falciparum in the peripheral blood of these patients is noteworthy in view of the frequency with which this parasite is encountered in blood-film surveys in Uganda.

Clinically these patients do not show any specific diagnostic features apart from marked splenomegaly and a lesser degree of hepatomegaly with evidence of secondary hypersplenism and a short red-cell life. Holzbach *et al.* (1964) have shown that increased red-cell sequestration in the spleen correlates with an increase in splenic size regardless of the underlying cause of the splenomegaly. The association of haemolytic anaemia in pregnancy with splenomegaly, hepatic sinusoidal changes, and a raised malarial antibody titre has also been noted at Mulago (Gebbie *et al.*, 1965, in preparation). Finally, it must be mentioned that the specificity of the malaria antibody test used here is still not precisely delineated. Also the scanty *P. malariae* parasitaemia could be a result rather than the cause of this marked splenomegaly.

Summary

Patients with large spleens are common in the wards at Mulago Hospital, 64 being investigated in a period of eight months. Like previous workers, we could find no cause for many of the enlarged spleens. An unusual liver-biopsy appearance with sinusoidal infiltrates of lymphocytes and plasma cells was noted in many of the patients in the "idiopathic" group. Most of these patients were anaemic, and Leather's finding of an increased intrasplenic pressure in such cases was confirmed.

In a group of patients with sinusoidal infiltrates *P. malariae* trophozoites were found in the peripheral blood of 45% of patients after a prolonged search and malarial antibody titres were elevated when compared with control groups. There is therefore a suggestion that *P. malariae* is implicated in a number of such cases in Uganda, and also that the liver biopsy may be helpful in the diagnosis of this syndrome. The relationship between splenomegaly, these hepatic findings, and infection with quartan malaria requires further study.

ADDENDUM.—Since this paper was written eight rhesus monkeys with chronic malarial infections of one to ten years' duration have had liver biopsy specimens examined. These represented simian infections of quartan and vivax types. Only one showed histological changes resembling those described in this paper. This monkey had had the infection for the longest time—namely, 10 years—with *Plasmodium inui*. Studies on monkeys with long-standing infections are being continued.

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Comparative Clinical Evaluation of Chlordiazepoxide and Promazine in Treatment of Alcohol-withdrawal Syndrome

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Withdrawal from a prolonged state of alcohol intoxication is characterized by a variety of symptoms, some of which merely produce discomfort to varying degrees, while others constitute a potential hazard to life (Johnson, 1961). The principal sources of discomfort are sleeplessness, agitation, tremor, sweating, anorexia, nausea, and vomiting. A variable proportion of patients in the withdrawal state, approximately 10% of those seen in the clinic of this Foundation, develop more dangerous complications, including grand-mal seizures and delirium tremens.

The objectives of treatment for the withdrawal state are principally the amelioration of discomfort arising from the causes mentioned and the prevention of the more serious hazards. In recent years a succession of treatments have been employed, the classical sedatives being replaced to a considerable

extent by insulin therapy, and still later by tranquillizers. The replacement of an old treatment by a new one should logically occur only if the new treatment can be shown clearly and objectively to offer advantages over the old. There has been very little objective evaluation of any of the methods employed in the treatment of the alcohol-withdrawal syndrome. The most recent addition to the drug therapy for this condition has been chlordiazepoxide (Librium). To the best of our knowledge there has been no adequately controlled comparison between the efficacy of chlordiazepoxide and that of the various tranquillizers previously in vogue. The present study was therefore devised with two principal purposes: (1) to evaluate the effectiveness of chlordiazepoxide in the treatment of the withdrawal syndrome, in comparison with a typical phenothiazine tranquillizer (promazine: Sparine) and with placebo treatment; and (2) to evolve objectively quantifiable methods which would be applicable to the evaluation of other new drugs that might be proposed for the treatment of alcohol-withdrawal symptoms.

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Methods

Patients.—The subjects taking part in this study were 58 male alcoholic patients aged 28 to 59 years, all of whom entered the clinic voluntarily. The majority had been drinking up to the time of admission to the clinic; however, 17 of them had stopped drinking 10 hours or more before first being seen. The preceding period of heavy drinking had varied from five days up to several months. A few of the patients had palpably enlarged livers, but none had definite clinical evidence of cirrhosis. No patients were included in the study who showed definite evidence of any organic lesions other than those directly attributable to alcoholism.

Treatments.—The patients were assigned by rotation, according to the order of admission, to five treatment groups. The five treatments consisted of capsules containing, respectively, chlordiazepoxide 25 mg., chlordiazepoxide 50 mg., promazine 50 mg., promazine 100 mg., and placebo. All capsules were identical in size and appearance. The treatment schedule consisted of two capsules at 8 a.m., at noon, at 4 p.m., and at 10 p.m., so that the total daily dosage was chlordiazepoxide 200 or 400 mg., promazine 400 or 800 mg., or placebo.

The capsules were assigned code letters, their identities remaining unknown to the clinical staff until after completion of the study.

Measurements

Sleep.—The percentage of time slept was evaluated by the method described by Lasagna (1954). The patient was observed every half-hour, day and night, to see whether he was awake or asleep. According to the finding at each check, the patient's record was credited with a half-hour of either sleep or wakefulness. The total time slept was expressed as a percentage of the total time of the period of observation. For reasons extraneous to the design of the study, the observations recorded between midnight and 7 a.m. were thought to be of questionable reliability and were therefore excluded. The values presented below refer to the observation period from 7 a.m. to midnight each day.

Blood-pressure and Pulse Rate.—Both blood-pressure and pulse rate were measured with the patient sitting in a chair. Blood-pressure was measured by means of a mercury sphygmomanometer, and the pulse rate by direct palpation.

Tremor.—Hand-tremor frequency was measured by means of a photoelectric tremometer specially devised for this study (Llewellyn-Thomas, 1962). Spontaneous tremor was measured with the elbow, wrist, and fingers extended, the fingers slightly separated, and the arm abducted from the body and unsupported. The tremor recording is therefore a composite of shoulder, arm, and hand tremor. Intention tremor was measured with the arm again extended and unsupported, but with the patient holding in his hand a knife, which he was instructed to keep in such a position that the knife blade occluded one-half of the photocell aperture of the tremometer. Continuous recordings were made for a period of 30 seconds.

Skin Resistance.—This was measured by means of a Simpson galvanometer. The finger electrodes were placed on the second and third digits of the right hand, the fingers being held apart to avoid contact between the electrodes. The patient was instructed to place his hand on the table, palm downward, and press firmly to ensure good electrode contact and prevent tremor. Skin-resistance readings were taken in ohms, but for comparative purposes in the evaluation of treatment effects the logarithm of the direct reading was employed.

Calorie Intake.—The patient's food and fluid intake were recorded throughout the 24-hour period, and the calorie value was obtained by conversion from standard food charts.

Experimental Procedure

On admission each patient was questioned concerning the duration of his drinking bout, and the time of his last alcohol intake. He was then given a complete physical examination, and the tests listed above were carried out. Treatment was begun after completion of the tests, and was continued for 72 hours after the first examination. The experimental test procedures were repeated twice daily, two hours after the nearest preceding treatment. In most cases this meant that the tests were carried out at 10 a.m. and 6 p.m., but in a few cases, principally over week-ends, the afternoon testing was at 2 p.m. rather than 6 p.m.

For the period of the experiment the patients were confined to bed except for bathroom privileges and for the testing sessions described above. They had no access to radio, T.V., or other entertainments, and were in communication with not more than two other patients undergoing acute treatment. No medication other than the capsules under investigation was given to the patients on this study unless they developed delirium tremens or convulsions, in which case their participation in the study was terminated and the appropriate medication was employed. To meet the requirements of the experimental design, patients who developed these complications were not included in the results of the study unless the episode of delirium tremens or the convulsion occurred on the last day of the observation period.

Results

Sleep

It can be seen from Table I that all four drug treatments were more effective than the placebo in increasing the percentage of time slept, at some point during the study. On the first day the relative order of effectiveness of the various drug treatments was promazine 200 mg. > promazine 100 mg. = chlordiazepoxide 100 mg. > chlordiazepoxide 50 mg. However, there appeared to be a steady decrease in the effectiveness of promazine in this regard from the first to the third day. In contrast, chlordiazepoxide, particularly the larger dose, maintained its effect relatively unchanged.

TABLE I.—Comparison of Treatment Effects on Percentage of Time Spent Sleeping

Treatment*	% Time Slept	P Values for Between-Group Differences				
		Plac	Chl 50	Chl 100	Pro 100	Pro 200
Day 1						
Plac	10.6	—				
Chl 50	22.5	N.S.	—			
Chl 100	35.9	<0.01	N.S.	—		
Pro 100	37.7	<0.005	<0.05	N.S.	—	
Pro 200	59.5	<0.001	<0.001	<0.02	<0.02	—
Day 2						
Plac	4.7	—				
Chl 50	15.5	<0.02	—			
Chl 100	26.6	<0.02	N.S.	—		
Pro 100	19.7	<0.01	N.S.	N.S.	—	
Pro 200	31.6	<0.001	<0.01	N.S.	N.S.	—
Day 3						
Plac	6.0	—				
Chl 50	12.4	N.S.	—			
Chl 100	27.9	<0.01	<0.01	—		
Pro 100	12.7	N.S.	N.S.	<0.02	—	
Pro 200	15.9	N.S.	N.S.	N.S.	N.S.	—

* The following abbreviations are employed in all tables to designate the various treatment groups: Plac = Placebo. Chl 50 = Chlordiazepoxide, 50-mg. dose. Chl 100 = Chlordiazepoxide, 100-mg. dose. Pro 100 = Promazine, 100-mg. dose. Pro 200 = Promazine, 200-mg. dose.

Blood-pressure and Pulse Rate

Fig. 1 illustrates the change in group mean values for systolic blood-pressure and pulse rate during the whole course of the experiment. The maximum differentiation between the various treatment groups was observed at the second observation period after the start of treatment. A statistical analysis was made of the results at this time, and at the sixth observation (Table II). It can be seen from these results that all four drug treatments

lowered the systolic blood-pressure in comparison with the placebo group. However, chlordiazepoxide produced this hypotensive effect gradually and progressively, while the effect of promazine was abrupt and immediate. At the second observation during the period of treatment it can be seen that promazine caused a significantly greater fall in blood-pressure than either dose of chlordiazepoxide or the placebo. There was no appreciable difference between the effects produced by the high and low doses of promazine, or between the high and low doses of chlordiazepoxide. By the sixth observation all four drug treatments caused a significantly lower blood-pressure than the placebo, but did not differ from each other.

A further comparison between the various treatments was made in terms of the frequency of occurrence of potentially dangerous hypotensive reactions. Such reactions were defined as those episodes in which the systolic blood-pressure fell to an arbitrarily selected level of 100 mm. of mercury or less. As shown in Table III, promazine 200 mg. caused more such reactions than any other treatment group, while chlordiazepoxide 100 mg. also produced significantly more reactions than

did the placebo.

At the second observation after the start of treatment both doses of promazine were found to raise the pulse rate significantly in comparison with the placebo. Both doses of chlordiazepoxide also raised the pulse rate in comparison with the placebo group, but the difference was not statistically significant (Table IV).

TABLE IV.—Change in Pulse Rate Between Admission and Second Observation During Treatment Period

Treatment	Plac	Chl 50	Chl 100	Pro 100	Pro 200
Mean change (beats/min.)	-10.3	-1.7	-8.3	+13.5*	+12.8*

* Significantly higher than placebo ($P < 0.05$ in each case).

Tremor

The changes in frequency of spontaneous tremor and intention tremor during the period of treatment, expressed as differences from the corresponding admission values, are illustrated in Figs. 2 and 3. Statistical analysis of these differ-

FIG. 1.—Effect of treatments on mean values for brachial systolic blood-pressure and pulse rate in relation to pretreatment values. Patients were in the sitting position during measurements. Treatments: ○—○ placebo; ○—● chlordiazepoxide 200 mg. daily dose; ●—● chlordiazepoxide 400 mg.; ●—● promazine 400 mg.; ●—● promazine 800 mg.

TABLE II.—Change in Systolic Blood-pressure from Admission Values with Treatment

Observation	Treatment	Mean Change (mm. Hg)	P Values for Significant Differences
Second	Plac	+1.9	
	Chl 50	-5.7	
	Chl 100	-12.9	
	Pro 100	-32.0	Plac, < 0.05 ; Chl 50, < 0.01
	Pro 200	-32.4	Plac, < 0.01 ; Chl 50, < 0.01
Sixth	Plac	-2.0	
	Chl 50	-27.8	Plac, < 0.01
	Chl 100	-28.7	Plac, $= 0.05$
	Pro 100	-31.7	Plac, < 0.05
	Pro 200	-31.6	Plac, < 0.05

TABLE III.—Occurrence of Hypotensive Episodes in Various Treatment Groups*

Treatment	Episodes	Observations	P Values for Group Differences				
			Plac	Chl 50	Chl 100	Pro 100	Pro 200
Plac	1	48	—	—	—	—	—
Chl 50	8	102	N.S.	—	—	—	—
Chl 100	10	83	< 0.04	N.S.	—	—	—
Pro 100	7	79	N.S.	N.S.	N.S.	—	—
Pro 200	18	78	< 0.001	< 0.02	N.S.	< 0.02	—

* Hypotensive episode is defined as a systolic pressure of less than 100 mm. Hg. the sitting position.

FIG. 2.—Effect of treatments on mean values for spontaneous tremor frequency in relation to pretreatment values. Treatments indicated as in Fig. 1.

FIG. 3.—Effect of treatments on mean values for intention tremor frequency in relation to pretreatment values. Treatments indicated as in Fig. 1.

ences at the second observation during treatment showed that the high dose of promazine significantly decreased the frequency of spontaneous tremor in comparison with both doses of chlordiazepoxide and with the placebo (Table V). Because of wide variation within groups, this effect of promazine was not demonstrable in terms of the mean group values for tremor frequency. However, it was revealed by the fact that a fall in tremor frequency occurred in most of the patients receiving promazine 200 mg., while most of those receiving chlordiazepoxide or placebo showed a rise in tremor frequency. By the sixth observation the variation within groups had diminished and significant group differences in mean tremor frequency were demonstrable: in the promazine groups the frequency remained at admission levels, while in the other groups it rose, especially on the high dose of chlordiazepoxide (Table V).

TABLE V.—*Change in Frequency of Spontaneous Tremor from Admission Values*
2nd Observation

Treatment	% of Group Showing Increased Frequency	P Values for Group Comparisons				
		Plac	Chl 50	Chl 100	Pro 100	Pro 200
Plac	100	—	—	—	—	—
Chl 50	90	N.S.	—	—	—	—
Chl 100	89	N.S.	N.S.	—	—	—
Pro 100	72	N.S.	N.S.	N.S.	—	—
Pro 200	44	<0.01	<0.04	<0.04	N.S.	—

6th Observation

Treatment	Mean Change (beats/min.)	P Values for Group Comparisons				
		Plac	Chl 50	Chl 100	Pro 100	Pro 200
Plac	+14	—	—	—	—	—
Chl 50	+10	N.S.	—	—	—	—
Chl 100	+24	N.S.	<0.025	—	—	—
Pro 100	-1	N.S.	N.S.	<0.025	—	—
Pro 200	+1	<0.05	<0.025	<0.001	N.S.	—

Because of large variations within groups, there were no significant differences between the treatment groups with respect to intention tremor until the sixth observation. At this point the mean frequency for the group on the high dose of chlordiazepoxide was significantly higher than that for the group on the high dose of promazine ($P < 0.05$). There were no other significant differences between groups.

Skin Resistance

The change in log skin resistance from the admission value to the second observation during the treatment period is shown in Table VI. All four drug treatments tended to increase the log skin resistance, but because of fairly wide individual variations within groups, the only statistically significant increase was shown by promazine 200 mg., in comparison with both doses of chlordiazepoxide and with the placebo.

TABLE VI.—*Change in Log Skin Resistance from Admission to Second Observation During Treatment*

Group	Mean Change (log units)	P Values of Group Differences				
		Plac	Chl 50	Chl 100	Pro 100	Pro 200
Plac	-0.110	—	—	—	—	—
Chl 50	+0.051	N.S.	—	—	—	—
Chl 100	+0.177	N.S.	N.S.	—	—	—
Pro 100	+0.402	N.S.	N.S.	N.S.	—	—
Pro 200	+0.723	<0.001	<0.001	<0.005	N.S.	—

Calorie Intake

In Table VII are shown the mean calorie intakes for the various treatment groups on each of the three days of treatment. Because of wide individual variations within groups, there were no significant differences between groups. However, the

tendency was toward a greater food intake by the placebo group than by other treatment groups.

TABLE VII.—*Calorie Intake During Three Treatment Days*

Group	Mean Calorie Intake		
	Day 1	Day 2	Day 3
Plac	1,500	2,780	2,640
Chl 50	1,380	2,480	2,450
Chl 100	1,550	2,420	2,450
Pro 100	1,220	2,610	2,780
Pro 200	1,180	2,430	2,620

Convulsions and Delirium Tremens

During the whole period of the study one patient in the placebo group developed delirium tremens. In the promazine 100-mg. group two patients suffered grand-mal seizures, and one patient developed delirium tremens. Two patients on the promazine 200-mg. dose suffered grand-mal seizures. None of the patients on either dose of chlordiazepoxide developed convulsions or delirium tremens.

Qualitative Observations

The clinical staff participating in this study were unable to detect any appreciable difference between the various treatment groups, including the placebo group, with respect to evident well-being and behaviour of the patients. Their attempts to identify the placebo treatment in retrospect, after conclusion of the study, were quite erroneous.

Discussion

As indicated in the introduction to this paper, treatment of the alcohol-withdrawal syndrome is aimed both at alleviation of discomfort and at the prevention, so far as is possible, of the potentially dangerous complications. Since the illness is of relatively short duration and seldom fatal, the value of a treatment must be judged by its speed and effectiveness in achieving these goals and its freedom from new hazards. In the evaluation of therapy, drug-induced hazards should not be taken lightly. From the results presented above it is evident that the 200 mg. dose of promazine achieved the greatest beneficial effect with respect to certain of the signs, but also introduced the greatest hazard.

The most important of the beneficial effects produced by all four drug treatments was an increase in the percentage of time slept. On the first day the large dose of promazine produced the greatest benefit. However, as can be seen in Fig. 4 A, the log dose-response lines for chlordiazepoxide and for promazine were virtually continuous with each other within the limits of experimental error. Therefore the two drugs must be considered equally potent, milligram for milligram, on the first day. It is noteworthy, however, that the dose-response line for chlordiazepoxide continued virtually unchanged on the second and third days, while there was a striking decrease in both the absolute level and the slope of the dose-response line for promazine on each of the succeeding two days. On the second day promazine appeared to be only about 60% as potent as chlordiazepoxide and on the third day only about 34% as potent. These changes indicate a rapid development of tolerance to promazine, with corresponding loss of therapeutic value.

The same sequence of changes is demonstrated by the measurements of skin resistance. While skin resistance is the resultant of various factors, it is probably most closely dependent upon the extent of sweating. The findings in Table V are therefore taken to indicate that all four treatments resulted in a decrease in sweating in comparison with the placebo group.

In this respect there is again a clear diminution of effectiveness of promazine from the first to the second and from the second to the third days of the study. On the first day promazine appeared to be approximately 50% more effective than chlordiazepoxide; on the second day they were virtually of equal potency; while on the third day promazine was less than half as potent as chlordiazepoxide, which continued to show essentially the same activity throughout the study (Fig. 4 B).

The progressive development of tolerance to some of the effects of phenothiazines has been noted by other investigators. Kornetsky *et al.* (1959) observed that a single test dose of 200 mg. of chlorpromazine produced significant impairment of performance on a group of psychomotor tests; after continuous treatment with 200 to 400 mg. daily for 11 days, the same test dose no longer impaired performance. Denham and Carrick (1961) reported that thiopropazine, 5 mg. t.i.d., initially caused marked somnolence, but after two to four days of continuous treatment this effect disappeared. The progressive loss of effect of promazine upon sweating has not, so far as we are aware, been reported previously. This rapid development of tolerance is evidently selective, since it was not observed with respect to the other effects of promazine in the present study, and is not ordinarily encountered in the antipsychotic use of phenothiazines.

The effects of treatment upon tremor showed a somewhat different pattern. Intention tremor was not significantly bene-

fited by any of the treatments, and the reason for this lack of effect is not clear. In contrast, spontaneous tremor was significantly ameliorated by both doses of promazine, and this beneficial effect was sustained throughout the period of observation (Fig. 4 C). Chlordiazepoxide was relatively ineffective with respect to spontaneous tremor at the beginning of the study, but the high dose appeared actually to increase both spontaneous and intention tremor throughout the period of treatment, so that at the last observation the frequency of both types of tremor was significantly higher in the chlordiazepoxide 100-mg. group than in the other active treatment groups. This finding is in keeping with the reported production of ataxia by large doses of chlordiazepoxide (Randall *et al.*, 1960; Tickin and Schultz, 1960; Roy *et al.*, 1963; Koutsy and Sletten, 1963).

Among the undesirable and potentially dangerous effects of all four treatments the most consistent and frequent were the production of hypotension and associated tachycardia. It may be that hypotension, by producing a feeling of weakness and giddiness, contributes in part to the sedative effect, since the patients are not anxious to get out of bed. However, this is a dangerous manner of achieving the goal, because of the risk of coronary or cerebral vascular thromboses occurring during hypotensive incidents, especially in older patients with vascular lesions (Witton, 1961). Promazine appeared to be much more potent than chlordiazepoxide in this respect, since both doses produced an almost immediate and virtually equal effect. This indicates that both doses employed were already past the rising phase of the dose-response curve and were on the plateau of maximal effect. In contrast, the fall in mean blood-pressure was much more gradual with chlordiazepoxide, and the frequency of occurrence of hypotensive episodes was lower. However, there were still significantly more such reactions in the chlordiazepoxide group than in the placebo group.

Chlordiazepoxide has been reported to increase food intake and weight gain in experimental animals (Randall *et al.*, 1960), and to increase the appetite in human patients (Baroody *et al.*, 1962; Chesrow *et al.*, 1962; Roy *et al.*, 1963). The present observations do not bear this out. Calorie intake tended to be higher, though not significantly so, in the placebo group than in the drug groups. It is not clear whether this is suggestive of a slight anorexiant effect or is merely a reflection of the fact that those in the drug groups slept more.

Because of the small numbers of patients suffering grand-mal seizures or delirium tremens no statistical comparison was made between groups with respect to the frequency of these complications. It is noteworthy, however, that while there were no such cases in the two chlordiazepoxide groups one case occurred in the placebo group and five cases in the two groups receiving promazine. These observations are in harmony with the reported anticonvulsant effect of chlordiazepoxide (Randall *et al.*, 1960) and the lowering of the convulsive threshold by promazine and various other phenothiazines (Fink and Swinyard, 1960).

Of the beneficial effects obtained by drug therapy in this experiment, the most important is the increase in sleep compared with the placebo group. In this respect the two drugs appear equally potent on the first day, but promazine loses its effectiveness rapidly, while chlordiazepoxide seems to maintain its potency relatively unchanged for several days. For this reason, together with its lower tendency to produce serious hypotensive episodes and its apparently greater ability to prevent complications in the central nervous system, chlordiazepoxide is superior to promazine in the treatment of the alcohol-withdrawal syndrome. However, it should be noted that the tendency to produce increased frequency of tremor with prolonged treatment is an undesirable characteristic, and the number of hypotensive reactions produced, while lower than with promazine, is not negligible.

The problems inherent in the clinical evaluation of psychopharmacological agents, such as the drugs employed in

FIG. 4.—Comparative dose-response lines for chlordiazepoxide (●—●) and promazine (○---○). (A) Percentage of time spent in sleep. (B) Electrical resistance of skin, as change from admission values, corrected for change in placebo group. (C) Spontaneous tremor frequency, as change from admission values, corrected for change in placebo group. Comparative potencies of the two drugs with respect to a given criterion on a given day can be assessed roughly by reading the doses corresponding to the same level of effect. In some cases this requires extrapolation of one of the dose-response lines.

the present study, have been outlined by Chessick and McFarland (1963). They emphasize the need for carefully controlled observations and for quantitative comparisons of new drugs with those previously in use. Within the past three years numerous reports have appeared of clinical trials of chlordiazepoxide in the treatment of alcohol-withdrawal symptoms, claiming highly beneficial results of the drug. A number of these studies (Ticktin and Schultz, 1960; Cohen, 1961; Baroody *et al.*, 1962; Roy *et al.*, 1963; Drolet *et al.*, 1963; Margat and Creton, 1963) illustrate the difficulties in the interpretation of uncontrolled observations. None of them included a control group, either placebo or an alternative form of therapy. In all of them the patients were given varying amounts of other drugs at the same time as chlordiazepoxide, so that it is impossible to determine the relative contributions of the various agents used, or to rule out a placebo effect. No objectively measurable criteria were employed for evaluating the effect of treatment, and in some of the reports the criteria are not even defined.

A report by Koutsy and Sletten (1963) illustrates the futility of such uncontrolled studies: in uncontrolled preliminary trials of chlordiazepoxide they gained the impression that it was an excellent agent for the treatment of alcohol-withdrawal symptoms, but in a subsequent double-blind study they came to the conclusion that it was no better than saline solution. Rosenfeld and Bizzoco (1961) conducted an apparently well-designed double-blind controlled study which indicated that chlordiazepoxide was significantly better than placebo. However, they did not describe the criteria by which the response was assessed, nor did they compare the effect of chlordiazepoxide with that of other drugs currently in use.

Such considerations are of great importance in reaching a valid conclusion about the relative merits of different drug therapies, or even the real usefulness of any of the drugs available. The findings of the present study suggest that the benefits produced by the active drugs added only slightly to the major benefits produced by the therapeutic environment. All the placebo patients were able to carry on through the three days of the study with no serious ill effects except for one case of delirium tremens. They slept moderately well at night (data not included here), and ate at least as well as the patients in the active drug groups. As noted above, the clinical staff were unable to detect any difference in their behaviour or apparent well-being in comparison with the other groups. It may well be that the placebo effect of giving any type of medication is an important part of the therapeutic environment for alcoholic patients (Bartholomew and Guile, 1961). If this is so, it is all the more important to weigh carefully any additional benefit conferred by an active drug against the hazards which it may involve.

The techniques employed in the present study appear to have been quite adequate for the purposes outlined. The methods employed for objective quantitative assessment of response consumed very little more of the physician's time than would have been required for ordinary clinical observation. Together with the double-blind organization of the study, they effectively prevented the introduction of personal bias into the assessment of the drug effects. This pattern of investigation should be equally useful for the future study of other types of therapy which may be introduced for the alcohol-withdrawal syndrome.

Summary

A double-blind comparative evaluation was made of placebo, chlordiazepoxide, and promazine for the treatment of withdrawal symptoms in 58 male alcoholics admitted to hospital within 24 hours of their last drink. Chlordiazepoxide was given in total daily doses of 200 and 400 mg., and promazine in doses of 400 and 800 mg. The five treatment groups were compared with respect to hours of sleep, blood-pressure, pulse rate, spontaneous and intention tremor (measured photoelectrically), electrical resistance of the skin, and calorie intake. Observations were made before the start of treatment and twice daily for three days on treatment.

Both promazine and chlordiazepoxide were more effective than the placebo in promoting sleep and diminishing sweating, but tolerance developed quickly to promazine while chlordiazepoxide remained effective. Promazine reduced tremor significantly, while chlordiazepoxide did not, or even increased it. Promazine rapidly produced a marked postural hypotension and compensatory tachycardia, while chlordiazepoxide caused a more gradual onset of hypotension. Neither drug improved the appetite compared with the placebo. Grand-mal seizures or delirium tremens occurred in five patients on promazine, one on placebo, and none on chlordiazepoxide.

Chlordiazepoxide appeared to be the better drug for the treatment of alcohol-withdrawal symptoms, but the total benefit produced by it constituted a relatively small addition to the placebo effect.

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