

A PRELIMINARY REVIEW OF THE USES OF CHLORPROMAZINE IN PSYCHIATRIC DISEASES*

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Amongst the recent advances in psychiatric treatment by means of drugs, chlorpromazine is playing an ever increasing and important role. It was first used clinically by Laborit and Hugenard in 1951 in relation to anaesthetics and later (1953) by Delay and Deniker¹ in psychiatry. It has been adopted generally for virtually every known psychiatric illness and varying opinions have been expressed concerning its efficacy. At the Oranje Hospital it has been in active use for the past 8 months with varying—sometimes startling—results. It has been tried alone or in combination with other drugs or electroconvulsive therapy (etc.).

Clinical Effects

According to reported observations the most striking clinical property of chlorpromazine is its ability to induce somnolence leading to a state of detached unconcern, yet without interference with mental ability. Lomas² points out that even when a soporific state is produced the patient is as easily roused as from normal sleep, and tends to fall asleep only if he has no external interests at the time. Thus it is entirely different from any of the barbiturates or other sedatives in common use. Its indications in psychiatry were originally based on this ability to induce somnolence and ease tension, and thus to secure a so-called 'chemical leucotomy'. Numerous investigators have applied it in states of increased psychomotor activity, whether of manic, schizophrenic, epileptic or other origin. All seem to be agreed that a tranquillizing effect, whether temporary or permanent, can be produced in as short a time as a few days by an injection of 50 mg. 8-hourly. At the same time various observers have noticed concomitant improvement in behaviour, appetite and sleep with a resulting increase in weight.

In addition to the functional conditions chlorproma-

zine has been found to be of use in certain organic disorders (Cohen³); e.g. in delirium tremens, for agitated senile arterio-sclerotics, for post-encephalitics, and in post-traumatic personality disorders. This we have confirmed.

In the psychoneuroses conflicting opinions have been expressed. Some, e.g. Winkelman⁴, believe that it can reduce severe anxiety and diminish phobias and obsessions while Cohen, agreeing to some extent, points out that the results are disappointing in hysteria, hypochondriasis, the usual depressions, and obsessive-compulsive and phobic neuroses. The weight of opinion seems to be that its value in the psychoneuroses is limited.

Davies⁵ states that it controls aggressiveness *per se* and in various grades of mental deficiency, leading to improved behaviour and thus easing the nursing problem. Others have found that the discontented aggressiveness often associated with paranoid conditions is modified or considerably relieved, even though the paranoid constitution itself is unaffected.

Seager⁶ has reported its use in elderly psychotic women and found it to be efficacious in 71% of his cases.

Gatski⁷ has used it in the treatment of acutely disturbed and acting-out maladjusted children, and maintains that they became more tractable and could learn to conform to the norm with greater ease.

An interesting report is that of Benda and Klein,⁸ in which they discuss 4 cases of status epilepticus which responded to the intravenous use of the drug after the usual methods had failed. This has been our experience on 2 occasions.

Fazekan *et al*¹¹ have used it in the management of acute alcoholism and post-alcoholic states. The major benefit was in the control of excitement and anorexia.

ORANJE HOSPITAL: INDICATIONS AND RESULTS

At the Oranje, Hospital we have used chlorpromazine in the form of Largactil. The drug has been used from

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2 aspects, viz. (1) in the treatment of clinical entities, and (2) in the management of individual symptoms irrespective of the diagnosis.

1. Treatment of Clinical Entities.

In the manic depressive group very promising results have been obtained in the manic phase, either alone or in conjunction with ECT. We have found that the number of shocks required to control the hyperactivity of the manic phase is considerably reduced by the concurrent use of chlorpromazine. We have found that, to control an acute case of mania, as many as 2 shocks *per diem* for 5 days or more were necessary; since using chlorpromazine we have found that 2 shocks are all that is necessary to bring this phase under control. As a result of the experience we consider that the major indication for the use of chlorpromazine is in the manic phase of the manic-depressive psychoses.

Amongst our cases, J. R. E. duP., ME* 3209, who has been a patient on several occasions and was treated previously with ECT, we found that on his last admission ECT was unnecessary, and he was brought under very rapid control with chlorpromazine only. In fact, within 3 days of admission his severe increase in psychomotor activity was greatly reduced, and within 10 days he was well on the way to a full remission.

In other similar cases a regime of 2 or 3 shocks on alternate days, with oral chlorpromazine and small doses of phenobarbitone or amytal, has rapidly brought the patient under control with a minimum of risk and nursing requirements.

Furthermore as regards the chronic manic who displays periodic exacerbations of his condition, and who was a severe nursing problem and required frequent repeat administrations of ECT, we have found that the shock treatment could largely be replaced by chlorpromazine. In 5 cases of the chronic mania type, 3 have become fit for leave of absence, and 2 are much more easily managed and less burden on a depleted nursing staff. Of these cases C.A.D., FE† 2092, diagnosed as chronic hypomania, and who, until put on chlorpromazine 4 months after admission, was markedly overactive, inconsequent and difficult to manage, settled down very quickly. Her relatives were most diffident in taking her on leave, and it was only after a struggle of some 6 months that we eventually succeeded in persuading her daughter to give her a trial. A letter written by the daughter some 2 weeks after her release is extremely interesting; she writes, 'You will be pleased to know that Mrs. D. continues to keep well'. We feel that should she display signs of relapse, early therapy should obviate the necessity for readmission.

We believe that, as a group, the senile psychoses, with or without hypertension or arterio-sclerosis, benefit considerably by the use of chlorpromazine. The aimless, restless and interfering patient is rapidly brought under control. The drug eliminates or reduces the necessity for other forms of treatment and lessens the amount of sedatives. It eliminates the hazards of ECT given in old age. We have found in some cases that its calming effect

is enhanced if it is preceded or combined with intensive nicotinic-acid therapy and supplemented by barbiturates of moderate action. Although this series comprises only a small group, it is felt that the results are important. All these patients were well known to the staff for a long period, and therefore the easing of symptoms stood out clearly against a very definite background, after the institution of chlorpromazine. One case, C.J.R.L., ME 3220, relapses into a restless and mildly agitated state, whenever his treatment is discontinued for any length of time. This state responds within 7 days to 2 tabs. *ids* orally, and thus instead of being a constant burden he becomes an easily manageable individual. Another case, H.V.T., FE 2079, becomes resistive and confused, and requires much attention from every aspect. On 150 mg. daily she improves sufficiently to eat on her own, she becomes fairly cooperative, and conversation with her becomes possible. The third case, A.J.L., ME 3229, did not show the same measure of improvement, but his resistiveness to attention became less. Unfortunately his result was blurred by the advent of jaundice and fever.

As already mentioned, chlorpromazine has been used in an attempt to bring status epilepticus to an end. On 2 occasions we have used it intravenously after other methods had failed, and in both cases the seizures were brought to an end—in one case after 3 more seizures, and in the other after 5. However, as this method is still in its infancy the more recognized treatments should still be depended upon, and chlorpromazine should only be used as a last resort. Both our cases died, the one after some weeks and the other after some days, both from intercurrent disease (pneumonia).

As regards possible complete cure, as compared with remission in a manic episode, we feel that we obtained this result in a patient with a post-traumatic psychosis. This patient, a male Native J.R., MN 6041, received several blows on the head and suffered from severe cerebral injuries. On admission he was confused, excited, disorientated and incoherent. He was tried on ECT. He was given intensive nicotonic-acid therapy, and intensive sedation. The ECT was used in an effort to control the excitement. After 4 months, having shown no signs of improvement, he was tried on chlorpromazine, and within 3 weeks there was a marked improvement. He has since been discharged, recovered, and has returned to his former employment.

Our experience with chlorpromazine treatment of the psychoneuroses is limited; we only had 2 suitable cases, and in both the beneficial results were limited. In both there was considerable anxiety, hypochondriasis and a lack of self-confidence. Both cases required other treatments and, in our opinion, the only value of chlorpromazine was that it helped the 2 patients to settle down to their surroundings more easily.

2. Management of Individual Symptoms.

In spite of the apparent contra-indication of chlorpromazine in epilepsy—it is thought by some to increase the tendency to seizures—we have tried it in a group of 7 Native males and 2 European females with the object of reducing the aggressive content, irritability and

* ME = Male European.

† FE = Female European.

restlessness. This experiment has been carried out over an average period of 10 weeks with a maximum dose of 150 mg. per day, and the customary anti-convulsants were continued. Although they all showed an increased tendency to drowsiness, the following features were observed:

In 5 patients the numbers of seizures remained unchanged, in 3 cases there was a slight reduction in the number of seizures in comparison with a similar period before treatment, and in 1 case the number of seizures was increased, though not significantly.

There was no change at all in the aggressiveness, irritability and restlessness in 4 cases. In 5 cases there was a moderate improvement, in that their symptoms were less severe and of shorter duration, and for this one reason we consider it necessary to carry out further trials with considerably larger doses over a longer period of time.

Chlorpromazine has already been shown to be of value in manic and senile conditions *per se*; we have also tried it for excitement in schizophrenic conditions but, possibly because the dose was too small, our results have been disappointing. The treatment, however, was only used for short periods when a patient was particularly impulsive or excited.

In 10 cases of chronic schizophrenia, mostly showing delusions, restlessness, impulsiveness and sleeplessness, there was no change in 3 cases, some degree of improvement was noticed in 6 cases but not sufficient to warrant enthusiasm—it would appear from the recent work of Delay and Deniker that doubling of the doses may prove more beneficial—and in 1 case the patient displayed unexpected emotion in the way of tearfulness and depression. We have used chlorpromazine in some paranoid conditions and the patients have shown a lessening of their unpleasant and aggressive attitudes, though no change in the mental content. In one case, C.A.S., ME 3179, who before its use was extremely abusive, angry, and markedly suffering from persecutory delusions, his delusions changed their character with this treatment; he became amiable and grandiose, but since cessation of treatment his delusions have reverted to their former state.

REVIEW OF CASES

In Tables I and II a review is given of cases who received fairly concentrated treatment with chlorpromazine (numerous other patients were given the treatment but are not included because they have been treated for too short a period).

Method of Dosage and Technique

The chlorpromazine may be given orally, intramuscularly or intravenously:

Orally it has been our practice to give 25 mg. *tds.* increasing to 250 mg. daily and it can be continued for as long as necessary, provided no complications occur.

Intramuscularly 50 mg. every 8 hours for 2—3 days. The injection is very painful and it is advisable to change over to the oral regime as soon as possible.

We have used the intravenous method only for

status epilepticus. The dose must be diluted to the extent of 50 mg. in 10 c.c. of sterile water and it must be injected very slowly.

It is our view that much larger doses can be safely used and it is our intention to intensify the treatment in the schizophrenic group. Several workers have already given as much as 800 mg. daily, and more.

Toxic Action and Side-effects.

Toxic symptoms did not occur very frequently in our series. This may be due to the fact that our periods of treatment were comparatively short and the dosage moderate. Amongst the toxic effects we have noticed are:

1. *Jaundice.* This occurred in one case, an old man 80 years of age, who was very restless and confused, disorientated and difficult to manage. He was on 150 mg. daily for 4 weeks when symptoms first developed. He was reported as having had a syncopal attack, apparently as described by Lomas in the aged, and on the following day the symptoms of jaundice were obvious. A rise of temperature up to 100—101°F was recorded over the next 3 weeks. His recovery, although slow, was uneventful. He was treated with penicillin with the object of avoiding any intercurrent infection.

2. *Sudden drop of Blood Pressure.* In a patient with arteriosclerosis and hypertension (systolic blood pressure 190 mm. Hg), there was a sudden fall of 40 mg. at the end of the first day's treatment by intramuscular injection. He was extremely drowsy and unable to stand, but he could be roused. With a reduction in the dosage his untoward symptoms subsided, and treatment was continued by the oral route without further difficulty.

3. *Incoordination.* This occurred in a young patient who was a competent pianist, and was manifested by the fact that he became unable to carry out the finer movements necessary for the exercising of his talent. The incoordination was so mild that we did not interrupt the treatment. (Goldman⁹ describes a syndrome resembling paralysis agitans. In his mildest case he found some rigidity of the extremities, with stooping posture, and there is little doubt that this case of ours is a still milder example of this side-effect. In the severer types of this complication he describes characteristic pill-rolling tremor, changes in gait and speech, and salivation.)

Agranulocytosis has been described by Goldman,¹⁰ Lomas² and others in chlorpromazine treatment of mental-hospital cases. We have not thus far encountered it. According to Lomas *et al.*¹⁰ toxic effects occurred in 7.4% of cases, viz. jaundice, blood dyscrasias, skin reactions, oedema, and epileptic fits. Thus a history of liver dysfunction or previous blood dyscrasia is an absolute contra-indication to treatment with chlorpromazine. An interesting fact referred to by Lomas *et al.*¹⁰ is that side-effects (in contradistinction to toxic effects) occur much less frequently in the psychotically disturbed than in others. These authors do not regard incoordination as a toxic effect, but rather as a side-effect. The following are the commonest side-effects: Tachycardia, dryness of mouth, constipation, pronounced increase in appetite (a factor we are at present

observing in one patient), gain in weight, and increase in the quantity of urine.

CONCLUSIONS

The conclusions we have arrived at from our cases under treatment are as follows:

(a) Chlorpromazine is not a *curative* agent against any established psychosis (except perhaps in one case in which the post-traumatic confusion was cleared).

(b) It is an extremely valuable addition to our psychiatric armamentarium, and should play an important role in the reduction of admissions to mental hospitals in the senile group, and a reduction in the duration of manic phases, thus permitting of a shortening in the period of detention.

(c) It leads to an increase in the number of patients able to go on leave.

(d) It aborts attacks in frequently recurrent mania, or brings the attacks under more speedy control. It reduces the number of electro-convulsive shocks necessary in the more resistant cases.

(e) Perhaps its greatest benefit in these days of depleted nursing services, lies in its ability to ease the nursing problem, by the decrease in attention the restless patient usually demands.

(f) In schizophrenics and epileptics, very little actual benefit is achieved on the moderate dosage schemes we have used. In epilepsy, judging by the remarks of others, it may be contra-indicated and in fact should not be used except in conjunction with the anti-convulsants. Our conclusions (apart from high-dosage treatment) conform with opinions of other investigators such as Vaughan *et al*,¹² Lomas *et al*,¹⁰ and Delay and Deniker¹.

SUMMARY

A preliminary review of chlorpromazine treatment at the Oranje Hospital, Bloemfontin, is undertaken in this paper, and reference has been made to its value in the manic depressive, senile, schizophrenic and epileptic groups, from the aspect of both clinical entities and individual symptoms. The toxic effects are referred to. The conclusion is that it is a very valuable adjunct to psychiatric treatment in general.

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POSTSCRIPT

Since this article was written several workers have experienced rather distressing symptoms in cases being treated with ECT and chlorpromazine or Serpasil, and a number of unexplained deaths have occurred.