AN EVALUATION OF CHLORPROMAZINE ("LARGACTIL") IN PSYCHIATRY

By

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DURING the last two years, considerable interest has been aroused in the use of chlorpromazine in psychiatry, particularly on the Continent. A full report on the pharmacological properties of the drug appeared in 1953 (Courvoisier *et al.*), and a short account was given in the first paper describing the effects of chlorpromazine in the treatment of mentally ill patients in this country (Anton-Stephens, 1954). In that study, the drug was administered to patients in several diagnostic categories. A reduction in the disturbed behaviour of excited patients was observed, but considerable variation in response to the drug occurred. Small doses orally were ineffective, and a parenteral daily dosage of 200 mgm. was initially required to produce a clinical response.

This paper describes the results obtained in 42 female in-patients treated with chlorpromazine. Because many of the patients had previously or subsequently received other treatments, a limited comparison of the efficacy of chlorpromazine with electroshock, insulin, etc., may be made.

The patients, irrespective of diagnosis, were selected because they all showed increased and pathological psychomotor activity. They therefore represented serious nursing problems, and included patients showing such patterns of behaviour as severe restlessness, interference with and provocativeness towards other patients, destructiveness to clothing or bedding, window smashing, impulsive attempts at self injury, and assaults on staff or other patients. Many of these patients required nursing and management in single rooms, and their case papers recorded frequent occasions when seclusion was necessary.

METHODS

1. *Administration of chlorpromazine by mouth*

It was desired to gain further information on the effect of the drug given by mouth compared with parenteral administration. Several authors (Staehelin and Kielholtz, 1953; Delay, Deniker and Harl, 1952; Anton-Stephens, 1954), have reported that the effect differs according to the method of administration of the drug, the parenteral route being the more effective in producing a central inhibitory effect. In this series, if a patient was considered possibly to be showing some response to oral administration of chlorpromazine, the active tablets were replaced by dummy ones, unknown to the patient, and an equal period of observation on this regime instituted.

2. *Administration of chlorpromazine alone by injection*

Chlorpromazine was injected intramuscularly, diluted with an equal volume of N saline. This method was also applied in a small group selected from patients who had shown no response to oral administration.

3. *Administration of chlorpromazine by injection, combined with other drugs according to the technique of Deschamps (1952)*

This is named "artificial hibernation" on the Continent, and is really a form of prolonged narcosis. The central sedative effect of chlorpromazine is utilized to diminish the quantities of barbiturate needed to produce narcosis for a period of about 14 days.

https://doi.org/10.1192/bjp.100.421.882 Published online by Cambridge University Press

Group 1. Administration of chlorpromazine by mouth

Table I

Schizophrenia of less than 5 years' duration	8
Schizophrenia of more than 5 years' duration	6
Manic–depressive psychosis: mania	3
Manic–depressive psychosis: depression	3
Obsessive–compulsive state	1
Schizo–affective state	1
Total	22

The results in this group can be quickly dismissed. No observable alteration in the mental state or behaviour of any of these patients occurred, which could be directly attributed to chlorpromazine, administered orally in a daily dosage of from 75–300 mgm. The average daily dose was 150 mgm. Duration of treatment varied from 10–106 days, averaging 33 days. Side effects were commonly observed. Tachycardia occurred in 13 patients, and 8 patients complained of somatic symptoms, the commonest being giddiness, palpitations, lassitude, weakness, dry mouth, and thirst.

Three of the schizophrenics had shown temporary remissions following courses of insulin given at an earlier stage in their illnesses. Two schizophrenics and 1 depressed patient had responded temporarily to courses of electroshock, and 2 schizophrenics improved considerably following pre-frontal leucotomy carried out after completion of their courses of chlorpromazine.

Group 2. Administration of chlorpromazine by intramuscular injection

Table II

Classification by diagnosis

Schizophrenia of more than 5 years' duration	7
Schizophrenia of less than 5 years' duration	1
Manic–depressive psychosis: mania	8
Obsessive–compulsive state	1
Mixed puerperal state	1
Total	18

(Including 7 patients from Group 1, who had received chlorpromazine by mouth.)

The results in this group are shown in Table III.

Effects of intramuscular chlorpromazine on the mental state of excited patients

Half to one hour after an intramuscular injection of 50 mgm. of chlorpromazine the patient becomes drowsy and may even sleep, this effect being more pronounced during the first 2 or 3 days of treatment. This initial drowsiness soon wears off, being replaced by a general diminution of psychomotor activity. Manic patients become more subdued, restlessness and aggressiveness diminish, pressure of talk decreases, and rapport becomes possible, so that occupational therapy may be initiated when previously impossible. The general quietening effect on the patient permits easier management by the nurses, and greatly reduces the demands made on the nursing staff in the disturbed wards.

Delay and his colleagues report that the administration of chlorpromazine leads to a typical state (after the first 48–72 hours), which has been named the "4560 R.P. psychic syndrome" or "chemical lobotomy", because of its resemblance to the characteristic mental state following pre-frontal leucotomy. The patients are described as motionless and relaxed; staring, disinterested, and

TABLE III

Administration of chlorpromazine by intramuscular injection

Case No.	Age	Diagnosis	Duration of illness (years)	Response to earlier treatment	No. of days treated	Average daily dose (mgm.)	Response
1(T)	31	Schizophrenia	1	Transiently to electroshock	12+7	200	Indifference, with diminution of tension and impulsiveness during 1st course. Little or no result from 2nd course.
2(T)	43	Schizophrenia	6	Well to E.C.T. relapsing on discontinuance	56	200⟶50	Indifference with diminution of tension and hostility, although still deluded. Former aggressive outbursts controlled on maintenance dose of 50 mgm. daily.
3(T)	44	Schizophrenia	11	Nil	11	150	Reduction of agitation and restlessness not maintained on 300 mgm. daily p.o.
4	30	Schizophrenia	8	Ever-shortening remissions with E.C.T. and insulin	10+28	200⟶100	Recent leucotomy without improvement. After 200 mgm. c.p. daily, disappearance of aggression, with increased accessibility but lethargic and disinterested. Relapsed on discontinuing.
5	36	Mental defect. Schizophrenia	20	Nil (leucotomy)	14	200	Disappearance of aggressiveness, with increased accessibility. Now occupied and much improved in habits.
6	52	Schizophrenia	14	Nil (E.C.T.)	14	200	No effect on noisy, aggressive, and assaultive behaviour necessitating permanent nursing in side room.
7	30	Mental defect. Schizophrenia	7	——	42	200⟶100	From noisy, violent and senseless behaviour, became mute, tractable, and able to be occupied.
8	33	Schizophrenia	7	Very slight to insulin	28	50	Marked reduction of tension, with cessation of noisy outbursts, and lessening of preoccupations.
9(T)	66	Rec. mania	Present attack: 1½ years.	Nil to E.C.T.	7	150	Slight reduction in psychomotor activity not maintained on same dose p.o.
10(T)	57	Mental defect. Chronic mania	13	Temporarily to E.C.T.	48	200⟶50	Marked reduction in aggressiveness and overactivity. As good symptomatic improvement as with E.C.T.
11(T)	45	Rec. mania	Present attack: 1½ years.	——	48	200⟶100	Initial reduction in aggressiveness and overactivity. Effect maintained on smaller dose.
12(T)	45	Mental defect. Mania	Present attack: 9 months.	Nil to E.C.T. and narcosis	10	200	Temporary reduction in psychomotor activity followed by relapse after 7 days. No result from 300 mgm. daily by mouth.
13	58	Mania	35 Present attack 5 weeks	Responds to E.C.T.	7+7+7	75, 150, 300	No effect. Slight jaundice, and bilirubin in urine on maximum dose. Treatment stopped. Later responded to E.C.T.
14	27	Mania	1st attack. About 4 months	Nil to E.C.T.	60	50⟶200 ⟶50	Dramatic reduction in psychomotor activity following 50 mgm. chlorpromazine intravenously in 20 c.cm. N saline. Effect not maintained with later doses, but 200 mg. daily i/m controlled excitement. Patient remained well on 50 mgm. maintenance daily.
15	53	Mania	20 Present attack: 5 months	Temp. to narcosis	6	75⟶300	Slight reduction in psychomotor activity with 300 mgm. daily. No improvement after subsequent leucotomy. Four weeks after this, while on 150 mgm. c.p. by mouth, suddenly collapsed and died. Coronary thrombosis at autopsy.
16	33	Mixed psychosis	13	Transiently to leucotomy	15	100⟶200	Reduction of psychomotor activity with maintained improvement when drug stopped. Has remained stable for 6 weeks, and is fit for discharge.
17(T)	44	Obsessive–compulsive state	2½	Temporarily to E.C.T.	9	200	Slight reduction of tension and anxiety.
18	27	Puerperal state	9 weeks	Nil to E.C.T.	14	200	Doubtful reduction of resistive and restless behaviour, with relapse after 7 days treatment.

(T) = no response previously to chlorpromazine by mouth in dosage of from 75–300 mgm. per day.

remote, but not drowsy, and with consciousness unimpaired. They are disinclined to talk, and their responses are of the briefest. This state may perhaps be likened to the mental state described in patients suffering from encephalitis lethargica.

In this series of 18 patients, the state described above was observed in 4 patients only—all schizophrenics. It was not observed in manic patients.

The response to chlorpromazine is very variable and cannot be predicted. For example, cases with little or no response to daily doses of 300 mgm. were seen, as well as those showing or maintaining improvement on 50 mgm. daily. After some days of treatment, the initial beneficial effect may wear off, and the patient slowly relapses.

Results

In the 8 schizophrenics, some symptomatic improvement occurred in 7, and was very marked in 4.

Case 2.—This woman aged 43, became increasingly suspicious of her husband at the beginning of 1948, and accused him directly of misconducting himself. The illness progressively gathered momentum, so that when she came under treatment she was intensely paranoid, agitated and hostile, asserting that her husband was unfaithful to her, that the food was tampered with, and that she had been placed in hospital by her husband to get her out of the way. Her vision was very poor from extensive choroidoretinal degeneration with myopia, and she wore thick pebble lenses. This doubtless partially accounted for the numerous and ever-changing misidentifications she made in the ward, and which led to painful scenes as she abused and upset patient after patient. As long as she was receiving E.C.T. she remained fairly calm and friendly, but relapsed into her former state immediately this was stopped.

No effect on her mental state was observed after 1 month of 150 mgm. chlorpromazine daily by mouth compared with an equal period on dummy tablets. After receiving 200 mgm. chlorpromazine daily intramuscularly in divided doses she showed within 3 days the "chemical lobotomy" described by Delay. The dose was reduced to a single daily injection of 50 mgm. after 10 days, and she has remained quiet, friendly, and occupied ever since, although still extravagantly deluded. The result here has been as good as that obtained with E.C.T.

Case 4.—A University graduate aged 30 holding a degree in philosophy. She had been ill since 1944 with remissions of 7 years and 1 year following insulin comas. Her present (third) relapse dated from May, 1952, when insomnia, restlessness, self-reproach and suspicion were soon followed by an incoherent, hallucinated, semi-stuporose state. Her behaviour again changed to aggressiveness, smashing, assaults on staff, while disorder of thought and paranoid ideas were very marked. She was extremely hostile to her husband, a neurotic, rather inadequate academic individual, and much of this hostility seemed displaced on to the staff. Any attempt at contact with her would usually provoke an aggressive outburst.

Modified pre-frontal leucotomy was carried out in February, 1954 without much change in her condition, apart from some immediate post-operative apathy. She soon relapsed into her usually sullen, spiteful, and assaultive behaviour and had to be nursed in a side room. She was given 200 mgm. chlorpromazine daily parenterally, and on the 2nd day was already improved in behaviour. On the 4th day of treatment she was up and dressed, occupied, and permitted to visit the canteen. After 10 days treatment she was pleasant in manner and co-operative, although her conversation was incoherent at times, and delusions were still in evidence. She relapsed 4 days after the drug was stopped, and did not respond again when the drug was resumed in daily doses of 100 mgm.

Case 5.—A mental defective aged 36, with super-added schizophrenia of 20 years' duration. She hoarded large quantities of rubbish, becoming very aggressive when separated from her treasures. Sudden window-smashing and assaults upon the staff had lately become a feature of her behaviour. Pre-frontal leucotomy was performed in January, 1954 with improvement in her behaviour over the following three weeks. She then relapsed into a stubborn resistive state during the day, with noisy restlessness and incontinence at night. Window-smashing promptly followed, precipitated by the removal from her possession of much accumulated rubbish.

She was given 200 mgm. chlorpromazine intramuscularly daily, and on the 2nd day of treatment was tranquil and approachable, readily persuaded to get up and dress, and was usefully employed in the ward. Urinary and faecal incontinence ceased. She maintained her improvement when the drug was stopped after 2 weeks treatment.

Case 7.—Mental defective aged 30. Superimposed schizophrenia of 7 years' duration. She was always overactive—at her best noisy, erotic and childish, and at her worst, destructive,

abusive, and violent, dashing about the ward and upsetting (literally), the other patients. Her talk was full of strange phrases, and quite incoherent. After receiving 150 mgm. chlorpromazine i/m, she was very much more subdued by next day, and thereafter on 200 mgm. per day, showed the "chemical lobotomy" effect, becoming silent and with much reduction of her former restlessness. She remained practically mute, although smiling in response to jokes, and understanding commands. She was now tractable and co-operative, and has remained so on 100 mgm. daily.

In 7 cases of mania, the results were less impressive. Two cases, however, recovered after receiving the drug, and another case showed improvement comparable with that obtained earlier with E.C.T.

Case 10.—Mental defective aged 57. Chronic mania of 14 years duration. Mostly elated, extravagant and irresponsible in behaviour, making the wildest accusations against the staff, with more acute phases of threatening behaviour or actual assault upon other patients. A few days improvement had been obtained over the past year with short courses of E.C.T., but latterly it had become impossible to produce a convulsion.

150 mgm. chlorpromazine by mouth did not lead to the slightest improvement in this patient's behaviour, but the same dose given intramuscularly led to marked quietening of her noisy overactive state. After a further 7 days' treatment she was quiet, pleasant in mood and fully occupied. She has remained well on a reduced dose of 50 mgm. daily i/m.

Case 14.—Married woman of 27. Father depressed, once tried to gas himself. Since the patient's husband had developed a depressive psychosis and threatened repeatedly to take his life, she gradually became excited, and was admitted to hospital with all the classical features of mania, losing weight, and developing many septic skin lesions. There was no response to 3 consecutive daily E.C.T. administered early in the illness, and for the next 3 months she remained in a hostile resentful mood, talking incessantly, and profoundly regressed in behaviour.

There was a dramatic improvement following 50 mgm. chlorpromazine given intravenously, diluted in 20 c.cm. N saline, and she remained quiet for 48 hours before gradually relapsing. The drug was repeated on alternate days, the patient becoming tranquil, but for shorter periods. The drug was then administered intramuscularly in daily doses of 200 mgm., since when she has been up and dressed, and quiet and controlled in behaviour. Marked increase in weight and appetite have been observed, and the patient has remained well on 50 mgm. daily.

Case 16.—Single woman of 33. Recurrent psychotic illnesses since the age of 20. The earlier ones were characterized by schizophrenic features, and the onset seemed to have followed some disappointment over a man friend, with her engagement a few months later to a cripple. At this time she was described as unresponsive, mute, incontinent at times, but gradually emerged, then being slow, inclined to giggle, wandering and manneristic. Some improvement followed cardiazol, but 3 years later was in a catatonic excitement: ". . . restless in an aimless way, with a limited range of activity. She rushes out of bed, waves her arms, stands in corners and gesticulates. She has stripped herself, knelt, or taken up other fixed attitudes . . ." Declamatory and rambling in speech, limited range of topics and content bizarre, referring repetitively, for example, to her grandfather's Indian medals.

After a short remission of a few months, she relapsed again, did not respond to E.C.T., but improved after pre-frontal leucotomy. However, within a year she was back in hospital, but this time was more typically manic with overactive behaviour, flight of ideas, and expansiveness, e.g. declared she had been married for years and had produced a large family. A second leucotomy carried out about 7 years after the onset of her illness again resulted in temporary remission, but 2 years later she required re-admission, and since the end of 1950 had been constantly in hospital, apart from a period of about 12 months. She had spent about 50 per cent. of the last 13 years of her life in hospital.

Before treatment she was typically manic—decorated, overactive, shouting obscenities at the pitch of her voice, with flight of ideas, and irritability changing at once to aggressive abuse at the slightest frustration. 100 mgm. chlorpromazine, intramuscularly, increasing to 200 mgm. daily on the 4th day of treatment led to a reduction in all this activity. After 7 days, all that was observed was some pressure of talk, and after 14 days she was allowed town parole, and the drug stopped. She has remained well since (6 weeks at the time this was written), and is considered fit to be discharged.

Side effects

These were similar to those encountered when the drug was administered by mouth and deserve little comment. The experience in this series was largely similar to that reported by Anton-Stephens (1954). Complaints of giddiness, weakness, and tremulousness were common, and fainting occurred in 3 patients,

who quickly recovered on being kept recumbent. Arnold *et al.* (1953) recommend that the patients be kept in bed for the first 2 weeks of treatment, while Anton-Stephens (1954) advises confinement to bed for the first 4 days. In this series the mental improvement was taken as indicating whether the patient should get up or remain in bed. Patients were encouraged to get up on the 3rd or even the 2nd day of treatment if able to do so, and the rarity of fainting appears to have justified this policy.

Despite the precautions taken to dilute the drug before injection (i.e. to 50 mgm. in 4 c.cm.), 5 patients complained of tenderness at the injection site, or were found to have tender indurations. These rapidly cleared up without special measures after discontinuing treatment.

No consistent effect on the white cell count was observed. In 2 cases slight increases occurred, almost certainly due to local indurative reactions from the chlorpromazine associated with slight rises of temperature.

Complications

1. Jaundice of slight degree was observed in a manic woman of 58, after 3 weeks' treatment in which an initial daily dosage of 75 mgm. was successively increased to 300 mgm. per day (Case 13). The jaundice disappeared within 48 hours of discontinuing the drug.

2. In one patient (not included in this series), an injection of 50 mgm. chlorpromazine (2·5 per cent. strength), was inadvertently given into the subcutaneous tissues of the thigh. Considerable pain and swelling of the thigh immediately followed, with sloughing and ulceration of the skin and subcutaneous tissues. Skin grafting was later required.

3. One death occurred while a patient was receiving chlorpromazine by mouth:

Case 15.—This was a woman of 53 who had suffered from several attacks of depression and mania since 1934. She was admitted on this occasion in August, 1952, severely depressed and suicidal, gradually improving following a long course of E.C.T., but then passed into a manic state a year later with much noisiness, aggression and destructiveness. A daily dosage of up to 300 mgm. chlorpromazine intramuscularly produced only a slight reduction in her psychomotor overactivity. Pre-frontal leucotomy was carried out in November, 1953, without any effect on her excitement, and chlorpromazine 150 mgm. daily by mouth was recommenced, with phenobarbitone 150 mgm. t.d.s. This regime led to some reduction in her excitement, but 4 weeks after the leucotomy, and 2½ weeks after recommencing chlorpromazine she suddenly collapsed and died at once. Autopsy showed extensive thrombosis of the left coronary artery.

The possibility at once arises that the hypotensive effect of chlorpromazine and the leucotomy, together with the increased demands made on the myocardium from the tachycardia so often associated with the drug, led to the fatal coronary thrombosis.

GROUP 3. ADMINISTRATION OF CHLORPROMAZINE COMBINED WITH BARBITURATES, PHENERGAN AND DIPARCOL (DESCHAMPS, 1952)

Technique

In this method, a state of narcosis lasting 2 weeks is produced by using chlorpromazine to "potentiate" the effects of relatively small quantities of barbiturate. In addition phenergan and diparcol are used, partly for their central hypnotic effects, and in addition because diparcol has a vagal blocking action which complements the mainly anti-adrenergic effect of chlorpromazine. Withdrawal phenomena, especially nausea and vomiting, have been described if the drugs are stopped suddenly, so that "tapering off" has been carried out as a routine. The quantities of drugs recommended by Deschamps were found to be somewhat low, and in this series (0·6 gram.) of barbiturate per day, together with 150 mgm. chlorpromazine, 150 mgm. diparcol, and 50 mgm.

phenergan were found necessary in most cases to produce 12–14 hours sleep per day.

One patient, a married woman of 32 was suffering from agitated depression, having had 2 previous attacks each of mania and depression. Six months before undergoing chlorpromazine narcosis, she had been treated by "orthodox" continuous narcosis while she was in a state of mania. A comparison of the two techniques is interesting (Table IV). Although the clinical states during the two treatments were quite different, the very small quantities of barbiturate required to produce almost as much sleep per day (when combined with chlorpromazine), as in the "orthodox" continuous narcosis, is very striking. In 7 patients treated by this method, 12½ hours sleep per day was obtained on average, the patients remaining in a drowsy torpid state for the remainder of the time.

The patient undergoing chlorpromazine narcosis appears much less toxic than in the earlier described methods. The depth of sleep is certainly less, and they are more readily rousable, less ataxic and confused, and recover more quickly, without any post-narcosis insomnia or fits. Albuminuria was not seen, the fluid balance was readily maintained, and ketosis was not observed. Depression of respiration and pulmonary complications were absent. Although the patients were very pale (due to the chlorpromazine), cyanosis was not seen. Slight depression of the blood pressure was the rule, but sudden and serious falls did not occur. Tachycardia was present in all cases, usually of moderate degree, with pulse rates ranging from 80–110. Cardiac irregularities did not occur.

A minor complication which caused some alarm earlier, until its significance was appreciated, was the rise of temperature resulting probably from the local irritative effect of chlorpromazine, which occurred in 4 out of the 11 cases. This complication has the disadvantage that masking of any underlying infection could occur. In the absence of clinical signs of infection elsewhere, it was not regarded as an indication for stopping treatment.

TABLE IV

Comparison of "orthodox" continuous narcosis with chlorpromazine narcosis

"Orthodox" narcosis—February, 1953.
Clinical state: mania.

Day No.	Morph. gr. ¼ Hyosc. gr. 1/100	Parald. (drams)	Sod. amytal (mgm.)	Barbitone (mgm.)	Hours sleep
1	3	2	500	500	10½
2	2	4	1,000	—	14
3	2	2	800	1,000	12¼
4	2	4	400	1,000	15¼
5	2	2	400	500	12½
6	2	2	1,200	500	15¼
7	2	4	400	1,000	14¾
8	1	4	800	500	19¼
9	2	2	860	1,000	16
10	2	4	400	1,000	13
11	1	4	800	1,000	16
12	2	2	800	500	14
13	1	4	400	1,000	15
14	2	2	400	500	13¼
				Total	201

Average: 14⅓ hours per day

https://doi.org/10.1192/bjp.100.421.882 Published online by Cambridge University Press

Chlorpromazine narcosis—August, 1953.
Clinical state: depression.

Day No.	Mgm. Chlorprom.	Mgm. Phenerg.	Mgm. Diparc.	Mgm. Luminal.	Mgm. Butobarb.	Hours sleep
1	50	50	100	150	100	10
2	150	50	100	200	200	9½
3	150	50	150	300	200	17
4	150	50	150	400	200	15
5	150	50	200	400	200	13½
6	150	50	200	400	200	13½
7	150	50	150	250	200	16½
8	150	50	150	250	200	11
9	150	50	150	250	200	10½
10	150	50	150	250	200+25 mg.	13½
11	150	50	150	250	200+25 mg.	11
12	150	50	150	250	200+25 mg.	10
13	150	50	150	250	200+25 mg.	13
14	150	50	150	350	—+25 mg. pethidine	12½
					Total	176½

Average: 12½ hours per day

Results

Classification by diagnosis

Schizophrenia of more than 5 years' duration	3
Manic–depressive psychosis: mania	4
Manic–depressive psychosis: depression	4
	11

The patients were selected because of (1) excitement or pathological and increased psychomotor activity, (2) agitation, (3) severe tension.

The outcome of treatment in these 11 cases was disappointing. In only one patient, a 29 year old single woman suffering from a recurrent depressive state with much agitation and tension, was there some symptomatic improvement. This improvement was no more pronounced or sustained than the results of electroshock, modified insulin, and narcosis given her in previous attacks.

Discussion

In the past two years, a number of reports have described the use of chlorpromazine in the major psychoses. Hamon *et al.* (1952), first described in a case of mania, the use of intravenous chlorpromazine combined with pethidine and thiopentone for 19 days. A markedly sedating effect persisting for several hours was produced after each injection. Cossa *et al.* (1953), reported favourable results in the treatment of 6 maniacal patients. Delay *et al.* (1952) have reported that chlorpromazine alone has a marked symptomatic effect in states of excitement and confusion, in daily doses of from 75–150 mgm., administered parenterally. Sigwald and Bouttier (1953), among 48 out-patients treated with chlorpromazine, included a group of 5 "chronic hallucinatory psychoses", which, from the brief case histories given are clearly schizophrenics. Symptomatic improvement with doses as low as 75 mgm. per day given parenterally occurred in 2 cases.

Staehelin and Kielholtz (1953) described marked improvement in 2 cases of acute schizophrenic excitement with doses of 100–150 mgm. daily given intramuscularly. In chronic schizophrenics, symptomatic reduction of aggression

and excitement was observed, without any effect on the delusions and hallucinations. A suppressive effect on the agitation of a depressed patient was observed, and in another patient commencing an attack of mania, the symptoms here were similarly suppressed. In all their cases they noted a marked tendency to relapse when the drug was discontinued. Arnold *et al.* (1953) reported 66 patients treated with chlorpromazine. Their series included 19 confusional states of varying aetiology, 9 manias, and 6 depressive psychoses. In the confusional states resulting from senile dementia and cerebral arteriosclerosis, symptomatic relief followed the administration of 75–100 mgm. daily by injection. Manic states responded less well, the patients appearing to become habituated to the drug. The authors stressed that the immediate result was better than that obtained by E.C.T. in mania, because of the absence of amnesia, thus leading to the possibility of forming a psychotherapeutic relationship. Chronic hypomanic states were not influenced. In depression, symptomatic relief occurred only during the treatment, relapse occurring directly the drug was stopped. Schizophrenic excitements were favourably influenced by the drug, but without affecting the basic structure of the illness.

Lehmann and Hanrahan (1954) in a valuable paper, reported that chlorpromazine administered parenterally, was far more effective than when given orally, but that tolerance quickly developed, necessitating an increase in dosage after a few days to maintain the effect. They gave up to 800 mgm. daily to a series of 71 patients over a period of 4 months. The best results were observed in manic or hypomanic patients, but the drug was effective in other severe excitements of varying aetiologies. The authors also used the drug in excited patients who had already undergone pre-frontal leucotomy (presumably without improvement). They agreed with earlier reports that chlorpromazine does not influence delusional systems or hallucinatory phenomena.

Deschamps (1952, 1953) was the first worker to use chlorpromazine combined with phenergan, diparcol, and barbiturates in the treatment of acute psychoses, where promising results were observed. Chronic cases were unaltered. Ey and Berard (1954) found that the best results with this technique were obtained in the psychoneuroses. They combined sodium amytal, phenobarbitone, and chlorpromazine. In chronic psychoses good results were not obtained (Berard). The experience in the present series is very similar, and although the method of chlorpromazine narcosis is a technical improvement over the earlier drug combinations, it is unlikely to find its maximum usefulness in the treatment of the major psychoses. In this connection Gillespie's (1939) conclusions may be quoted: "The recovery rate in continuous narcosis in recent psychoses never exceeds, and usually falls short of the ultimate spontaneous recovery rate."

Toxic effects and complications

1. Local irritant effect. Painful muscle indurations may result from injections (Anton-Stephens, 1954). Injections of chlorpromazine solution are irritant, depending to some extent on the concentration, and may cause ulceration, as was observed by Anton-Stephens and the present author. Dilution of the drug renders this complication unlikely (Deschamps, 1952; Staehelin and Kielholtz, 1953; Arnold *et al.*, 1953).

2. Febrile response. Unexplained rises of temperature have been reported by several workers (Staehelin and Kielholtz, 1953; Delay *et al.*, 1952; Anton-Stephens, 1954). Experience in this series suggests that fever, often associated with leucocytosis, may be due to the local irritant effect. However, it is possible

that the central hypothermic effect of chlorpromazine may occasionally be reversed.

3. Severe tachycardia and dyspnoea sufficient to necessitate ending treatment have been reported in patients receiving up to 150 mgm. per day of chlorpromazine by intramuscular injection (Bensoussan and Klein, 1953). Although tachycardia seems to be a common side effect of chlorpromazine, it did not lead to interference with treatment in this series. The exclusion, wherever possible, of patients with a history or evidence of cardiac disease, when selecting psychiatric cases for chlorpromazine therapy, need hardly be stressed. Present knowledge indicates that chlorpromazine does not affect the electrocardiogram (Friend and Cummins, 1953).

4. Nausea, anorexia, and epigastric distress were described by Lehmann and Hanrahan (1954) in 8 per cent. of their patients, and allergic reactions were observed in 13 per cent. A maximum dosage of 800 mgm. per day was given. These authors pointed out that such effects were particularly interesting, because chlorpromazine has powerful anti-emetic properties (Friend and Cummins, 1953), and also belongs to the group of anti-histamine drugs. Similar complications were not seen in the present series.

5. Toxic jaundice has been observed in 3 patients treated for from 2–4 weeks (Lehmann and Hanrahan, 1954). The jaundice cleared up within 10 days of stopping the drug, whose dosage in those cases was not stated. In the present series, 1 patient developed a transient toxic jaundice after receiving 3·7 grams chlorpromazine over 3 weeks, the maximum daily dose being 300 mgm. intramuscularly. The condition disappeared in 48 hours after treatment was stopped and did not recur. After this experience, the daily dosage was not increased above 200 mgm.

Lehmann and Hanrahan also reported slight changes in the cephalin-cholesterol flocculation test in about half their patients. Thirty per cent. of their patients showed changes in total serum proteins, and albumin-globulin ratios, mostly of minor degree.

6. Varying accounts of alterations in the leucocyte count have appeared. Staehelin and Kielholtz (1953), described transient increases in W.B.C.s following initial injections of chlorpromazine. Friend and Cummins (1953), Lehmann and Hanrahan (1954), found no change in W.B.C.s, the former authors giving up to 100 mgm. chlorpromazine per day by injection for periods of 3 months. Anton-Stephens (1954) recorded falls in W.B.C.s in 11 out of 23 cases receiving daily injections totalling 200 mgm. chlorpromazine, but not in those receiving the drug by mouth. He also observed rises of sedimentation rate during treatment.

In the present series no consistent alteration of W.B.C. count was observed, with the exception of a leucocytosis associated with the febrile response mentioned above.

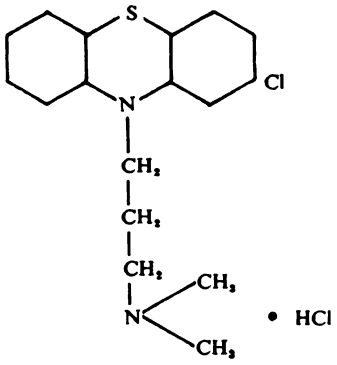
Mode of action

The mode of action of chlorpromazine is quite unknown. Lehmann and Hanrahan (1954) postulate that the effect of chlorpromazine is exerted selectively on the reticular substance of the brain stem, with little effect on cortical metabolism, citing results which indicate that the drug has little effect on psychological functions which are cortically mediated. Such a theory would not explain all the effects of chlorpromazine, and in particular its hypothermic effects, and its potentiating action on barbiturate sedation.

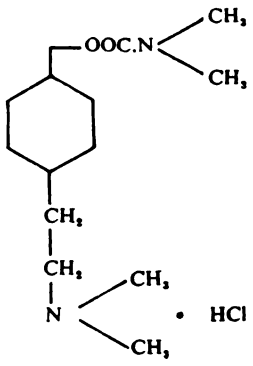
Structurally, chlorpromazine has a resemblance so far as its side chain is

concerned, to other tertiary ammonium compounds such as eserine and hordenine.

Tertiary ammonium compounds have the property of giving rise to free base, which, being lipoid-soluble may well dissolve in the nerve cell membrane thus entering the cell, where conceivably, some anti-cholinesterase activity might occur. The concentration gradients of chlorpromazine within the central nervous system would then be a function of density of cell population. There is in fact evidence that chlorpromazine acts selectively on nuclear structures. For example it is powerfully anti-emetic (Friend and Cummins, 1953), presumably by a direct action on the vomiting centre. Related tertiary compounds like phenergan (promethazine hydrochloride), and lysivane (ethopropazine hydrochloride) similarly are "anti-Parkinsonian" drugs with a selective action on the basal ganglia, and a weak central sedative effect.



Chlorpromazine hydrochloride



Dimethyl carbamic ester of hordenine hydrochloride

It is known that the EEG after chlorpromazine in intramuscular doses of up to 100 mgm. gave readings comparable with those of physiological sleep, and did not show the characteristic modifications of barbiturate sedation (Terzian, 1952).

On the basis of these somewhat scattered observations the following hypothesis of the central action of chlorpromazine is offered. Chlorpromazine as a tertiary ammonium compound gives rise to free base in the central nervous system, which has the property of entering nerve cells, and like related compounds will achieve its maximum effect according to the density of cell population. Such a differential concentration would explain the anti-emetic and hypothermic effects of chlorpromazine. If selective concentration in the basal ganglia including the thalamus were to occur, this might account for the peculiar "chemical lobotomy" effect first reported by Delay. The efficiency of chlorpromazine in the reduction of pathologically increased psychomotor activity would depend then on its interference with corticothalamic circuits.

The peripheral effect of chlorpromazine is mainly anti-adrenergic. Oral administration in ordinary doses might not produce adequate concentrations within the central nervous system, and merely lead to the side effects described, i.e. tachycardia, fall of blood pressure, thirst, etc., due to its peripheral anti-adrenaline activity.

Summary

The results of parenteral administration of chlorpromazine in a series of 27 female in-patients have been described. The drug was administered alone, and in combination with phenobarbitone, butobarbitone, phenergan, and diparcol. Symptomatic improvement occurred in 7 out of 8 excited and impulsive, or aggressive schizophrenics, and was very marked in 4 cases. These effects were brought about by an average daily dosage of 200 mgm. The results in mania were less impressive, but 2 out of 7 patients obtained remissions after treatment with chlorpromazine. Another patient with a mixed psychosis, who had had earlier remissions after two pre-frontal leucotomies, again remitted following chlorpromazine.

The drug was inactive in 22 major psychoses when administered by mouth in doses of up to 300 mgm. per day, although the presence of side effects showed that it was being absorbed.

When combined with barbiturates, phenergan, and diparcol, chlorpromazine can be used to produce a continuous narcosis, which gives rise to considerably fewer toxic effects than in the earlier described methods of drug narcosis. In this sense, the method of "artificial hibernation" (chlorpromazine narcosis), represents a distinct advance, but is unlikely to find its major application in the treatment of the psychoses. In the present series of 11 patients, only one showed any benefit from the treatment. This experience is identical with that of Continental workers.

The main toxic effects of chlorpromazine are (*a*) local irritation, which can largely be prevented by adequate dilution, i.e. 50 mgm. chlorpromazine in 5 c.cm., or a 1 per cent. solution, and (*b*) toxic jaundice, which so far has been observed in occasional cases on varying doses of chlorpromazine. The undesired side effects of the drug, i.e. tachycardia, orthostatic fainting, etc., do not appear to be a contraindication to its use in the control of psychotic excitement.

On the basis of the present results, chlorpromazine is regarded as the drug of choice in the management of acute excitement, being in this respect probably as efficacious as electroshock. The drug is most effective in schizophrenic excitements. The rapid reduction of aggressiveness, diminution in psychomotor overactivity, without the production of drowsiness or confusion, renders the drug particularly valuable in facilitating psychotherapeutic contact. Unfortunately, tolerance quickly develops in some patients, so that the beneficial effect may disappear after 10–14 days. Despite this limitation, however, chlorpromazine represents a definite therapeutic advance in the treatment of psychotic excitement.

Acknowledgment

I am indebted to Dr. J. Harper, Medical Trials Unit, May & Baker Ltd., Dagenham, Essex, for his kindness, courtesy, and help in this investigation. Messrs. May & Baker provided generous supplies of "Largactil" Brand of chlorpromazine hydrochloride for the study.

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Note

Since this paper was written, further experience in the use of oral chlorpromazine has been published. Howell *et al.* (*Practitioner*, 1954, 172) observed a reduction in the restlessness and agitation of 18 out of 20 senile psychotics to whom chlorpromazine was given orally in doses of up to 75 mgm. per day.