A CONTROLLED TRIAL OF ETHYLCROTONYLUREA

By

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INTRODUCTION

OVER the past few years, there has been an increasing interest in drugs having a tranquillizing or ataractic effect on the central nervous system. Pharmaceutical houses, both here and on the other side of the Atlantic, have vied with one another to be the first to introduce the perfect tranquillizer, providing relief from tension and anxiety with no unpleasant or dangerous side-effects or tendency to addiction, and at the same time if possible to effect an improvement in the management of, if not the cure of, the psychoses.

An initial enthusiasm for these drugs, based on inadequate clinical trials and backed by a large advertising campaign, has in many cases been followed by disillusionment, both in the effects of a drug when carefully compared with a placebo and in the later description of undesirable actions and side-effects.

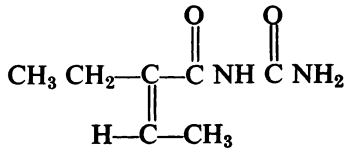
It was therefore particularly stimulating to be given the opportunity of investigating a new compound, the low-melting isomer of ethylcrotonylurea, by means of a double-blind controlled clinical trial before a decision was made whether or not to add this drug to the many similar ones already on the market.

The report which follows details the results of the comparison of the new drug with chlorpromazine and a placebo in a group of chronic psychotic in-patients. This study forms part of a larger investigation, as yet incomplete, which includes out-patients and in-patient neuroses.

ETHYLCROTONYLUREA

Pharmacology

This substance is an unsaturated open-chain ureide and has the following structural formula:



In previous studies (reported below) in America, the high-melting isomer was used. The manufacturers of the drug in this country believed that the low-melting isomer might offer certain advantages and this form of the drug was used in the present trial.

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Preliminary laboratory investigation (Ross, A. F., 1959) gave the following results:

1. *Toxicity by Mouth*

(A) *Acute Toxicity*

Acute LD_{50} determination, made in albino mice:

High Melting Isomer	3·0 gm./Kg. ±7 per cent.
Low Melting Isomer	1·7 gm./Kg. ±7 per cent.

(B) *Toxicity on Repeated Dosage*

In a controlled study on young male albino rats, there were no deaths attributable to the drug when given in doses of up to 400 mg./Kg. of the low-melting isomer five days a week over a period of twelve weeks. Percentage weight increase in rats receiving ethylcrotonylurea was less than that of the controls but it was considered that this might have been due to the sedating effect of the drug which was apparent in high dosage. Histological examination of the stomach, liver, kidney, adrenal, spleen, heart and lung revealed no pathological change.

2. *Hypnotic and Sedative Effects*

(A) *Hypnotic Effect in Mice*

The oral Hypnotic $Dose_{50}$ was:

High Melting Isomer	2·3 gm./Kg. ±9 per cent.
Low Melting Isomer	1·4 gm./Kg. ±6 per cent.

From these studies it will be seen that while the low-melting isomer is slightly more toxic it has also a slightly greater hypnotic activity. The onset of effects after oral administration was more rapid; thus, it is probable that its greater toxicity and hypnotic effects are due to more rapid absorption.

(B) *Extension of Barbiturate Sleeping Time*

Mice pre-treated with both isomers of ethylcrotonylurea showed a definite increase in barbiturate sleeping time but there was considerable individual variation in response.

(C) *Effect on Spontaneous Activity*

Spontaneous nocturnal activity of the rat was studied by means of an activity cage constructed so that each movement of the rat completed an electrical circuit actuating an electro-magnetic counter. Oral administration of 400 mg./Kg. ethylcrotonylurea reduced the spontaneous activity of the rat by about 50 per cent. It is known that chlorpromazine is active in this test at an oral level of 5 mg./Kg.

Sedation is estimated to occur at 25 per cent. of the acute toxic dose as compared with 50 per cent. in the case of phenobarbitone and 64 per cent. with meprobamate. Hypnotic effects occur at 82 per cent. in the case of the low-melting isomer and 77 per cent with the high-melting isomer, the latter figure being slightly lower than that reported by American workers (Lim *et al.*, 1956).

Thus, in the late appearance of hypnotic effects as compared with the acute toxic dose, ethylcrotonylurea tends to resemble chlorpromazine and reserpine.

Indications

Early studies in the United States had suggested that this drug was particularly useful as a calmative in patients who were subject to abnormal behaviour

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due to anxiety and tension, and that moderately overactive patients might benefit from doses of from 100 to 300 mg. three times a day. The manufacturers of the drug in this country were hopeful that it might have some specific beneficial effect on the behaviour of psychotic patients in addition to its action on tension and anxiety.

Dosage and Administration

The drug is administered orally, and in human subjects has been given up to 1,800 mg. daily. In the present trial, it was supplied in 100 mg. tablets and was given up to a maximum of 1,200 mg. per day, as in a previous series of cases in America reported by Ferguson and Linn (Ferguson *et al.*, 1956), it had been found that doses of more than 900 mg. did not produce significantly different results.

Occasional side-effects such as rash, nausea, dizziness or drowsiness have been reported, but blood, urine and liver function investigations have all been within normal limits, and no changes in the pulse, respiration, temperature or blood-pressure have been reported even in a patient to whom 5·4 g. of the drug had been accidentally administered.

METHOD

It was decided to select a group of 25 chronic psychotic patients from the total population of the female side of the hospital, less the following categories:

(*a*) Patients of under two years stay.
(*b*) Epileptics.
(*c*) Patients suffering from intercurrent physical illness on whom the participation in such a trial might have a deleterious effect.

The patients selected, who thus represented a small cross-section of the chronic hospital population, had the following characteristics:

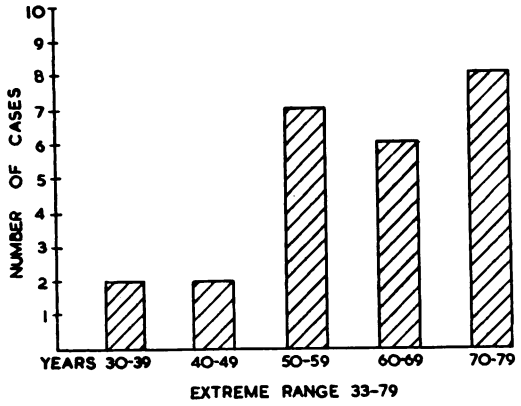


FIG. 1.—Age range of therapeutic group.

In order to be able to allow for any possible general shift in the hospital population towards better or worse behaviour due to circumstances outside the trial, a control group of 30 patients was rated at the beginning and the end of a twelve-month interval which covers the period of the trial.

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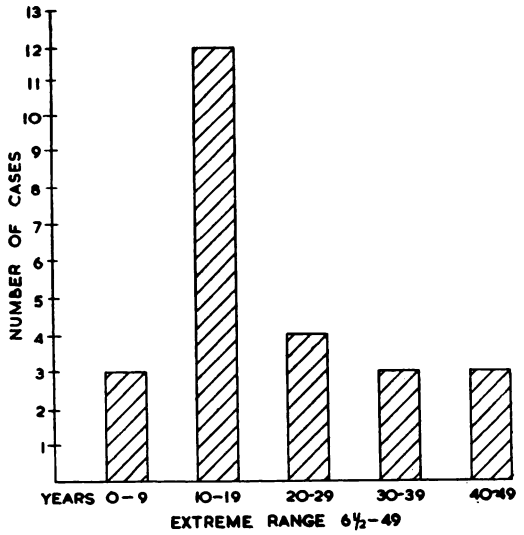


FIG. 2.—Length of stay in hospital of therapeutic group.

TABLE I

Diagnoses of Patients in Therapeutic Group

	Number of Cases
Schizophrenia:	
Simple	6
Hebephrenic	4
Catatonic	4
Paranoid	7
Involutional melancholia	2
Manic-depressive illness	1
Senile psychosis	1
Total	25

COMPARISON OF EFFECTS

The effects of ethylcrotonylurea were to be compared with those of chlorpromazine and a placebo. These three substances were supplied in matching tablets by Messrs. Smith & Nephew, the sponsors of the new drug. Each chlorpromazine tablet contained 25 mg. of the drug, the ethylcrotonylurea 100 mg., and the placebo 325 mg. of lactose.

Each patient was to act as her own control and would thus receive each of the three substances consecutively, the order of administration being determined by random selection. The period of administration of the drug was to be 5 weeks in each case, leaving an interval of one week between each drug. The instructions for taking the tablets were similar in each case, namely, two tablets three times a day for the first week and four tablets three times a day for the following four weeks. This scheme gave the following total dosage:

Chlorpromazine, 150 mg. daily for the first week, 300 mg. daily for the next four weeks.

Ethylcrotonylurea, 600 mg. daily for the first week, 1,200 mg. daily for the next four weeks.

Placebo (Lactose), 1·95 and 3·90 gm. daily, respectively.

The total number of tablets for each five-week period (378) were put in a separate envelope, labelled "A", "B", or "C" and a code was kept showing

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which tablets any patient was taking during any given period. The code was to be used only in the event of an emergency occurring during the course of the trial. It was thus possible to keep the handling and the knowledge of the identity of the tablets under the control of a person other than the psychiatric assessor of results until the trial was completed.

It was considered that if there was to be any marked beneficial effect from ethylcrotonylurea, this would probably become obvious within the five-week period. This was suggested by the experience of Charmian Elkes (Elkes, 1957) in reporting rauwolfia trials in chronic psychotics, which shows that in most cases likely to gain much improvement, this occurs within five weeks. This view has also been more recently supported in the case of chlorpromazine by J. Crawford Little (Little, 1958) who shows that, contrary to the commonly held view that chlorpromazine does not exert its full effect until it has been given for six weeks, such effect as it does have is equally apparent within three weeks.

It was arranged that the patients who were already having tranquillizing drugs of any kind should discontinue these for a period of at least two weeks before the beginning of the trial.

Method of Assessment

In order to assess the improvement or otherwise of the group of chronic psychotic patients, an objective method of rating their behaviour which could be treated statistically was desirable. For this purpose, the Parkside Behaviour Rating Scale (P.B.R.S.) was selected. This has been described in full by K. E. Schmidt (Schmidt, 1957) and has the advantage of being simple to administer, extremely reliable as shown by significance tests, and well validated by experience.

Briefly, each of six behavioural characteristics is rated on a five-point scale. The characteristics are:

(*a*) Self care.
(*b*) Orientation as far as communicated.
(*c*) Communication and socialization.
(*d*) Psychotic behaviour.
(*e*) Co-operation and occupation.
(*f*) Mood and reaction to environment.

Thus, the worst possible behaviour would carry a rating of six points, as against a maximum of thirty points for a model patient.

Control Group

The patients in the control group were selected in exactly the same manner as those in the trial group, and constitute a similar random sample of the chronic hospital population.

Table II

Diagnoses of the 27 Patients Rated in the Control Group

	No. of Cases	
Schizophrenia	18	(1 spontaneous recovery, sent on indefinite leave)
Involutional melancholia	3	
Manic-depressive illness	1	
Senile psychosis ..	1	
Senile dementia	2	(including 1 patient who died during the year)
Mental defective ..	2	(including 1 patient who was transferred to another hospital)
Total	27	

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Three of these control patients died before the first assessment was made, leaving 27 for rating, and during the twelve-month period, one further patient died, one was transferred to another hospital, and one recovered and was sent on indefinite leave. The average P.B.R.S. rating of the control group was 18·8 points. At the end of twelve months, the shift was less than 0·1 points of P.B.R.S., an insignificant change.

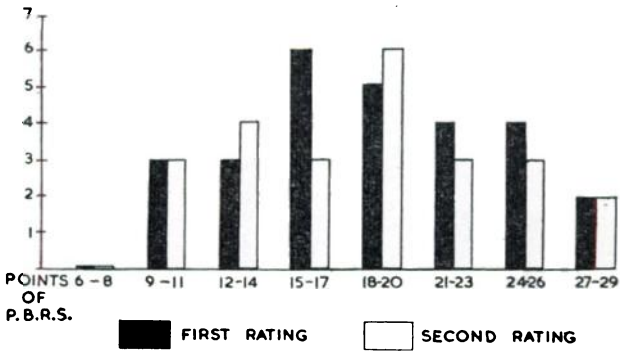


FIG. 3.—Rating and re-rating of the control cases with an interval of one year.

The standard deviation between rating and re-rating was 3 points of P.B.R.S., and a significant improvement or deterioration over the earlier rating would require, at the 5 per cent. level, a movement of at least 5 points. Only four patients qualified for this distinction. Three were significantly worse. Of these, one had a recurrent depression at the time of the second rating; one sustained a fractured femur; the third became bedridden due to senile cardiovascular degeneration, and increasing dementia.

The fourth patient, who improved, was a chronic schizophrenic, disturbed at the time of the first rating and refusing food; her improvement followed a short course of electrical treatment and was maintained at the second rating.

The inference to be drawn from this control group, therefore, is that there was no significant shift in behavioural characteristics in the chronic hospital population over the period of the trial.

THERAPEUTIC GROUP

ANALYSIS OF RESULTS

A complete analysis of the rating and re-rating of these patients after chlorpromazine, ethylcrotonylurea and the placebo is shown in Figure 4 on page 857.

The order in which the drugs were given is indicated in Table III in parenthesis. Diagnoses and any side-effects are shown in each case. There were no deaths in this group, but one patient (Case 120) was so unco-operative in taking tablets that it was decided to abandon the attempt, in her case.

The average rating of the group before treatment was 17·3 points of P.B.R.S. The average shifts in P.B.R.S. are as follows:

After placebo:	0·25 points (increase).
After chlorpromazine:	0·45 points (increase).
After ethylcrotonylurea:	0·2 points (decrease).

As the standard deviations were around three points from the original rating, only shifts of plus or minus five points could be considered significant. A change

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TABLE III.

Analysis of the Therapeutic Group

Case Numbers	Diagnosis	Preliminary				After Placebo					After Chlorpromazine					After Ethylcrotonylurea					Side-Effects
		P.B.R.S.	B.P.	Hb. %	W.B.C.	Order	P.B.R.S. Rating	Shift	B.P.	Hb. %	W.B.C.	Side-Effects	Order	P.B.R.S. Rating	Shift	B.P.	Hb. %	W.B.C.	Side-Effects
101	Sch S.	14	160/110	93	6·350	(2)	10	−4	160/80	96	7·450		(3)	16	+2	160/110	91	6·700	D, F	(1)	14	160/80	86	7·250	
102	Sch S.	22	130/90	96	5·090	(3)	20	−2	170/90	94	9·350		(1)	19	−3	120/90	86	8·450		(2)	22	130/90	90	7·900	
103	Sch P.	18	200/120	95	7·125	(1)	23	+5	200/100	97	6·100		(2)	23	+5	190/120	101	5·200		(3)	25	180/110	101	6·500	
104	Sch H.	11	150/90	95	5·500	(3)	13	++2	120/80	87	7·150		(2)	12	++1	140/90	94	6·950		(1)	10	160/100	89	6·000	I
105	Sch P.(D)	20	150/90	86	7·150	(3)	19	+1−0	140/80	85	5·100		(1)	20	0	150/90	82	7·150		(2)	22	120/80	88	5·700	
106	Sch H.	14	140/90	92	7·170	(1)	14	0	176/96	90	7·800		(3)	12	−2	180/110	97	8·200		(2)	13	160/100	85	7·350	
107	Sch C.	18	170/90	102	8·670	(2)	21	+3	180/80	102	7·750		(3)	16	−2	150/90	101	7·050		(1)	22	160/100	99	7·200	
108	Sch H.	22	130/80	96	7·910	(3)	22	0	130/80	98	7·850		(1)	24	++2	120/80	89	5·050		(2)	21	130/80	95	6·250	
109	Inv. Mel.	22	150/70	98	8·160	(1)	28	+6	160/84	91	5·975		(2)	25	+3	130/70	93	6·600		(3)	21	150/80	92	5·050	
110	Sch C.(D)	12	150/100	93	7·400	(3)	13	+1	120/80	94	7·000		(2)	21	+1	130/80	92	8·950		(1)	13	180/90	92	9·200	
111	Sch P.	20	220/80	99	9·350	(2)	23	+3	200/90	94	5·850		(1)	12	+1	190/80	90	5·900	O	(3)	24	150/70	95	6·700	
112	Sch C.	10	120/80	91	5·100	(1)	12	+2	170/100	94	4·850		(3)	15	+2	110/70	94	5·150		(2)	12	140/100	96	5·600	
113	M.-D.	18	160/80	98	7·500	(2)	12	+6	190/120	90	5·750		(3)	15	−3	150/80	95	8·250		(1)	15	150/80	92	7·950	
114	Sch H.	20	120/76	86	5·900	(3)	15	−5	120/76	85	5·600		(1)	19	−1	110/80	86	13·610	V	(2)	8	120/76	88	6·600	
115	Sch P.(D)	20	210/84	91	5·350	(1)	20	0	170/80	86	6·200		(2)	19	−1	180/70	90	6·250		(3)	19	170/84	90	7·650	
116	Sch S.	15	180/130	101	5·180	(3)	16	+1	190/120	104	10·750		(2)	19	+4	210/120	97	10·300	P, O	(1)	15	200/120	96	8·350	
117	Inv. Mel.	26	180/110	98	9·500	(2)	25	−1	140/90	97	7·400		(1)	25	−1	100/70	96	8·250	F, O	(3)	25	180/100	94	9·400	
118	Sch S.	16	160/80	100	6·960	(1)	17	+1	150/80	92	6·300		(3)	16	0	140/80	99	6·200	F	(2)	16	150/80	97	5·800	
119	Sch C.	18	210/110	99	8·450	(2)	19	+1	170/90	93	5·400		(3)	19	+1	160/100	96	7·250		(1)	19	160/90	93	7·950	
120	Sch P.	18	170/100	93	6·100	(1)	9	−1	136/76	88	5·300		(2)	13	+3	120/68	84	6·950		(3)	9	140/80	92	6·200	
121	Sch S.	10	112/72	93	7·800	(3)	11	−3	130/76	90	9·350		(2)	15	+1	130/80	93	8·400		(1)	14	130/70	91	9·600	
122	Sch S.	14	120/80	92	5·560	(2)	25	+1	130/90	95	4·800		(1)	27	+3	140/110	88	5·500	F	(3)	22	140/100	96	3·500	
123	Sch P.	24	130/80	97	5·775	(1)	17	+2	170/100	89	8·100	O	(3)	15	0	160/120	94	7·400		(2)	15	160/120	97	7·025	
124	Sen. Psy.	15	210/120	104	7·150	(3)	18	+1	150/90	102	5·800		(3)	16	−1	150/90	94	6·450	F	(1)	17	170/100	88	8·100	
125	Sch P.	17	200/100	94	8·250																				

Diagnosis:
Sch = Schizophrenia
C = Catatonic
S = Simplex
H = Hebephrenic
P = Paranoid
Inv. Mel. = Involutional Melancholia
M-D = Manic-Depressive Disease
Sen. Psy. = Senile Psychosis
(D) = Dementing, due to senile change

CODE
Order = Order in which drug was given, 1st, 2nd, 3rd.
P.B.R.S. = Points of Parkside Behaviour Rating Scale.
B.P. = Blood Pressure.
Hb. = Haemoglobin per cent.
W.B.C. = White Blood Cell count.
Side-Effects:
D = Drowsiness.
F = Fainting.
I = Incontinence.
O = Oedema, Ankles or Face.
P = Parkinsonian Symptoms.
V = Vomiting.

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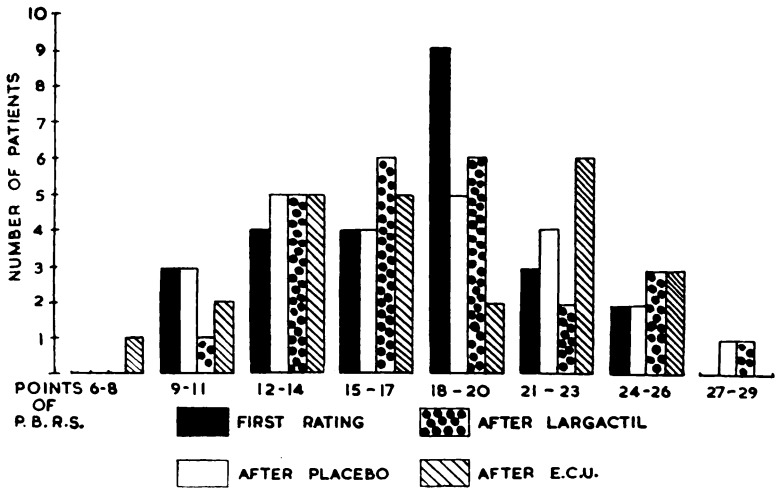


FIG. 4.—Rating and re-rating of trial cases following (1) Placebo, (2) Chlorpromazine (3) Ethylcrotonylurea.

of this order occurred in only four cases, the change being analysed as follows:

Case 103. The patient maintained a significant improvement after all three drugs, and since the first drug administered was the placebo, it was considered that the improvement was due to the extra attention given to the patient as a result of the trial, rather than to any pharmacological effect.

Case 109. The patient showed a significant improvement after the placebo only. This, again, was the first drug administered, and the patient who was a chronic involutional depressive stated that she felt more lively after it. At the end of the trial, however, she said that she felt much better when she was not taking any tablets at all!

Case 113. This was a manic-depressive patient who became significantly worse after the placebo, after a gradual deterioration whilst taking the other two drugs, this downward course being due to a natural swing in her illness.

Case 114. This patient became very disturbed, impulsive and offering sudden violence to others. She was a hebephrenic who was subject to periodic outbursts of this kind. This episode started while she was on chlorpromazine, which did not help her in any way, and continued when the drug was changed to ethylcrotonylurea. In the end, she had to be given electrical treatment, and this produced a seven-point improvement in P.B.R.S., but she was still significantly worse at the end of the trial.

SIDE-EFFECTS

1. *General*

All side-effects, however minor, were recorded. These consisted of:

Drowsiness	Vomiting
Faintness	Parkinsonian symptoms
Oedema (ankle or face)	Incontinence of urine

and were shown by eleven cases out of the twenty-five.

In eight cases, the side-effects occurred during chlorpromazine administration and consisted of drowsiness, faintness, oedema of the ankles and face, vomiting, and Parkinsonian symptoms. Of the two cases on ethylcrotonylurea showing side-effects, one patient had a previous incontinence which became somewhat worse whilst she was taking this drug; the other case had an increase in ankle oedema which was present beforehand. It is therefore probable that these side-effects had nothing to do with the drug. The remaining case showed an increased tendency to ankle oedema whilst on the placebo, this being due to cardiovascular degeneration.

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Thus, our experience confirmed the widely held impression that chlorpromazine carries a high risk of side-effects—in this series of cases 30 per cent. of patients were affected whilst on this drug, and included all the more severe reactions of those listed above.

Ethylcrotonylurea, on the other hand, appeared to be devoid of side-effects.

2. *Blood-pressure Recordings*

The general picture of the blood-pressure readings is one of lability. Readings were all taken under normal day-to-day conditions, without any special precautions, and in the sitting position. Only marked fluctuations are considered.

In three patients (Cases 119, 124, and 125) the initial blood-pressure was much higher than that during the administration of any of the drugs. This may have been due to the psychological stress of the first blood-pressure examination. In one patient (Case 111) there was a marked fall after ethylcrotonylurea, but this appears to have been due to a continued improvement in the patient who was a paranoid schizophrenic, over the period of the trial, irrespective of the drug taken, the ratings being plus 1 after chlorpromazine, plus 3 after the placebo, and plus 4 after ethylcrotonylurea. There was one marked fall after chlorpromazine (Case 117) and one gain (Case 116). In three other patients (Cases 102, 112, and 113), blood-pressures were higher on the placebo tablets than at the initial rating or after the other drugs.

Thus, it is fairly clear that, in the present series at any rate, there were no marked pharmacological effects on blood-pressure. The expected fall with chlorpromazine did not occur, nor were any significant changes in blood-pressure found with ethylcrotonylurea.

3. *Haemoglobin Estimations*

These revealed no significant changes with any of the drugs, the average level varying between 92 per cent. and 95 per cent., the lower figure appearing in the chlorpromazine series.

4. *White Cell Counts*

Average white cell counts varied between 6,660 and 7,340, the lesser figure following the placebo and the greater figure occurring after the chlorpromazine, this higher average being partly due to two patients (Cases 114 and 116) both of whom had a white cell count of over 10,000. In Case 114 the cause of this leucocytosis was not apparent, but Case 116 suffered from sun-burn blisters which took some time to clear, and the leucocytosis persisted during the administration both of chlorpromazine and the placebo tablets.

There were no significant alterations in white cell counts arising during the administration of ethylcrotonylurea with the exception of Case 123, who showed a gradual reduction in the count throughout the trial. This could have been initiated by chlorpromazine, but certainly continued during the administration of the placebo. Despite this rather low count, the patient has remained in good physical health and the latest white cell count, taken several months after the completion of this trial and after the prolonged administration of chlorpromazine, was 6,150, the differential count being normal.

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Discussion

Several facts emerge from an analysis of the results in this comparison of ethylcrotonylurea, chlorpromazine and placebo.

Ethylcrotonylurea is a safe drug when administered within the limits recommended by the manufacturer, namely, in doses of up to 1,200 mg. per day. There have been no side-effects which could have been attributed unequivocally to the drug, nor have there been alterations in blood-pressure or haemopoiesis.

On the other hand, ethylcrotonylurea does not appear to have any specific pharmacological effect on chronic psychotic illness, but in this respect, at any rate as far as this trial goes, it cannot be differentiated significantly either from chlorpromazine or placebo.

This tends to confirm the present trend of opinion that factors other than pharmacology may have been responsible for the improvement of patients seen in recent years, and previously wholly attributed to drugs such as those of the phenothiazine series. In this trial, the only patient who maintained a significant improvement (Case 103) did so during the administration of the placebo.

It cannot be too strongly stressed, however, that the group of patients under consideration are psychotic cases of long standing who have already had most of the modern treatments known to psychiatry, including the so-called tranquillizing drugs, and are in their present condition because they have failed to respond to any of these treatments. They therefore represent a highly selected group, and it is not surprising that they fail to show any significant overall improvement.

Summary

A study is reported of the effect of a new tranquillizing drug, ethylcrotonylurea, on a representative group of chronic psychotic patients by means of a double-blind controlled trial, as compared with chlorpromazine and a placebo.

Alterations in behaviour were assessed objectively by means of the Parkside Behaviour Rating Scale.

A parallel rating of a similar group of 30 control cases was made at the beginning and the end of a twelve-month interval which covered the period of the trial. From observations on this group it could be concluded that there had been no significant alteration in the behavioural characteristics of the chronic hospital population over this period.

Observations were made on side-effects, blood-pressure, haemoglobin levels and white cell counts.

From this study, it is concluded that ethylcrotonylurea is a safe drug when administered in doses of up to 1,200 mg. per day, but that it produces no significant improvement in the behaviour of chronic psychotic patients whose stay in hospital had varied between 6 and 49 years.

Studies of the effects of chlorpromazine tended to confirm the recent trend of opinion that this drug is also of little use in the treatment of this category of patient. Undesirable side-effects followed its administration in more than 30 per cent. of cases, and no patient showed any significant improvement in mental state which could be attributed to this drug.

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