A DOUBLE-BLIND CONTROLLED COMPARISON OF THE EFFECTS OF CHLORPROMAZINE, BARBITURATE AND A PLACEBO IN 142 CHRONIC PSYCHOTIC IN-PATIENTS

By

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INTRODUCTION

SINCE the original article by Elkes and Elkes (1954) numerous reports have been published in the world literature on the use of chlorpromazine in chronic psychotic in-patients. The majority of these studies indicate that the drug is indeed effective in improving the behaviour of these patients; a small minority of authors is more sceptical including Mitchell (1956) using doses up to 300 mg. daily, Sarwer-Foner and Ogle (1956) with doses of 150–400 mg. daily, and Trelles and Saavedra (1954) using sleep treatment. The literature contains numerous reports of controlled and uncontrolled studies on chlorpromazine and comparisons of its effects with those of a placebo, Reserpine, Azacyclonal, etc.; attention is now turning to the effects of such drugs in various combinations.

However, for many years barbiturates had been the main sedatives used in attempting to modify the behaviour and tension of chronic psychotic patients and it was felt it would be of value to compare the results of chlorpromazine therapy with those obtained by barbiturates, the traditional standby. This point was raised by Tewfik (1955) who wrote "chlorpromazine . . . must also be controlled against drugs producing equivalent sedative effects before the word 'special' as a description of its effect can be justified. Until this has been proved chlorpromazine should not be allowed to supplant the much less toxic cheaper sedatives in common use."

Although a review of the literature shows that the great majority of workers find chlorpromazine effective for chronic psychotic patients, nevertheless there is room for criticism of the methodology of many of the studies, a large number of which are not controlled, while in others the samples are too small to draw definite conclusions. In view of the increasing popularity of this expensive and potentially lethal preparation it was felt that a well-controlled study using an adequate number of patients was desirable, firstly to establish its effectiveness as compared with an inert placebo, and secondly to determine whether it has in fact a superior action to the well tried, less toxic and cheaper barbiturates. No study of this basic problem has so far been reported in the literature.

MATERIAL AND METHOD

Material

The project was carried out at St. Luke's Hospital, Middlesbrough.

It was decided to utilize as many chronic patients as possible in the hospital, but certain groups had to be eliminated—e.g. the infirmary wards, chronic

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working patients not under observation and certain wards where other research was in progress. In all 5 wards were chosen, 3 male and 2 female, with a total of 142 patients, of whom there were 85 males and 67 females. One hundred and twenty-seven patients were certified and 15 under voluntary status.

TABLE I

Diagnostic Groupings

Reaction Type	Sub Group	Number of Patients
Schizophrenic	"Schizophrenia"	80
	Schizophrenia with mental deficiency	10
	Paranoid schizophrenia	12
	Catatonic schizophrenia	7
		109
	Paraphrenia	12
Affective	Chronic depressive	4
	Manic depressive psychosis	2
		6
Organic	Disturbed mental defective	2
	G.P.I.	7
	Senile and pre-senile dementia	3
	Epileptic psychosis with dementia (no recent fits)	2
		14
Neurotic	Anxiety state	1
	Total	142

TABLE II

Age Distribution

Extreme range 21–75 years:

Age groups (in years)	20–29	30–39	40–49	50–59	60–69	70–79
Number of patients	9	31	39	24	33	6

Total: 142 patients

Duration of In-patient Stay

Extreme range 6 months to 51 years:

Duration in years since first admission	Under 1 year	2–3 years	4–10 years	11–35 years	Over 35 years
Number of patients	3	13	38	83	5

Total: 142 patients

Of the 142 patients 74 had received E.C.T. with a recorded result and it had proved effective in some degree in 37 (50 per cent.). Of the 19 patients on maintenance E.C.T. this treatment was stopped in nine cases during the trial as the

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nursing staff did not feel it was required. This was irrespective of the drug being used, and may be attributed to the beneficial psychological effect of the trial on patients and staff. Twenty-one patients had received insulin coma therapy with some improvement in 10 (in 3 this was temporary only), and leucotomy or topectomy had been carried out in 27 patients with some improvement in 13 (in 4 of these the effect was temporary only). All the cases of G.P.I. had received malaria, arsenic or penicillin in various combinations. These figures only refer to the results of previous treatment in patients who have not left hospital, and in no way reflect their general efficacy in psychiatric practice. Prior to the trial 55 patients, mostly on the refractory wards, were regularly receiving some sedative drug. It was not possible to withdraw these drugs entirely, but they were reduced to some degree a month before the trial started: 40 patients were receiving sodium amytal or nembutal in doses of 6–12 grs. daily; this was reduced to one half or one-third. The remaining 15 patients on small doses of 3 grs. per day of one or other of these drugs, or similar amounts of other sedatives, were allowed to continue as before.

A month before the start of the trial much sedation was gradually withdrawn. When this proposal was first suggested the nursing staff, particularly on the refractory wards, expressed considerable anxiety as to possible violence, thus most of the disturbed patients were only reduced to a smaller dose of sedative. After the first week, during which there was some excitement, both patients and staff settled down and there appeared to be very little difference in the general behaviour, which was assessed as a base line for comparative purposes during the trial.

Method

A double-blind controlled experimental situation was set up in the following manner: a survey was made of all patients in each ward and the infirm and epileptic were eliminated from the trial, several reports having suggested that chlorpromazine may aggravate a dysrhythmic tendency. Also excluded were three patients who refused to co-operate.

The remaining 142 patients were divided at random into 3 groups (I, II, III). As chronic patients were chosen for the study, their mental state being more or less stationary, it was feasible to use each patient as his own control. Messrs. May and Baker kindly prepared the following tablets in identical form: amylobarbitone gr. 1, chlorpromazine 25 mg. and an inert preparation for use as a control. It was decided to keep the duration of the trial as short as possible in order to minimize such variables as staff holidays and changes. To this end the standard duration for giving each drug was three weeks. It is known that barbiturates act fairly rapidly but it has been claimed that chlorpromazine does not exert its full action until it has been exhibited for a period of six weeks or so. In order to test this hypothesis, chlorpromazine was given for two consecutive periods (C1, C2). The drugs were given to the groups in the following order:

TABLE III

Group	Consecutive 3 Week Periods			
I	C1	C2	I	B
II	B	C1	C2	I
III	I	B	C1	C2

Where C1 = Initial 3 weeks on chlorpromazine
C2 = Second 3 weeks on chlorpromazine
I = 3 weeks on inert (placebo) tablets
B = 3 weeks on barbiturate (amylobarbitone)

In conference with the charge nurse or sister of the ward, the mental state over the past three months was outlined and the significant clinical features noted. *An initial tension rating* was allotted on a 4-point scale:

H — persistently high tension.
HS — tension usually normal or low but high sporadically.
N — normal tension.
F — flattened or below normal tension.

In order to test the validity of these tension ratings as carried out by the senior nurse on each ward, the deputy matron and deputy head male nurse were independently invited to indicate their assessments using the same rating scale and a high degree of correspondence was revealed.

It was decided to use a dosage scale of two tablets of each preparation three times a day, i.e. amylobarbitone 6 grs., chlorpromazine 150 mg., or 6 inert tablets per day, working up to this maximum over four days in all cases. Each patient was allotted a pill box with his name on it and the investigator (J.C.L.) dispensed the drugs into these boxes according to the patient's treatment group (I, II, III). The boxes were then sent to the ward and the tablets given under the direct supervision of the charge nurse or sister at the standard rate of two tablets t.d.s. As chlorpromazine is known to cause immediate hypotensive effects in some patients, it was arranged that all patients should sit down for half an hour after taking the tablets. This also had the effect of concealing from the nursing staff the fact that some patients responded in this way and avoided the danger, from the experimental point of view, of one group being differentiated in a supposedly blind procedure. The only information available to the charge nurse or sister was the name on the box and the standard dosage schedule. It had been explained that various different tablets were being used but no information was given as to their nature.

The senior ward nursing personnel acted as assessors of the effects of treatment and kept detailed notes of any change in the mental state and of manifestations such as flushing, unsteadiness and drowsiness, and were warned to check for any signs of jaundice or infection, especially sore throat.

Initially, and at the end of each three-week period, the white blood count was estimated and pulse and temperature recording were carried out twice daily. Also at the end of each three-week period the investigator received a report from and questioned the appropriate assessor for: (*a*) drowsiness, (*b*) any other side effects, (*c*) changes in tension, (*d*) changes in any of the clinical features already listed, and (*e*) the general change in the patient from a nursing point of view. This was assessed on a 7-point scale: Very much worse (≡), Definitely worse (=), Slightly worse (—), No change (0), Slightly improved (+), Definitely improved (++), and Very much improved (+++). Any attempt at suggestion of expected effect on the part of the investigator was carefully held in check. This, however, was not considered likely to be a serious factor, since there were one hundred and forty-two patients in the trial and it was obviously impossible to remember which preparation a given patient was receiving at any given time. No definite criteria were laid down for the assessor's judgments, but the main points under consideration were changes towards normality—lessened aggression and more co-operation and sociability in the refractory patients, and more drive and spontaneity in the apathetic. The assessors tended to score adversely any excessive or prolonged drowsiness, their desire being to have their patients co-operative and active.

At the end of each three weeks trial period the tablets were changed by the

investigator and the next trial period commenced. Thus at no time was the person assessing the effects aware of the drug being used.

Results

Of the 142 patients who started 137 completed the trial (1 elderly female patient died of perforated carcinoma of rectum; 2 patients were subjected to leucotomy towards the end of the trial; 1 refused to continue after 6 weeks; and 1 overstayed her leave).

The particular sequence in which a drug was given in the three groups is shown by the χ^2 test not to cause a significant difference at the 5 per cent. level in its overall effect. Further, a comparison of the effects of chlorpromazine after the initial 3 weeks (C1) with its effect after a total of six weeks (C2) shows that there is statistically no significant difference in the general effect at the 5 per cent. level. Thus in the following tables the results after 3 weeks treatment (C1) have been used for the comparison with the effects of the placebo and barbiturate. The comparison of the general effects of the three preparations is shown in Table IV and illustrated in histogram form in Figure 1.

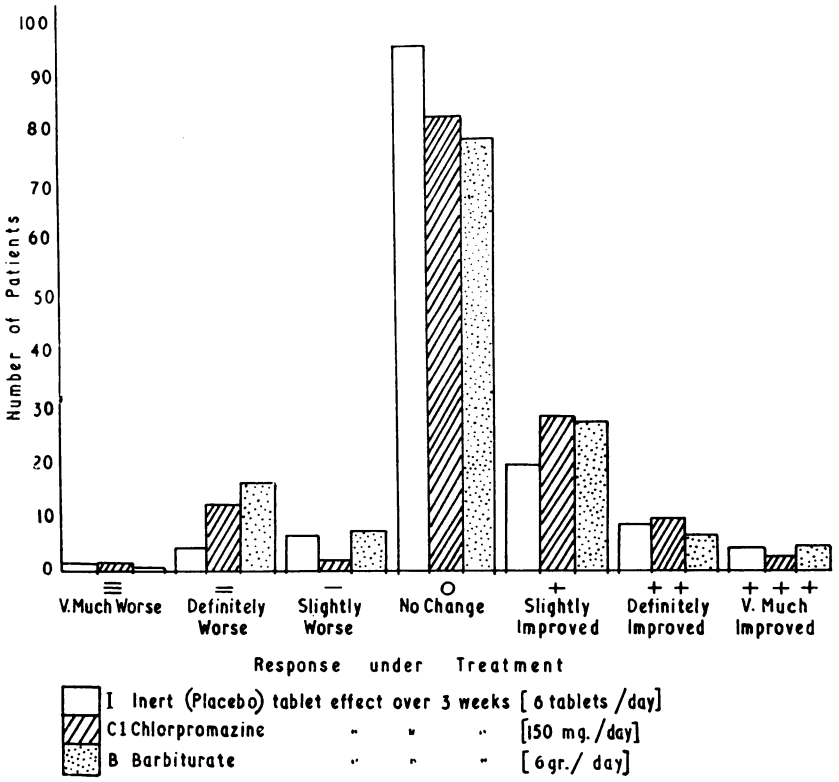

FIG. 1.

TABLE IV

General Response to Treatment in Total Group

Preparation	Response to treatment							Total
	≡	=	—	0	+	++	+++	
I (inert tablet)	1	4	6	95	19	8	4	137
C1 (chlorpromazine) ..	1	12	2	82	28	9	2	136
B (barbiturate)	Nil	16	7	78	27	6	4	138

Figures refer to numbers of patients.

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TABLE V

Analysis of Effect of the 3 Preparations by Initial Tension Ratings (H, HS, H+HS Combined, N,F.)

Tension Rating	α or β Grouping	On Inert Placebo Tablets Treatment Response							
		☰	=	—	0	+	++	+++	Totals
H ..	.. ..	Nil	2	1	23	6	2	1	35
	α ..	← 3 →			← 23 →		← 9 →		35
	β ..	← 2 →			← 30 →		← 3 →		35
HS	.. ..	1	Nil	4	24	7	Nil	Nil	36
	α ..	← 5 →			← 24 →		← 7 →		36
	β ..	← 1 →			← 35 →		← Nil →		36
H plus HS	..	1	2	5	47	13	2	1	71
	α ..	← 8 →			← 47 →		← 16 →		71
	β ..	← 3 →			← 65 →		← 3 →		71
N ..	.. ..	Nil	2	Nil	19	4	6	3	34
	α ..	← 2 →			← 19 →		← 13 →		34
	β ..	← 2 →			← 23 →		← 9 →		34
F ..	.. ..	Nil	Nil	1	29	2	Nil	Nil	32
	α ..	← 1 →			← 29 →		← 2 →		32
	β ..	← Nil →			← 32 →		← Nil →		32
								Total	137

Tension Rating	α or β Grouping	On Chlorpromazine (Cl) Treatment Response							
		☰	=	—	0	+	++	+++	Totals
H ..	.. ..	1	3	Nil	19	9	1	1	34
	α ..	← 4 →			← 19 →		← 11 →		34
	β ..	← 4 →			← 28 →		← 2 →		34
HS	.. ..	Nil	2	1	18	10	4	1	36
	α ..	← 3 →			← 18 →		← 15 →		36
	β ..	← 2 →			← 29 →		← 5 →		36
H plus HS	..	1	5	1	37	19	5	2	70
	α ..	← 7 →			← 37 →		← 26 →		70
	β ..	← 6 →			← 57 →		← 7 →		70
N ..	.. ..	Nil	5	Nil	20	5	4	Nil	34
	α ..	← 5 →			← 20 →		← 9 →		34
	β ..	← 5 →			← 25 →		← 4 →		34
F ..	.. ..	Nil	2	1	25	4	Nil	Nil	32
	α ..	← 3 →			← 25 →		← 4 →		32
	β ..	← 2 →			← 30 →		← Nil →		32
								Total	136

Tension Rating	α or β Grouping	On Barbiturate Treatment Response							
		☰	=	—	0	+	++	+++	Totals
H ..	.. ..	Nil	5	1	17	8	2	2	35
	α ..	← 6 →			← 17 →		← 12 →		35
	β ..	← 5 →			← 26 →		← 4 →		35
HS	.. ..	Nil	4	2	18	10	1	1	36
	α ..	← 6 →			← 18 →		← 12 →		36
	β ..	← 4 →			← 30 →		← 2 →		36
H plus HS	..	Nil	9	3	35	18	3	3	71
	α ..	← 12 →			← 35 →		← 24 →		71
	β ..	← 9 →			← 56 →		← 6 →		71
N ..	.. ..	Nil	4	2	18	7	3	1	35
	α ..	← 6 →			← 18 →		← 11 →		35
	β ..	← 4 →			← 27 →		← 4 →		35
F ..	.. ..	Nil	3	2	25	2	Nil	Nil	32
	α ..	← 5 →			← 25 →		← 2 →		32
	β ..	← 3 →			← 29 →		← Nil →		32
								Total	138

Figures refer to number of patients.

In order to keep the figures large enough for statistical purposes, the responses under treatment can be grouped together in various ways; two alternatives have been chosen here: (1) α Grouping ($\equiv$, $=$, —) (0) (+, ++, +++), which compares overall worsening and improving effects with the "no change" response; (2) β Grouping ($\equiv$, $=$) (—, 0, +) (++, +++), which groups minor degrees of change with "no change", and highlights the more marked degrees of altered behaviour. From the clinical point of view the latter is perhaps the more desirable, as we wish to induce quite definite changes in our patients rather than subtle and slight alterations which make little difference to the overall atmosphere of the ward. The χ^2 test using both alpha and beta groupings shows that in a comparison of the total results there is no significant difference between the general effect obtained with chlorpromazine, barbiturate and the placebo tablet. The total number improving with the chlorpromazine and barbiturate is almost identical, and there is no trend towards an advantage over the placebo using either the alpha or beta groupings.

The comparison of the general effect with each of the three preparations was broken down and considered separately for each of the four "Initial tension ratings" (H, HS, N, F). These results are shown in Table V using the α and β groupings of response to treatment, and are demonstrated in the form of a histogram in Figure 2.

It is readily seen that a more favourable response is occurring in the H and HS groups, and as the results in all groups show no difference between the three preparations, the chance of obtaining any significant effect must lie here. By eliminating from consideration the patients whose initial tension state was normal or flattened, and abstracting the figures for the 70 odd patients who show persistently or sporadically raised tension (H, HS) the difference between the drug responses is still not significant at the 5 per cent. level, but a trend in favour of the drugs as against the inert preparation is discernible.

Leaving out of consideration the worsening effects and concentrating entirely on the improving effects, the following results are obtained (see Table VI).

TABLE VI

Table of Comparison by Improving Effects Only

	Preparation	Treatment Response Groups (++, +++)	Per cent.	Treatment Response Groups (+, ++, +++)	Per cent.
(1) All Tension Groups	Placebo ..	12 out of 137	(9·0)	31 out of 137	(22·5)
	Chlorpromazine	11 out of 136	(8·0)	39 out of 136	(28·5)
	Barbiturate ..	10 out of 138	(7·5)	37 out of 138	(27·0)
(2) Groups H. and H.S. only	Placebo ..	3 out of 71	(4·25)	16 out of 71	(22·5)
	Chlorpromazine	7 out of 70	(10)	26 out of 70	(37)
	Barbiturate ..	6 out of 71	(8·5)	24 out of 71	(33·5)

None of these differences is significant at the 5 per cent. level.

Once again a moderate suggestion of improvement emerges in the groups with heightened psychological tension; this is, however, much less aparent when only considering the "marked improvement" groups (++, +++).

Although numerous "tranquillizing" drugs are now in general use, there are few indications as to which is likely to be most beneficial in a particular

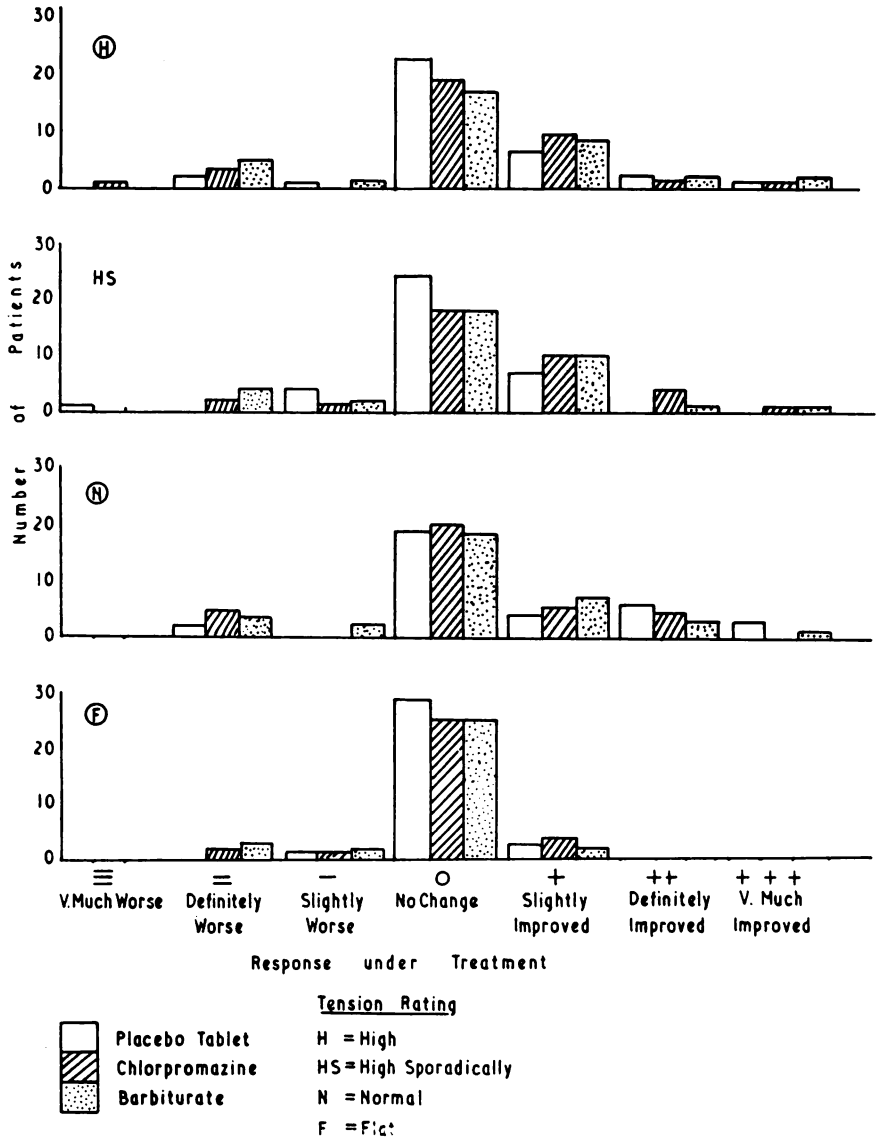

FIG. 2.

case. Thus a fairly detailed account is given of some findings in this trial related to this topic. Once it has been shown that equal *numbers* of patients improve with either of two treatments, there is still a possibility that the two groups are not identical and that some patients respond to one drug and not the other. In order to investigate this point a comparison of the two drugs (B and C1) was made for each patient in order to determine whether a preference was shown for one drug or the other. For the purposes of this assessment (—, 0, +) were regarded as being equivalent—this has been done in order to eliminate trifling differences in drug response. The results are shown in Table VII.

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TABLE VII

Illustrating Drug Preference Between Barbiturate and Chlorpromazine

Tension Groups	Same Effect With Either Drug	Chlorpromazine More Effective Than Barbiturate (Cl > B)	Barbiturate More Effective Than Chlorpromazine (B > Cl)	Total
N plus F	55	6	6	67
H plus HS	49	10	10	69
All cases	104	16	16	136

Thus: Over *all* cases the proportions showing a preference for B over Cl are not significantly different from the proportions showing a preference for Cl over B.

This also applies for tension groups H and HS combined and for groups N and F combined, but the proportion of cases showing *a* preference is higher in H and HS than in N and F (20 cases out of 69: 12 cases out of 67).

A search was made for any factors which might serve to differentiate the 16 cases showing a preference for Cl from the 16 preferring B. There was no striking difference in diagnostic groupings, age, and duration since first admission. One possible clue is in the response to previous E.C.T.: of the B preference group 14 patients had had E.C.T. with 10 responding favourably. In the Cl preference group 12 had received E.C.T. and 5 had responded favourably (this difference however, is not significant at the 5 per cent. level). The incidence of flushing and pallor were not significantly different in the two groups. By far the most striking result of this analysis of preference groups occurred among the female patients:

On one ward (ward 1), of 9 patients showing a preference 8 preferred B>C. Tension Ratings HS nil; H 4; N 3; F 1. On the other ward (ward 2), of 9 patients showing a preference 8 preferred C>B. Tension Ratings HS 6; H 2; N nil; F nil. All these 18 patients were schizophrenics.

These differences are highly significant and on attempting to explain them certain dissimilarities between these two female groups are apparent:

Ward 1 is a ward for young schizophrenics mainly. The average age of these 9 cases was 34½ years, and the average duration since first admission was 7 years, thus the average age at first admission was 27½ years. Much active treatment had already been carried out on this ward, 2 of these 9 patients having been leucotomized, 7 having received E.C.T. in the past (5 responding favourably in some degree) and 4 had had insulin therapy. Sedation was hardly used at all. The one patient from this ward who showed a preference for C>B was an older patient aged 41 with 9 years duration of stay, who had worsened on E.C.T. and required heavy sedation.

Ward 2 is a large refractory ward with rather older patients: the average age of these 9 patients was 45 years, and the average duration since first admission was 13½ years, thus the average age at first admission was 31½ years. None of these patients had been leucotomized or had received insulin therapy, but 6 had had E.C.T. previously—in only one was there a favourable response. Fairly heavy sedation was regularly taken by 6 of them. The one patient in this ward who preferred B>C differed only in that she had not been sedated at all previously.

The differences in favourable response to E.C.T. in the two groups (ward 1: 5 out of 7; ward 2: 1 out of 6) show a trend in favour of ward 1 which does not reach significant proportions however.

Caution is needed in interpreting these results. The figures are small and several of the factors noted have been based on subjective judgments on the ward sister's part, e.g. initial tension ratings and, to some extent, the effect of previous E.C.T. where it was not noted was based on the sisters' recollections.

Hence, the results would appear to suggest that among females at least, younger schizophrenic patients with various tension ratings but not given to violent outbursts, and who have responded well to E.C.T. in the past, show some preference for barbiturate sedation, whereas rather older schizophrenics given to violent outbursts and who have not improved with E.C.T. fare better on chlorpromazine. It may well be that the group on ward 2 are in fact catatonic schizophrenics—it should be noted that the average age on first admission in this ward was 31½ years, as against 27½ years in the other ward. Although aggressive outbursts were common with this group, no stuporose episodes were reported and statuesque posturing and flexibilitas cerea were not seen. This, however, may not be very surprising as many catatonic patients lose these significant features over the years. This question of drug preference and its relations to diagnosis, behaviour and E.C.T. response requires further study. But for the most part patients who respond in one way to one of the drugs under trial will respond the same way, and equally, with the other.

An assessment of the *overall psychological effect* of the trial in this whole group of chronic in-patients may be made by considering the total effect of the inert tablets, as compared with the previous (pre-treatment) state. See Table VIII.

TABLE VIII

The Effect of the Inert Tablet (Placebo) Analysed According to Initial Tension Rating

		Treatment Response			
	Initial Tension Rating	(≡, =, —)	(O)	(+, ++ +++)	Total
α Grouping	H plus HS ..	8	47	16	71
	N	2	19	13	34
	F	1	29	2	32
	All tension groups	11	95	31	137
	Initial Tension Rating	(≡, =)	(—, O, +)	(++ +++)	Total
β Grouping	H plus HS ..	3	65	3	71
	N	2	23	9	34
	F	0	32	0	32
	All tension groups	5	120	12	137

Thus using the *alpha* grouping a definite favourable effect on behaviour is seen in the group as a whole, most marked in the normotensive patients and absent altogether in the apathetic. With the *beta* grouping which is designed to reveal marked changes only, the favourable trend is only revealed in the normotensive group. Thus the psychological effect of the inert tablet only causes an overall degree of slight improvement, most marked in the group of patients whose tension is not markedly increased or decreased.

Useful results have been claimed for chlorpromazine in the treatment of various *paranoid psychoses*. The analysis of results in the group of twelve elderly certified paraphrenics is shown in Table IX and reveals that chlorpromazine and barbiturate in the stated dosage would seem to be singularly ineffective in this group.

TOXIC AND SIDE EFFECTS

These aspects have been commented on in numerous papers and are now well known, thus reference will only be made to a few special points.

Dry mouth is a rare complaint in chronic schizophrenics.

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TABLE IX

Results in 12 Chronic Paraphrenics

Case Numbers	Sex	Age	Duration of In-Patient Stay in Years	Initial Tension Rating	Treatment Response with the Different Preparations			
					C1	C2	I	B
130	M	74	30	F	0	0	0	0
7	M	56	2	N	0	0	0	0
22	F	63	14	N	0	0	0	0
37	F	65	24	N	0	0	0	0
85	M	49	8	N	0	+	++	++
112	M	61	9	N	0	+	+	0
117	M	56	11	N	+	+	+	+
113	M	69	21	HS	+	+	+	+
118	M	57	11	HS	+	+	+	+
122	M	52	4	HS	+	−	−	0
51	F	69	30	H	+	+	+	+
99	M	53	21	H	+	++	++	0

Jaundice and Agranulocytosis. No patient in the trial had to stop treatment because of toxic effects. Two developed transient jaundice but were able to continue. None developed agranulocytosis, but after the trial was completed a 52 year old female in an admission ward suffering from acute hypomania, from which she was recovering well, developed cellulitis of the face although the fauces were quite healthy. She had been receiving chlorpromazine 150 mg. daily for seven weeks (total 7·5 grams). The white blood count on that day was 2,000 per cu.mm.; polymorphonuclear neutrophils 4 per cent. (actual number 80 per cu.mm.). Penicillin was prescribed and next day the W.B.C. was 1,200 cu.mm.; polymorphs 1 per cent. (actual number 12 per cu.mm.). A sternal marrow biopsy revealed the myelocyte representation to be within the normal range but there was a complete absence of mature granulocytes. Eight days later the W.B.C. was back to 6,000 per cu.mm. The patient complained of no pain and felt perfectly well throughout. This sudden emergency should serve as a warning to those of us who make a custom of telling our out-patients (especially those of poorer intelligence) to report if they develop a sore throat. Had this particular woman, well on the way to recovery, been an out-patient she may well have died.

Drowsiness. It has been claimed as one of the virtues of chlorpromazine that it causes less drowsiness than barbiturates. In the present trial drowsiness or its absence was specially noted during each treatment period (see Table X).

TABLE X

Presence of Significant Drowsiness

Preparation	Number of Patients	Per cent.
Placebo (I)	15	(11)
Barbiturate (B)	28	(20)
Chlorpromazine (C1)	39	(28·5)
Chlorpromazine (C2)	24	(17·5)

Tests of significance on these results show: the difference in the numbers drowsy on I and B is significant. The difference between the numbers drowsy on I and C1 is highly significant, and the figure for C1 is also significantly

greater than that for B (using McNemar's statistical method (McNemar, 1947)). The difference between the numbers drowsy on C1 and C2 is also significant but the difference between I and C2 is not significant using McNemar's method. The difference between the numbers drowsy on B and C2 is not significant.

In other words chlorpromazine is associated with a high incidence of drowsiness (38·5 per cent.) during the first three weeks and this falls to an incidence subsequently (17½ per cent.) which is not significantly greater than that occurring with the inert tablet (11 per cent.). Barbiturate has been proved in this sample to be associated with an incidence of drowsiness (20 per cent.) significantly greater than that seen with the inert tablet. There is, however, no significant difference between the numbers of patients drowsy on barbiturate and chlorpromazine. These findings, although consistent with, do not support the general view that one of the virtues of chlorpromazine is a lesser incidence of drowsiness than with barbiturate.

Autonomic response. The only autonomic responses considered here are flushing and pallor which have both been reported as side effects of chlorpromazine therapy. Such responses occurred in 48 patients (34·5 per cent.) (see Table XI).

TABLE XI

Incidence of Autonomic Responses (Flushing and Pallor)

Preparation	Number of Patients		
	Flushed	Pale	Total
I (inert tablet)	16	1	17
C1 (Chlorpromazine)	18	7	25
C2 (Chlorpromazine)	16	6	23
B (Barbiturate)	12	1	13

Comparing the responses under this heading observed while on the drugs as compared with those observed while on the inert tablets, the only significant difference is between I and C1 with regard to pallor only. (Significant at the 5 per cent. level using Edward's modification of McNemar's method (Edwards, 1948).) Thus there is no evidence from this trial to support the view that flushing is a side effect of chlorpromazine therapy, but there is evidence that pallor is present to a significant degree during the initial three weeks of chlorpromazine therapy only, as compared with the period on inert tablets. No relationship was discernible between treatment response and these forms of autonomic reaction (flushing and pallor).

COMMENT

The principal conclusion derived from this trial, carried out on a reasonably large sample population of chronic psychotic in-patients, is that neither chlorpromazine nor barbiturate is shown to exert any effect significantly superior, from the nursing point of view, than can be obtained with an inert placebo tablet.

Other workers have used different criteria of the effect of drugs such as scoring methods based on the response under treatment of various symptoms. It is maintained here, however, that an assessment from the nursing standpoint is a valid and realistic one, as the care of such chronic patients is essentially a nursing and social one. Furthermore, the nurses spend more time with the

patients than anyone else, and are in the best position, by constant close observation, to assess the result of treatment. A general objection to scoring methods based on symptoms is that a situation can arise whereby many trivial symptoms improve while a few important ones remain unaltered or even worsen, the patient consequently achieving a raised overall score, while in fact deteriorating. In none of the trials reported in the literature using such a scoring method was any attempt made to weight scores according to the importance of symptoms.

In a drug trial on patients whose mental state fluctuates, and where the effect of suggestion can be so powerful on both patient and therapist, it is maintained that only the technique of the double-blind controlled trial can yield valid results. A survey of the literature on the effects of chlorpromazine in chronic psychotic groups reveals that of a total of seventeen studies nine are uncontrolled against an inert preparation. Of the remaining eight controlled studies two are confined to the older age group.

Vaughan, Leiberman and Cook (1955) report 70 per cent. improvement with chlorpromazine in doses of 150–200 mg. daily in a group of 103 chronic schizophrenics, the great majority of whom belonged to the catatonic and paranoid subgroups. It is understood that most of these patients relapsed after receiving an identical placebo. As a further study a controlled comparison was made using 48 excited "chronic patients of poor prognosis", 24 treated with chlorpromazine and 24 with a placebo. A significant difference at the 1 per cent. level was revealed in favour of chlorpromazine.

A possible explanation of the difference between the results of this and the present study may lie in the inclusion by Vaughan *et al.* of a very high proportion of catatonic and paranoid schizophrenics. There is general agreement that chlorpromazine helps acute cases more than chronic ones and the tense and aggressive more than the quiet. Furthermore, in no fewer than six papers attention is drawn to the fact that chlorpromazine would appear to benefit the catatonic and paranoid subgroups of schizophrenics rather than the simple and hebephrenic varieties. In the present study only nineteen cases are classified as catatonic and paranoid schizophrenia, but some doubt must be expressed about the adequacy of the classification of the schizophrenic group, many of whom were admitted many years ago when clinical notetaking and classification were less extended than today. With the passage of time many of these cases have deteriorated and it is difficult at this stage to distinguish the different clinical varieties. However, it is of interest that in the present study the drug proved singularly ineffective in a group of twelve chronic paraphrenics.

Five controlled studies are more strictly comparable with the present one, with regard to diagnosis, chronicity, age, etc.:

Elkes and Elkes (1954) carried out a carefully controlled study in 27 chronically overactive patients who were used as their own controls, a dosage of chlorpromazine of 150 mg. daily by mouth being used. It is only necessary here to consider the 13 patients suffering from chronic schizophrenic disorders who, being over-active, correspond with the group of seventy tense patients (groups H and HS) in the present study. Results assessed "blindly" by nursing and medical staff show that when on chlorpromazine as compared with alternating periods on control tablets 3 (23 per cent.) were definitely, and 5 (38·5 per cent.) slightly improved.

These numbers are small and, although much more favourable, a strict comparison cannot be made with the results of the present study, as a different method of comparison is used which does not lend itself to statistical handling.

Shepherd and Watt (1956) carried out a self-controlled study on twenty-four deteriorated schizophrenics. This included a comparison of the effects of 300 mg. daily of chlorpromazine and a placebo with the following results:

	Improved	Unchanged	Worse
On chlorpromazine	15	5	4
On placebo	11	9	4

The results in these small groups do not differ significantly and it is only by comparing the effect, not with the initial state, but with the state before each new drug was given, that a significant effect could be obtained.

Kovitz *et al.* (1955) report a well-controlled study which includes a comparison of chlorpromazine and a placebo in 150 chronic psychotics of whom 127 were chronic schizophrenics. The dosage used was 100–400 mg. daily and up to 600 mg. in a few cases. Fifty-eight per cent. of the patients are reported improved on chlorpromazine as compared with 24 per cent. on the placebo. The comparable figures for the present study for all grades of improvement in 138 patients are: on chlorpromazine 28 per cent. and on placebo 22 per cent. Some possible reasons for this discrepancy occurring in a report from the U.S. are discussed below.

Tenenblatt and Spagno (1957) in a controlled study, also from the U.S. on one hundred paired negro females, mostly schizophrenics, gave doses of 300–900 mg. of chlorpromazine daily for 16–116 days. The evaluation of results was carried out "by several people". The figures for all grades of improvement were: chlorpromazine 76 per cent.; controls 8 per cent.; and the figures for "all degrees of improvement above slight" were: chlorpromazine 40 per cent.; controls 2 per cent. It is of interest that when the catatonic and paranoid schizophrenics are eliminated the figure for improvement on chlorpromazine falls to 30 per cent. The low figure for improvement in the controls differs very greatly from those reported in most other studies on similar groups.

Mitchell (1956) in a carefully planned double-blind controlled experiment on sixty disturbed schizophrenic patients (mostly paranoid) used dosages of 150 mg. of chlorpromazine daily, repeating the experiment with double this dose. It was concluded that statistically there was no change in the symptoms of aggression in this group with the stated dosage of chlorpromazine.

There are two general factors regarding practice in America which merit consideration in any attempt to explain the more favourable reports from that country. Firstly, as Sargant (1956) has pointed out there tends to be a higher level of therapeutic endeavour directed towards the chronic patient in this country, thus leaving less scope for improvement with any further treatment. Details have been given of the previous physical treatments received by the patients in the present study, as it would be interesting to know how all this background activity compares with the position in American hospitals from which reports have been published.

A further possible reason for differences lies in the much higher doses usually reported from the U.S. A majority of British authors have advocated a daily dosage of about 150 mg. daily of chlorpromazine by mouth as being the optimum: Elkes and Elkes (1954); Lomas (1955); Baker (1955); Vaughan *et al.* (1955); Dewhurst (1955). Very few European workers report the use of more than 300 mg. daily.

In a comparable series of reports from the U.S. the following daily doses are mentioned: 200–300 mg. I.M. By mouth: 400–700 mg.; 50–400 mg.; 100–400 mg. "and up to 600 mg. in a few cases"; 300–900 mg.; "300 mg. with a maximum useful dose of 2,000 mg. daily". There is one report of seizures occurring on a dosage of "up to 4,000 mg. daily", and one of fatal hyperpyrexia in a patient who had built up to a dosage of 2,500 mg. on the eighteenth, nineteenth and twentieth days, death occurring on the twenty-first day, in a coma following after fits.

A consideration of all these reports suggests that a co-ordinated programme of research should be carried out on new preparations which are claimed to be of value in abnormal mental states. As is the practice in the M.R.C. trials many hospitals could co-operate using agreed classifications and criteria of severity of illness and of treatment response.

From the results of the present experiment it is concluded that if a sedative agent is to be used at all in chronic psychotic in-patients then barbiturates are preferable to chlorpromazine on grounds of safety and economy. Although Hunter *et al.* (1955) have pointed out that chronic barbiturate intoxication may cause mental symptoms, nevertheless, in controlled dosage the risks are negligible, and with the stock of the drug in the safe keeping of the hospital staff the suicide risk is virtually ruled out; on the other hand chlorpromazine is a toxic drug with the two potentially lethal complications of jaundice and agranulocytosis. The cost of chlorpromazine is six times that of amylobarbitone: the daily cost in the dosage used in this trial being one shilling for the chlorpromazine and twopence for the barbiturate.

Neither drug in the dosage used in this trial, however, was proved statistically to show a therapeutic advantage over the placebo tablet; a trend in their

favour was revealed and it could perhaps be that by increasing the number of cases in the trial a significant result would be achieved. However, it is felt that the failure to reach significance in a trial on 142 patients (including 70 with increased tension) suggests that the overall value of chlorpromazine or barbiturate in the stated dosage in improving the behaviour of chronic psychotic in-patients is very questionable.

Summary

1. In view of the numerous encouraging reports on the use of chlorpromazine in chronic psychotic in-patients, an experiment was set up using 142 patients to compare the results of this therapy with those obtained by a barbiturate, the traditional sedative in these cases, and the results with an inert placebo. The method used was the double-blind comparative method using identical tablets, the patients acting as their own controls.

2. The results fail to support the view that chlorpromazine does not exert its full effect until it has been given for six weeks, such effect as it does have being equally apparent in three weeks.

3. The results failed to show that there is any significant difference in behaviour on any of three preparations (chlorpromazine 150 mg. daily, amylobarbitone 6 gr. daily, or 6 inert tablets daily).

4. In the seventy patients showing increased tension in their pre-treatment state, a trend was shown in favour of both drugs as compared with results of placebo therapy. Considering improving effects only, and excluding all worsening effects, there was still no significant difference between results from the three preparations, although once again a trend in favour of the drugs is seen in the tense group. It is felt that with failure to reveal any significant difference between the responses in a group of this size, the value of barbiturates and chlorpromazine in the stated doses is highly questionable in such a group of chronic psychotic patients.

5. Although the numbers improving on both drugs are almost identical, nevertheless there are indications that some patients showing certain characteristics may show a preference for one drug as against the other. On the whole, however, a given patient will tend to respond in the same way and equally with either drug.

6. The psychological effect of the trial is shown to cause slight degrees of improvement most marked in patients whose initial tension state was neither raised nor lowered from the normal.

7. Both drugs were singularly ineffective in a group of twelve chronic paraphrenics.

8. The findings, although consistent with, do not support the view that one of the virtues of chlorpromazine as compared with barbiturates is a lower incidence of drowsiness. The results failed to support the view that flushing is a side effect of chlorpromazine therapy. On the other hand pallor did appear to be a side effect particularly during the first three weeks of medication. No relationship was discernible, however, between these forms of autonomic response and response to treatment.

9. Possible reasons for differences between these and other reported results are discussed and a plea made for a programme of co-ordinated research using agreed classification and criteria.

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