Waters were deprived of O.T., but it is difficult to see how this would affect the results. It is clear that further investigation will be necessary to resolve these discrepancies. If the present result is confirmed, the implications would be that, in any programme of intensive rehabilitation for chronic schizophrenics, the maximum value of tranquillizing drugs would be at the start.

It is worth recording that, on consulting the ward records after the trial, it was found that one patient receiving chlorpromazine had shown side-effects. He developed symptoms of Parkinsonism, but these disappeared in a few days after the dose was reduced, and did not return when the dose was increased again.

## Summary

A controlled investigation was designed to determine the relative values of a new drug thiopropazate dihydrochloride, chlorpromazine hydrochloride and occupational therapy on overactive and aggressive chronic schizophrenics.

Fifty-four patients were randomly allotted to six groups of nine. Three groups attended O.T. and three did not. The pharmacist allocated the two active drugs and similar placebos to paired groups from the O.T. and non-O.T. groups. This information he did not release until the end of the trial.

The patients were rated on their behaviour in the ward by the two charge nurses, and for symptoms by any two physicians not directly in charge of the patient. Practice ratings were made on a similar category of patient beforehand. The ratings were made before the treatments started, after 2 weeks and again after 8 weeks of treatment.

*Results:*

1. Behaviour in the ward was significantly improved by thiopropazate at the end of 2 weeks and 8 weeks. O.T. significantly improved ward behaviour in the first 2 weeks, but by 8 weeks the other patients had improved sufficiently to make the difference non-significant. Interaction between drugs and O.T. showed that at the end of 8 weeks both chlorpromazine and, to a lesser extent, thiopropazate exerted a significant inhibitory effect on the improvement due to O.T.
2. In the course of the trial, all groups of patients showed improvement in their symptoms, regardless of the combinations of treatment they received. This emphasized the importance of proper control groups in investigations on the effects of treatment.
3. For the P group of symptoms (apathy, mannerisms, hallucinations, etc.) the only significant result was that at 8 weeks patients on O.T. did not improve as much as the others.

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For the N group of symptoms (hostility, persecutory and other delusions) all groups of patients improved, but differences between groups were not significant at 8 weeks. At 2 weeks, the patients on O.T. were significantly better than the others, and the patients on placebo were significantly better than those on active drugs. These differences were temporary and had fallen below statistical significance by the end of 8 weeks.

For the total of all symptoms, neither O.T. nor drugs made any significant contribution to improvement.

Factors which may have influenced the results are considered. There is evidence to suggest that in a rehabilitation programme for overactive, aggressive, chronic schizophrenics the maximum value of tranquillizing drugs may be obtained from their use at the start of the programme.

There was no evidence of any soporific effect from these drugs given in the doses of: thiopropazate 10 mg. t.d.s. and chlorpromazine 100 mg. t.d.s. At the dosage level stated one patient receiving chlorpromazine developed, temporarily, symptoms of Parkinsonism but no patient receiving thiopropazate showed side-effects.

## APPENDIX

### The Response to Treatment of a Component of Chronic Schizophrenia

A scale designed for measuring schizophrenia requires a number of items, each measuring a different aspect of the disorder. If the items are all scored in the same way, from normal (absent symptom) to severe symptom, then a normal subject will score zero, and a severely ill patient will score highly on many or all of the items. The sum of the scores on the individual items will tend to be higher for those patients who show more symptoms, and who would therefore be regarded as more ill. It is implicit in such summing, that the items all measure the same thing, more or less.

When two items measure something in common, they will have a common variance, and the scores in them will show a positive correlation. Of course, if they measure opposite aspects of the same quality, they will show a negative correlation. For example, one item may measure an aspect of social adjustment and the other of maladjustment. In such a case, one item will have to be given a negative weight, i.e. its score will have to be subtracted from the other. Which one is given the negative weight depends on whether we are measuring adjustment or maladjustment.

When a set of items is properly designed to measure different aspects of one quality, then the intercorrelations will all be positive. (The reverse is not necessarily true). If the items measure nothing else, i.e. the non-common variance is all error variance, then the matrix of correlations will have its rows and columns proportional; in mathematical terms, it will be of unit rank, and in psychological terms it will have only one factor. In general, it is almost impossible to obtain such a set of items. In the case of schizophrenia, each item is concerned with a specific aspect of schizophrenia, which need not even be present in each patient. The matrix of correlations will therefore have a rank of more than one, i.e. it will have more than one factor.

The first or general factor can be extracted from the matrix of correlations mathematically, leaving residual correlations (strictly, covariances) which can be seen to fall into two groups. These groups are negatively correlated with each other, the items in each group being positively correlated. Such a matrix of residuals contains a bipolar factor (at least one). The first factor can also be eliminated experimentally, by selecting the subjects in such a way that they all have the same score (as much as possible) on the general factor. In order to obtain factor scores for the bipolar factor, one group of items must be given negative weights; and which group is given the negative weights depends on which direction the bipolar factor is measured from.

On turning to the intercorrelation matrix of the physicians' scale for symptoms, it is seen that the correlations fall into two groups, each of which is negatively correlated with the other, the items being positively correlated within the group. The items as designed, should have formed a matrix with all correlations positive, and indeed, it can be said that they would have done so had the subjects interviewed included a sufficient number of mild schizophrenic patients and normal subjects. In the light of the foregoing theoretical analysis, it is evident that intense selection has eliminated the general factor, leaving only the bipolar factor. In effect, the correlation matrix shows that the patients selected for the clinical trial form a homogeneous group of chronic schizophrenics. Despite the bipolar pattern of the correlations, it is meaningful to sum the scores on all the items and to use a diminution of such a total score as a measure of over-all improvement of the schizophrenic symptoms.

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A score for the bipolar factor can be obtained by subtracting the scores of the N group of symptoms from the P group. A high score means that the patient tends to show the pattern of the P group (unresponsive at interview, apathetic, bizarre behaviour), whereas a low (or negative) score means that he shows the N group of symptoms (delusions freely expressed, communicative at interview). A decrease in the patient's score does not measure improvement in his condition but a change in his symptoms from the P type to the N type.

The intercorrelations of the items in the nurses' scale for behaviour in the ward are all positive, but not high, the simple average being ·44. The conclusion to be drawn from this is that the items all measure ward behaviour as designed, and that despite the homogeneity of the symptoms of the patients, there is considerable variation in their behaviour. To those who are acquainted with the administration of mental hospitals, this is not unexpected. The P group of symptoms correlate positively with the nurses' ratings (P for positive) and the N groups correlate negatively (N for negative).

The foregoing discussion will now have made clear the reason for keeping the two groups of symptoms distinct. It will also have justified the next step, which is to *subtract* the improvement in N scores from the improvement in P scores. The resulting scores do not now measure improvement, but a change from P symptoms to N symptoms. The statistical analysis can be seen in Table IV. The results show that there is a general tendency for the patients to manifest their delusions and hostility, etc., more at the second and third assessment than at the first. This is much greater in those patients not receiving O.T. than the rest. The difference is highly significant after 2 weeks (7·4 points of change against 0·3 points respectively) and less, although still significant, at 8 weeks (9·4 points against 2·9 points). The decrease in the difference between the two groups is largely due to the change in those patients receiving O.T. The drugs do not produce any significant change, but there is significant interaction between drugs and O.T. at 2 weeks, the interaction being of such a nature that the drugs tend to inhibit or reverse this effect. Since the interaction effect has disappeared by 8 weeks, it would probably be wiser to await confirmation of its presence before drawing conclusions from it.

These results are very difficult to interpret. It may be that the interviewers become more skilled at interviewing these patients under these special conditions. It is more likely that the patients are becoming more accustomed to these interviews and responding to them in more normal fashion. In either case, it is even more difficult to understand why such changes, from P to N symptoms, should be inhibited by the experience of O.T. on five afternoons a week. In the circumstances, it is only possible to come to the empty conclusion that the response of chronic schizophrenic patients to the subtle "social" changes produced by a drug trial, including repeated interviewing and O.T., are very complex, and we do not understand them.

NURSE'S RATING SCALE FOR BEHAVIOUR IN WARD

| | |
|---|---|
| *Attitude to work* | |
| Normal attitude, co-operative | 0 |
| Can do simple jobs only | 1 |
| Requires some supervision | 2 |
| Needs constant supervision and urging | 3 |
| Refuses work, passively or actively | 4 |
| *Attention to dress and person* | |
| Attends to clothes and appearance normally | 0 |
| Dresses himself, but looks untidy | 1 |
| Dresses himself, but needs adjustments | 2 |
| Requires help to get dressed and cleaned | 3 |
| Has to be dressed and washed | 4 |
| *Relation to other patients* | |
| Helpful and friendly, co-operative in activities | 0 |
| Occasionally talks or helps others | 1 |
| Will talk when spoken to | 2 |
| Will only say a word or so | 3 |
| Ignores other patients and may strike them | 4 |
| *Relation to medical and nursing staff* | |
| As with 'other patients' | 0 |
| | 1 |
| | 2 |
| | 3 |
| | 4 |
| *Behaviour at meals* | |
| Normal manners and behaviour | 0 |
| Peculiar habits and unco-operative with others | 1 |
| Stealing and snatching food | 2 |
| Wolfing and gobbling food, seldom using cutlery | 3 |
| Requires supervision or encouragement to eat | 4 |

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*Toilet behaviour*

| | |
|---|---|
| Goes normally to lavatory | 0 |
| Requires to be taken or fetched out | 1 |
| Occasionally incontinent | 2 |
| Frequently incontinent | 3 |
| Smearing sometimes | 4 |

*Activity*

| | | |
|---|---|---|
| Normal activity and mobility | | 0 |
| Lethargic | Overactive | 1 |
| Tends to sit about | Restless | 2 |
| Has to be moved | Never still | 3 |
| Resistive and Rigid | Rushing about | 4 |

*Speech*

| | |
|---|---|
| Normal speech and conversation | 0 |
| Taciturn, inconsequential, no real conversation | 1 |
| Says only a few words, or speech disorganised | 2 |
| Occasional mumbles | 3 |
| Mute or incomprehensive speech | 4 |

PHYSICIAN'S RATING SCALE FOR CHRONIC SCHIZOPHRENIA
Adapted from the M.S.R.P.P. (Lorr Scale)

P. 1. How direct and relevant are his responses to questions or to the topic discussed?
0 Direct and relevant.
1 Somewhat rambling and tangential.
2 For the most part irrelevant.
3 Wholly irrelevant.

P. 2. Does he assume or maintain peculiar, unnatural or bizarre postures?
0 None
1 For short periods
2 Throughout most of the interview
3 Throughout the entire interview.

P. 3. Are his thoughts consistent with his mood, or is there a discernible lack of harmony between them?
0 Consistent.
1 A little disharmonious.
2 Distinctly disharmonious.
3 Appear totally unrelated.

P. 4. Does he exhibit any repeated peculiar gestures, grimaces or mannerisms?
0 None.
1 Occasionally.
2 Fairly frequently.
3 Throughout the interview.

N. 5. Does he tend to suspect or to believe on slight evidence or without good reason that people and external forces are trying to or now do influence his behaviour and control his thinking?
0 No unjustified suspicion.
1 Inclined to suspect.
2 Believes others are trying to control him.
3 Believes he is influenced or controlled.

P. 6. Are the elements of his speech logically consistent and connected by some idea or relationship, or do they tend to be inconsistent and disconnected? (Rate what is most representative during the interview.)
0 Coherent and consistent.
1 Slightly incoherent and inconsistent.
2 Distinctly incoherent and inconsistent.
3 Conspicuously scattered, disconnected or incoherent.

N. 7. Does he bear little hostility or a high degree of ill will, resentment, bitterness or hate?
0 No hostility.
1 Slight hostility.
2 Moderate hostility.
3 Much hostility.

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P. 8. Does he have any insight into his hallucinations? (Score 0 for no evidence of hallucinations.)
0 Full insight.
1 Possibly full insight.
2 Some insight.
3 No insight.

P. 9. How frequently does he speak, mutter or mumble to himself, seemingly to carry on conversations with hallucinatory voices?
0 Not at all.
1 Occasionally.
2 Fairly frequently.
3 Throughout the interview.

P. 10. Is there any evidence that the patient has auditory hallucinations?
0 None.
1 Doubtful.
2 Probable.
3 Certain.

P. 11. Does the patient ever glance up as if listening to auditory hallucinations?
0 Not at all.
1 Doubtfully or occasionally.
2 Fairly frequently.
3 Throughout the interview.

P. 12. Does he repeat certain words or phrases in a meaningless, stereotyped or mechanical fashion?
0 Never.
1 Occasionally.
2 Fairly frequently.
3 Almost constantly.

P. 13. Is his speech irregularly interrupted, halted or blocked for varying periods of time because of difficulty in finding words for his thoughts?
0 No speech blocks.
1 A few interruptions.
2 Many interruptions and conversation very difficult.
3 Patient is mute or almost mute.

N. 14. Does he have an exaggeratedly high opinion of himself, or an unjustified belief or conviction of having unusual ability, knowledge, power, wealth, or status?
0 No exaggerated high opinion of himself.
1 An exaggeratedly high opinion.
2 Conviction of unusual power, wealth, etc.
3 Conviction of grandiose or fantastic power, wealth, etc.

N. 15. Does he tend to suspect or to believe on slight evidence or without good reason that some people are against him (persecuting, conspiring, cheating, depriving, punishing) in various ways?
0 No unjustified suspicions.
1 Inclined to suspect.
2 Inclined to believe.
3 Has firm conviction.

N. 16. Does he tend to suspect or to believe on slight evidence or without good reason, that some people talk about, refer to, or watch him?
0 No unjustified suspicions.
1 Inclined to suspect.
2 Inclined to believe.
3 Has firm conviction.

N. 17. Is there evidence of false ideas or beliefs? If present, are these ideas or beliefs (*a*) sufficiently plausible as to be accepted by a normal person uninformed as to the facts, (*b*) implausible but not impossible, (*c*) impossible or bizarre (e.g. mind controlled by radio waves, heart removed or dead)?
0 No evidence of false beliefs.
1 Plausible to the uninformed.
2 Implausible.
3 Impossible or bizarre.

P. 18. Does the patient's mood and emotional response show blunting?
0 Not at all.
1 Slight blunting.
2 Severe blunting.
3 Complete apathy.

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*Inter-correlation Matrix of Physicians' and Nurses' Ratings of 54 Male Chronic Schizophrenic Patients*
*(Decimal points omitted)*

| Item No. | Title of Item | 1 | 2 | 3 | 4 | 6 | 8 | 9 | 10 | 11 | 12 | 13 | 18 | 5 | 7 | 14 | 15 | 16 | 17 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Relevant speech | 100 | | | | | | | | | | | | | | | | | | | | | | | | | |
| 2 | Bizarre postures | 1 | 100 | | | | | | | | | | | | | | | | | | | | | | | | |
| 3 | Inappropriate affect | 29 | 20 | 100 | | | | | | | | | | | | | | | | | | | | | | | |
| 4 | Mannerisms | 31 | 19 | 31 | 100 | | | | | | | | | | | | | | | | | | | | | | |
| 6 | Incoherent speech | 85 | 15 | 33 | 32 | 100 | | | | | | | | | | | | | | | | | | | | | |
| 8 | Insight into Hallucinations | 2 | 12 | 12 | 9 | 13 | 100 | | | | | | | | | | | | | | | | | | | | |
| 9 | Talking to voices | 26 | −6 | 13 | 19 | 29 | −2 | 100 | | | | | | | | | | | | | | | | | | | |
| 10 | Evidence of hallucinations | 13 | 14 | 31 | 23 | 18 | 82 | 10 | 100 | | | | | | | | | | | | | | | | | | |
| 11 | Glancing at hallucinations | 21 | 34 | 34 | 65 | 27 | 23 | 35 | 44 | 100 | | | | | | | | | | | | | | | | | |
| 12 | Stereotyped speech | 49 | 19 | 45 | 28 | 59 | −1 | 16 | 17 | 35 | 100 | | | | | | | | | | | | | | | | |
| 13 | Thought blocking | 5 | 57 | 19 | 30 | 16 | 3 | −3 | 11 | 26 | 33 | 100 | | | | | | | | | | | | | | | |
| 18 | Blunting of affect | 11 | 60 | 13 | 10 | 28 | 9 | 7 | 23 | 31 | 38 | 60 | 100 | | | | | | | | | | | | | | |
| 5 | Ideas of influence | −9 | −10 | 17 | −17 | −16 | 22 | −13 | 25 | −6 | −6 | −18 | −11 | 100 | | | | | | | | | | | | | |
| 7 | Hostility | 1 | 5 | −2 | −10 | −9 | −12 | −8 | −17 | −14 | −4 | −20 | −26 | 3 | 100 | | | | | | | | | | | | |
| 14 | Grandiose delusions | 5 | −20 | −6 | −20 | −12 | −12 | −7 | −9 | −19 | −22 | −36 | −38 | 11 | 20 | 100 | | | | | | | | | | | |
| 15 | Persecutory delusions | −3 | −18 | 3 | −12 | −13 | 20 | −13 | 17 | −9 | −9 | −23 | −33 | 26 | 36 | 23 | 100 | | | | | | | | | | |
| 16 | Ideas of reference | −11 | −20 | 1 | −29 | −19 | 35 | −12 | 28 | −14 | −22 | −18 | −18 | 49 | −3 | 18 | 59 | 100 | | | | | | | | | |
| 17 | Implausible delusions | 29 | −40 | 19 | −7 | 16 | −11 | 20 | 3 | −3 | 5 | −50 | −34 | 31 | 27 | 45 | 44 | 30 | 100 | | | | | | | | |
| 1 | Attitude to work | −9 | 24 | 1 | −1 | 5 | 10 | 8 | 15 | 15 | 7 | 27 | 39 | −19 | −4 | −7 | −5 | −8 | −22 | 100 | | | | | | | |
| 2 | Attention to dress | 14 | 29 | −16 | 4 | 13 | 14 | 11 | 15 | 10 | 2 | 32 | 39 | −11 | −15 | 3 | −4 | −10 | −29 | 52 | 100 | | | | | | |
| 3 | Relation to patients | 5 | 21 | 6 | 8 | 10 | 5 | 12 | 8 | 1 | 9 | 28 | 33 | −32 | 13 | −10 | −2 | −30 | −20 | 65 | 45 | 100 | | | | | |
| 4 | Relation to staff | 10 | 26 | 1 | 13 | 22 | −7 | 18 | −4 | 17 | 26 | 30 | 45 | −25 | 2 | −24 | −20 | −35 | −19 | 50 | 36 | 65 | 100 | | | | |
| 5 | Behaviour at meals | 9 | 19 | −11 | 10 | 11 | 6 | 15 | 7 | 2 | 6 | 35 | 35 | −17 | −13 | −1 | 1 | −13 | −33 | 54 | 59 | 54 | 42 | 100 | | | |
| 6 | Toilet behaviour | 27 | 34 | −5 | 2 | 25 | −14 | −6 | −1 | −4 | 23 | 43 | 47 | −29 | −20 | −11 | −20 | −20 | −23 | 36 | 49 | 30 | 27 | 38 | 100 | | |
| 7 | Activity | 1 | 7 | 4 | −8 | −7 | 10 | −6 | 7 | 3 | 2 | 30 | 16 | −16 | −11 | 5 | 9 | −12 | −17 | 36 | 51 | 45 | 28 | 42 | 30 | 100 | |
| 8 | Speech | 8 | 40 | 3 | 26 | 11 | 6 | 10 | 13 | 29 | 16 | 39 | 58 | −11 | −3 | −18 | −31 | −29 | −33 | 46 | 51 | 41 | 63 | 43 | 19 | 27 | 100 |

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REFERENCES

BICKFORD, J. A. R., "Chlorpromazine", *Brit. med. J.*, 1955, *i*, 1155.

EDISEN, C. B., and SAMUELS, A. S., "A clinical evaluation of Dartal chemotherapy for emotional disorders", *A.M.A. Arch. Neurol. and Psychiat.*, 1958, **80**, 481.

ELKES, J., and ELKES, C., "Effects of chlorpromazine on the behaviour of chronically overactive psychotic patients", *Brit. med. J.*, 1954, *ii*, 560.

FLEMING, B. G., and CURRIE, J. D. C., "Investigation of a new compound, B.W.203, and of chlorpromazine in the treatment of psychosis", *J. Ment. Sci.*, 1958, **104**, 749.

GRYGIER, P., and WATERS, M. A., "Chlorpromazine used with an intensive occupational therapy programme. A controlled study", *A.M.A. Arch. Neurol. and Psychiat.*, 1958, **79**, 697.

HALL, R. A., and DUNLAP, D. J., "A study of chlorpromazine: methodology and results with chronic semi-disturbed schizophrenics." *J. Nerv. Ment. Dis.*, 1955, **122**, 301.

LITTLE, J. C., "A double-blind controlled comparison of the effects of chlorpromazine, barbiturate and a placebo in 142 chronic psychotic in-patients", *J. Ment. Sci.*, 1958, **104**, 334.

LORR, M., "Multidimensional scale for rating psychiatric patients", *Hospital Form. Vet. Admin. tech. Bull.*, TB 10–507, Nov., 1953.

MERRY, J., "An experiment in a chronic psychotic ward", *Brit. J. med. Psychol.*, 1956, **29**, 287.

MITCHELL, P. H., "Chlorpromazine in the treatment of the chronic disturbed schizophrenic patient", *J. Ment. Sci.*, 1956, **102**, 151.

ROBIN, A. A., "The stabilizing effect of occupational therapy on chronic psychotics with a tendency to aggressive forms of behaviour", *J. Ment. Sci.*, 1957, **103**, 597.

SEAGER, C. P., "Chlorpromazine in treatment of elderly psychotic women", *Brit. med. J.*, 1955, *i*, 882.

VAUGHAN, V. F., and LEIBERMAN, D. M. "Chlorpromazine in psychiatry", *Lancet*, 1955, *i*, 1083.

WALSH, G. P., WALTON, D., and BLACK, D. A., "The relative efficacy of 'Vespral' and chlorpromazine in the treatment of a group of chronic schizophrenic patients", *J. Ment. Sci.* 1959, **105**, 199.

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