'PACATAL'—A CLINICAL TRIAL OF A NEW ATARACTIC DRUG

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The pharmacological control of emotional disorders and psychiatric conditions has become prominent in recent years. Few workers would consider such control in itself sufficient; indeed it is difficult to arrange matters, even with the 'double blind control' in which neither physician nor patient is aware of what tablet is being given, so that suggestion is completely excluded, for the mere giving of a placebo will make some impression on the patient. In the small series described below psychotherapy was given to each patient as was considered most fitting; no attempt has been made at rigid scientific control but the venture has been approached as a clinical trial, with as open and unbiased a mind as possible, against the background of fairly extensive use of chlorpromazine in an analagous group of patients seen in private practice.

The drugs commonly used as pharmacological aids in the various disorders which are by general acceptance termed 'functional' may be divided under several headings:

(*a*) The sedatives, which act largely on the cerebral cortex, and of which barbiturates represent by far the largest group;

(*b*) The stimulants, of which the amphetamine group, caffeine and some phenyliso-propylamine derivates such as Ritalin are representative;

(*c*) the hormones, such as thyroid, oestrogens, androgens and various steroid derivatives;

(*d*) relaxants of the dioxolane group, such as dimethylane and mephenesinium, which act by inter-neuronal blocking effects;

(*e*) abreactives, such as CO_2 used in inhalation therapy and acetylcholine used intravenously;

(*f*) the hallucinogens. of which lysergic acid is the most commonly used;

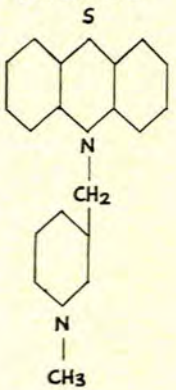
(*g*) sympathetic inhibitors such as reserpine; and

(*h*) the anticholinesterase drugs, such as chlorpromazine and the antihistamines.

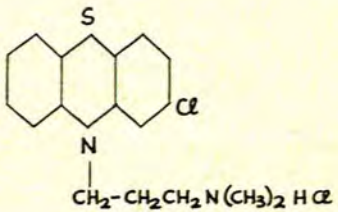
This list could be further enlarged and its subdivisions are by no means mutually exclusive as chlorpromazine as well as being an anticholonesterase has a sympathicolytic effect, but it is given to remind one of the complexity of the question of pharmacological control of the psyche.

Pacatal is a phenothiazine derivative with the formula:
N-methyl piperidyl-3-methyl phenothiazine

PACATAL



CHLORPROMAZINE



Owing to its heterocyclic chain structure it differs chemically from chlorpromazine. The two graphic formulae are as follows:

Pacatal has a relatively low toxicity and has been given continuously to dogs for 2 months, without any untoward effects, in doses of 10-20 mg. per Kg bodyweight, orally. It appears to have some depressant effect on the parasympathetic nervous system since it blocks the action of pilocarpine on salivary flow in rabbits and inhibits secretions in rats.[1] Its mydriatic activity is slight but it has a distinct drying effect on the upper respiratory passages.[2]

On the sympathetic system Pacatal has a depressant effect; it causes inhibition of contraction of the nictitating membrane. The cartoid-sinus reflex and pressor reflexes were inhibited but noradrenaline was not blocked. In normal individuals 50 mg. of Pacatal given intravenously was found to lower the blood sugar slightly.[3]

Pacatal, like chlorpromazine, potentiates the analgesic properties of morphine and phenacetin and reduces the reaction to pain by both a peripheral and central action.[4]

Pacatal has not the same effect as chlorpromazine on the circulatory system, because it does not lower the blood pressure or affect the pulse rate.[3]

In estimating the qualities of any drug clinically, the venue for the trial must be carefully chosen so as to show up the qualities of the drug most advantageously as well as define its limitations. It is obviously wrong to estimate the effect of a drug solely suitable for the sedation of mildly agitated persons by trying it only against wildly maniacal psychotics; a negative finding will be arrived at (that the drug is useless in mania) but no positive affirmation can be made. The negative discovery is of course of some value in defining the boundaries of future trials but it is not sufficient in itself.

In the following summary of a recent trial of Pacatal, 2 main groups of patients were used: (*a*) Ambulatory persons who were going about their daily tasks but who found certain difficulties such as tension, lassitude, insomnia and depression, interrupting their usual efficiency, and (*b*) patients who had been so severely affected as to warrant nursing-home treatment. There were no cases of the certifiable class. Amongst those who were receiving nursing-home care a further division could be made into those receiving some form of electroconvulsive or electronarcotic therapy and those who were not receiving this therapy.

Dosage. Pacatal was supplied in 50 mg. tablets and in ampoules of 50 mg. in 2 c.c. solution.

In most of the nursing-home group an initial deep intramuscular injection of 75 mg. was given followed by 100-200 mg. by mouth.

With ambulatory patients 50 mg. was given *t.d.s.*, or if the problem was mainly one of poor sleep an initial 100 mg. of the drug was given ½ hour before retiring. In a few cases the dosage was raised to 100 mg. *t.d.s.* With those who were treated in bed an initial dose of 75-100 mg. was given intramuscularly.

It was found that by diluting this dose with sterile water to 10 c.c. the pain of the injection was reduced. At first deep muscular injections were not given and most of the patients complained of severe pain; local anaesthetics such as 2% procaine were not found to be satisfactory in overcoming this pain, and when the anaesthetic effect wore off the patient continued to complain of pain for a further 24-48 hours. Later the injections were given deeply into the buttock muscles and this was found to be much less painful. Hyaluronidase was given with some of the intramuscular injections but apart from appearing to hasten the calming effect of Pacatal it did not seem to have any other effect and the injection site remained tender.

In the very excited, agitated and hypomanic cases the dosage required was very variable, and although 800 mg. a day in divided doses was usually sufficient to induce calm sleep, there were cases where this dosage was quite inadequate.

Finally, except in the ambulant cases, Pacatal alone was not usually sufficient to quiet the patient and the drug had to be used in combination with a barbiturate. A very satisfactory method of inducing therapeutic sleep for a week or 10 days was found by combining 200 mg. of Pacatal with 400 mg. of Noludar (Roche), i.e. 2 tablets of the latter drug every 6 hours. As some patients object to taking large numbers of tablets the Pacatal and Noludar were often crushed and given together as a powder to be swallowed with water.

SIDE-EFFECTS

Dryness of the mouth and a loss of taste was a frequent complaint of patients taking Pacatal. A few complained of blurring of vision and in those having high dosages dizziness and actual ataxia occurred. Many patients remarked on their vivid dreams while taking the drug, an effect which is shared with chlorpromazine.

There were no cases of jaundice or blood dyscrasia.

Of the 53 patients under treatment with Pacatal, 3 developed nausea and 1 vomited after being given the drug. Anorexia might be a side-effect in about a quarter of the patients, but this was difficult to estimate because in many patients anorexia was part of the symptom-complex which led them to consult their doctors.

Despite the experimental evidence that Pacatal had little anticonvulsant effect,[1] clinically in giving electroconvulsive treatment to patients it was found to have a very marked anticonvulsant effect. This is a drawback in electroconvulsion therapy since, if a convulsion is not produced, the patient is often confused for a considerable time after the treatment. It must, however, be remembered that part of this anticonvulsant effect is due to the potentiating effect of Pacatal on barbiturates and Noludar. It was noticed that intramuscular Pacatal alone had no adverse effect on electrocoma treatment, where a convulsion is not aimed at, and indeed it seemed to help considerably in this treatment, for patients who tended to wake up 2-3 minutes after the commencement of treatment were found to take the full 10-15 minutes of passage of electric current without waking after administration of the drug in its usual daily dosage.

CASE RECORDS

In starting trials with a new drug there are bound to be failures for two main reasons, firstly because the

medicament is used on unsuitable cases, and secondly because inadequate dosage or too high a dosage is used. Only by trial and error can an estimate be arrived at, and the over-all clinical impression at the end of the trial is probably of more importance than any study of statistical effects. The reader is therefore referred to the concluding remarks of this article before judging from the following figures.

Furthermore Pacatal alone in a few of the more severely affected cases was not sufficient, but by its potentiating effects it was most useful in cutting down the amount of barbiturates or other drugs given.

The following tabulation shows the satisfactory as compared wiht the unsatisfactory responses. The latter group include those in which the drug was abandoned either because it was ineffective or because of the resulting anorexia or nausea or dryness of the mouth.

Ambulatory Patients	*Satisfactory*	*Unsatisfactory*
Agitated depressions and tension states ..	8	2
Simple depression (reactive or cyclothymic)	1	4
Migraine and a typical facial neuralgia ..	5	2
	14	8
Nursing Home Patients		
Agitated depressions and tension states:		
with electrotherapy	10	2
without electrotherapy	6	2
Hypomania—with electrotherapy	2	0
Drug withdrawal	2	1
Alcohol withdrawal	6	0
	26	5

The patients who were depressed without a great deal of tension were those who did least satisfactorily on Pacatal. As with chlorpromazine the best results were those who were agitated, restless, sleepless and tense.

A few illustrative case notes may be of help in estimating the effects of Pacatal:

Case 1. H.W., a journalist 48 years of age, had for the last 3 years found himself becoming increasingly tense and sleepless. He had had a considerable amount of domestic anxiety and his work was unsatisfactory and frustrating. He had a typical tension-reaction to all this background of real worry and he found he could not concentrate or settle to anything and his sleep was broken and unrefreshing. He was a man of high intelligence and initiative and had no previous breakdown; he still did his work but he felt as if 'something would happen' if he did not achieve sleep and relaxation; amphetamine, various sedatives, a sea-trip and advice from a number of physicians had all been without avail.

After a preliminary psychotherapeutic interview and survey he was put on to Pacatal, 50 mg. *t.d.s.*, and when seen a week later he was much better. He felt less tense and, although he took nothing else to induce sleep at night, he slept well. He has been seen at weekly intervals for 6 weeks and has remained well. His impression is that Pacatal does not make him feel lethargic in any way during the day but helps him to sleep at night by giving him what he calls a 'more relaxed platform' to start off the night.

Case 2. A.P., a physician 49 years of age. For 7 years he had been taking drugs—omnopon, pethidine and large amounts of barbiturates. He was desperately trying to stop the drugs but when seen was in a state of great depression and agitation. He would pace up and down his room wringing his hands, clutching his head and appealing for help from his inner restless torment.

He was taken into a nursing home and given 75 mg. of Pacatal *i.m.* and put on 200 mg. *t.d.s.* He immediately became quieter and less agitated and slept for 14-18 hours a day with the aid of paraldehyde, 10 ml. by mouth twice daily.

A week later he began to complain of a restlessness in his legs, the 'jittery legs' of Ekbom, which did not respond to increased doses of Pacatal or chlorpromazine, but which responded temporarily to reserpine.

Comment. Both these patients were intelligent men trained, in different ways, to observe reactions. Both were quite certain that Pacatal was effective where other sedatives of the barbiturate, bromide and hyoscine groups had been ineffectual. In the doctor patient Pacatal failed to relieve the supervening intensely felt feeling of restlessness in the limbs although it calmed him inwardly in a satisfactory manner. In the first case, by dissolving the bands of his tension, it allowed the patient to continue at his work with better concentration and more zest than previously, and in the second case it produced calm sleep with quite small doses of paraldehyde in a man accustomed to taking big doses of various drugs.

Case 3. L.M., a European housewife aged 35 years, with occipital headache, frontal and periorbital pain, usually on the right side but sometimes on both sides. These headaches had been present for some years and were often precipitated by fatigue or emotional upset, but latterly had tended to become more and more frequent and to last up to a week at a time. The usual remedies for migraine had failed to help them and they were undoubtedly of that class of headache called 'muscle-contraction headache' by Tunis and Wolff.[5] On Pacatal, 50 mg. *t.d.s.* and 100 mg. at the very onset of a headache, she was much improved. Although she usually lay down for an hour or so after the 100 mg. dose she would avert the headache, which previously would have incapacitated her for at least a day.

Comment. The muscle-contraction type of headache is a common cause of distress and partial incapacitation amongst people of all classes, but particularly in the housewife in her thirties and forties with the usual press of duties and responsibilities and the stress of modern living. Psychotherapy certainly plays a major part in the resolution of this kind of headache, together with rearrangement of the living-pattern into a less stressful form, but what the patient usually craves for is something to take which will give an immediate relief from symptoms. Pacatal in the dosage given above, has been of great help in this kind of case.

Case 4. P.B. aged 40, a chemist by trade, had been undergoing a considerable amount of stress relating to a business partnership and building undertakings. He had always been a very quiet man, perfectly self-contained, but rather suspicious. For a week before being first seen he had been restless, talkative, and mildly elated. The day before he was seen his elation and activity increased, and when seen he was in a typical hypomaniac state with a great pressure of talk, flights of ideas, and moods which swung from an all-embracing euphoria to swift and angry aggressiveness. He knew a good deal about the effect of drugs and refused to take barbiturates in any form 'because of the danger of suicide' and refused to have chlorpromazine 'because it causes jaundice'. He was eventually persuaded to take Pacatal, 200 mg., and Noludar, 400 mg., crushed up together and was kept on this dosage 3 or 4 times daily for 10 days, during which time he had electroconvulsive therapy. He made a full and surprisingly uneventful recovery except for the 4th day of treatment, when he refused all drugs by mouth and became very elated and aggressive and had to be given 100 mg. of Pacatal by injection.

Comment. This case raised some extraneous difficulties in that the patient refused to have either barbi-

turates or chlorpromazine. Nevertheless Pacatal proved itself an excellent substitute and indeed, along with Noludar, it is difficult to see how the case could have been better controlled. It should be made clear that the Pacatal merely facilitated nursing and the giving of the electroconvulsive therapy—it was the latter which improved his hypomania—but without Pacatal the management of the case and the rapid recovery could not have been achieved.

CONCLUSIONS

Pacatal compares favourably with chlorpromazine in the control of a group of cases with emotional disorders, tension states, and muscle-contraction headaches. It is not in itself a nostrum but it does help the physician in the management of the patient and it helps the patient by lessening his inner tension. Nearly all those who took Pacatal said they felt calmer and slept more readily. The side-effects as compared with those of chlorpromazine are few—no rashes, no jaundice, no blood dyscrasia, no marked alteration of blood pressure or pulse rate. It did, however, produce a dryness of the mouth which was unpleasant in some cases; blurred vision, anorexia and, in big doses, ataxia were also produced, but it should be noted that the bigger doses were usually employed only in the most severely agitated cases and the side-effects were mild compared with the increased control of agitation and tension.

As with chlorpromazine, the dosage required for individual patients may vary from 100 mg. in one to 800 mg. in another, though they may be clinically comparable. In our experience, Pacatal proved somewhat more painful than chlorpromazine on injection, but by means of dilution with water and deep injection this can be ameliorated.

In using Pacatal one must remember its potentiating effects, which are like those of chlorpromazine, on hypnotics and analgesics. In electroconvulsion therapy Pacatal seems to have an anticonvulsant effect which may make the treatment more difficult, but in electric-coma treatment it helps, probably by potentiating the effect of the introductory intravenous thiopentone, in keeping the patient asleep while the current is being passed.

SUMMARY

Pacatal, a phenothiazine derivative, is structurally related to chlorpromazine but differs in its heterocyclic side-chain structure. Indications for its use are similar to those for chlorpromazine but it has less side-effects.

There is a very definite place for the use of Pacatal and some indications for its use are discussed.

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