OBSERVATIONS ON THE EFFECT OF LARGACTIL IN PSYCHIATRIC ILLNESS

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LARGACTIL is one of the phenothiazine group of compounds. It is, therefore, related to promethazine (phenergan) and diethazine (diparcol). It is also known as R.P. 4560 and chlorpromazine. It has been used on the Continent in psychiatric cases since 1951, because of the relaxation and calm it produces. It has been on trial at Netherne Hospital since 1953 and 80 patients have received this treatment.

It can be given orally or by intra-muscular injection. Concentrated solutions may cause considerable irritation when given by injection to some patients and in this case the dose should be diluted to 25 mg. in 5 cc. of saline as a minimum. The intra-muscular dosage is from 25–50 mg. 3 or 4 times daily. The oral dose needed is between 1 and 2 times the intra-muscular dosage. There is a wide individual variation in response, the usual oral dosage being between 150 and 200 mg. daily, but some patients can only tolerate 75 mg. while others appear unaffected by 600 mg. daily. In co-operative patients treatment was usually commenced with 25 mg. 3 times daily by mouth and as this as a rule produces little effect, 50 mg. 3 times daily was given the next day, then increasing to 75 mg. 4 times daily if necessary. In the acutely disturbed psychotic, it was found necessary to commence treatment with intra-muscular injections of 25–50 mg. four times daily.

French writers (1) have summarized its properties as "a compound possessing vagolytic, spasmolytic and sedative activity. It is also sympatholytic and adrenolytic, eliminating adrenaline-induced hypertension." They also say it has analgesic activity and enhances the action of other analgesics and hypnotics. An annotation in the *British Medical Journal* (2) pointed out that many of the claims were as yet unsubstantiated. Most Continental reports show that Largactil has been used together with a number of other drugs, so that it has been difficult to assess the precise role of any one of them. The investigation at this hospital was, initially, into the effects of Largactil used entirely by itself.

Largactil produces changes in both the physical and mental states of those who do respond to it. The most marked changes occur after intra-muscular injection. Examination of the nervous system then reveals muscular hypotonia. The pupils, if dilated at the onset of treatment, become reduced in size but reaction to light and accommodation is unaffected. There is often analgesia of an unusual kind. The patients seem indifferent to pain rather than unaware of it. For example, one patient with a recent acute psychosis had severe inflammation around injections in the thigh yet made no spontaneous complaint although when coming to the clinic she walked with both hips and knees

flexed, presumably because of reflex spasm. She admitted, when questioned, that in fact her legs were painful, but then at the end of the interview again hobbled back to bed and seemed indifferent to her disability. When this patient was taken off Largactil she then said that she remembered her leg had been very painful and hoped she would not need any more injections. Another example of retained reflex activity is that pinching the skin will produce a brisk pupillary dilatation, although the patient seems indifferent to the pain.

Heat regulation is disturbed. It is this property of Largactil, together with the lowering of basal metabolic rate which follows, which has led to the use of the term "hibernation" for its use in surgery and psychiatry on the Continent (3). In the case of patients in bed in the ward their temperature drops to 96° or 97° F.; we have not tried to produce any further fall. At this temperature they do not behave as if they felt chilled, the skin is warm to the touch and mild sweating is usual.

The cardiovascular system shows the following changes. The blood pressure falls, for example, in one case from 180/110 to 130/80. The fall is most marked in the systolic pressure, so that the pulse pressure is reduced. The fall in blood pressure is most marked in those patients who have a raised and labile blood pressure before treatment and is usually of the degree one would expect with rest in bed and sedation. The pulse rate increases, particularly at the onset of treatment. The facies usually becomes pale. Patients often have a dry mouth but appetite is usually good. Apart from a small increase in volume, no change in urinary excretion has been observed and the blood urea has not altered in any of the cases tested.

The mental state of patients who respond fully to Largactil shows some interesting features.

Such patients are relaxed and if in bed often lie curled on their side with a pale, disinterested facies. Few spontaneous movements are made and they will lie quietly staring at the wall. They are not, however, drowsy and respond to questions. If they do fall asleep in the day, sleep is light and they waken readily. They do not complain nor ask for anything. When food is brought they eat without comment and then lie down again. When they do speak their conversation reveals the disorder of mood and thought characteristic of their illness.

The emotional state is one of indifference and apathy, rather than euphoria, as described by some Continental writers. Questioning too, reveals that the basic mood disturbance continues. For example, a depressed patient who appeared calm and relaxed stated that she still felt depressed, had delusions of having committed some wicked deed and believed she should be punished. The sleep rhythm of depressed patients is also unaffected, early waking still occurs, although they now lie quietly instead of being restless.

There is a marked reduction in irritability, and aggressive impulses become easier to control. In spite of the apparent indifference, affective relationships, likes and dislikes develop. The stream of thought is retarded. Patients tend to answer very briefly but if questioning is persistent it can often be observed that there will be a considerable increase in response and a tendency for the original symptoms to return. For example, a manic patient on Largactil lay quietly in bed. Several questions brought monosyllabic answers but when a persistent effort was made to obtain more response, a brief conversation, in which flight of ideas was evident, ensued. The patient then relapsed into silence again. Delusions persist but the patients appear to be less disturbed by them. Several patients have stated that their hallucinations ceased when given the drug and were able to describe their hallucinatory experiences with insight. This can,

of course, occur when the acute phase of a psychosis subsides with or without treatment.

Undesirable responses occur in most patients, particularly at the beginning of treatment but later become less noticeable. Some complain of dizziness, particularly upon sitting or standing up. Three patients received minor cuts or bruises as a result of falling when getting out of bed to go to the toilet. A few have commented on the rapidity of their pulse rate. The dry mouth is an inconvenience and makes talking "sticky". A few have found lethargy and heaviness of the limbs unpleasant sensations. Several patients have complained of dizziness and malaise after a hot bath and I now warn patients to avoid this or any other way in which a large change in external temperature is likely to occur. More severe toxic effects have been observed in 3 cases not having large doses of the drug. In the first case the patient was taking 100 mg. daily in 4 doses and after 3 days complained of malaise and had a temperature of 102. There were no physical signs of infection to account for this and the drug was discontinued for a week. She then appeared quite well physically and a test dose of 50 mg. was given orally. A careful check for the next 4 hours showed little change in her temperature or pulse rate. She ate a good meal in the evening and prepared for bed. Seven hours after taking the drug she vomited and complained of abdominal pain. On examination her temperature was so low that it could no longer be recorded on the usual thermometer, her pulse was barely palpable and respiration shallow and sighing at 16/minute. Her blood pressure could not at first be recorded but gradually appeared at 90/70. Her pupils were contracted and her skin dry and cold. Her abdomen was distended and tense, without visible peristalsis and very little could be heard on auscultation. She vomited again and, as she was resuscitated with blankets and a hot water bottle, gradually recovered. The next day her condition had returned to that prior to taking the drug. Two cases have developed jaundice. This was mild and fluctuating in degree and full recovery occurred in 3 weeks when the drug was discontinued. Tests showed that the jaundice was not of typical obstructive or toxic type.

TABLE I

Clinical Results

No.	Diagnosis	Full relief of symptoms	Much Improvement	Slight Improvement	No Change	Worse
11	Acute Schizophrenic Excitement	—	6	3	2	—
12	Disturbed Deteriorated Schizophrenia	—	4	5	2	1
15	Chronic Schizophrenia ..	—	2	3	7	3
8	Mania	1	3	3	1	—
14	Endogenous Depression ..	2	4	3	4	1
14	Disturbed Senile Dementia	—	10	3	1	—
6	Anxiety State	—	3	—	3	—
—		—	—	—	—	—
80		3	32	20	20	5
—		—	—	—	—	—

The effects on psychiatric conditions deserve further discussion.

Acute schizophrenic episodes, it is found, respond most satisfactorily

if given large doses from the first. Treatment begins with 50 mg. intramuscularly 4 times daily the first day and 75 mg. 4 times daily the second day if the response is insufficient. Those cases which have shown marked improvement are those with great tension and aggressive impulses—the more destructive and aggressive, the more likely the patient is to respond. Those which failed showed childish over-activity with giggling and "silliness". It should be emphasized that although the patient may be quiet and even apparently co-operative, his psychosis continues beneath his calm. One patient who appeared to be responding very well was observed to have secreted a knife in her bedclothes and to have spent part of the night making a hole in the wall of the side-room. The effect of Largactil is most marked in the first few days in this group of patients. All have slowly relapsed and this is so constant that we now use the drug only as a temporary measure to enable a full examination to be made and then commence other treatment.

Two groups of chronic schizophrenic illness were treated, one consisted of "quiet" patients, most of whom had been managing in the community and who returned to it after treatment. The "disturbed" group were all long stay patients who had already had most known methods of treatment with no permanent benefit. This disturbed group contained some patients who improved considerably. As with the acute group, it was the tense, aggressive patient who showed the greatest benefit. It has enabled the staff to make considerable progress with their re-socialization—some have been regularly to occupational therapy who previously could be tolerated for brief periods only. Gradual relapse has led to a need for increased dosage in several, but so far none have required more than 400 mg. daily.

The quiet group of chronic schizophrenic patients showed little response. In those cases who did seem to respond, it was likely that other factors played a part—one patient, for example, said she felt much better because she was relieved to find she was not given E.C.T. This group contained 3 patients who became worse. These were all patients with somatic delusions.

The manic cases have also received large doses from the first day. The response is immediate and is also maintained for as long as the drug is exhibited. It has been found that the most convenient method of administration is to use intra-muscular injections for the first 2 days and then continue the drug by mouth, in roughly $1\frac{1}{2}$ times the intra-muscular dosage. The patient who appeared to make a full recovery had a history of several previous manic episodes. It is probable that recovery would have occurred without the drug, but her period in hospital may have been shortened—her attacks usually lasted 6 months, this one only 3 months.

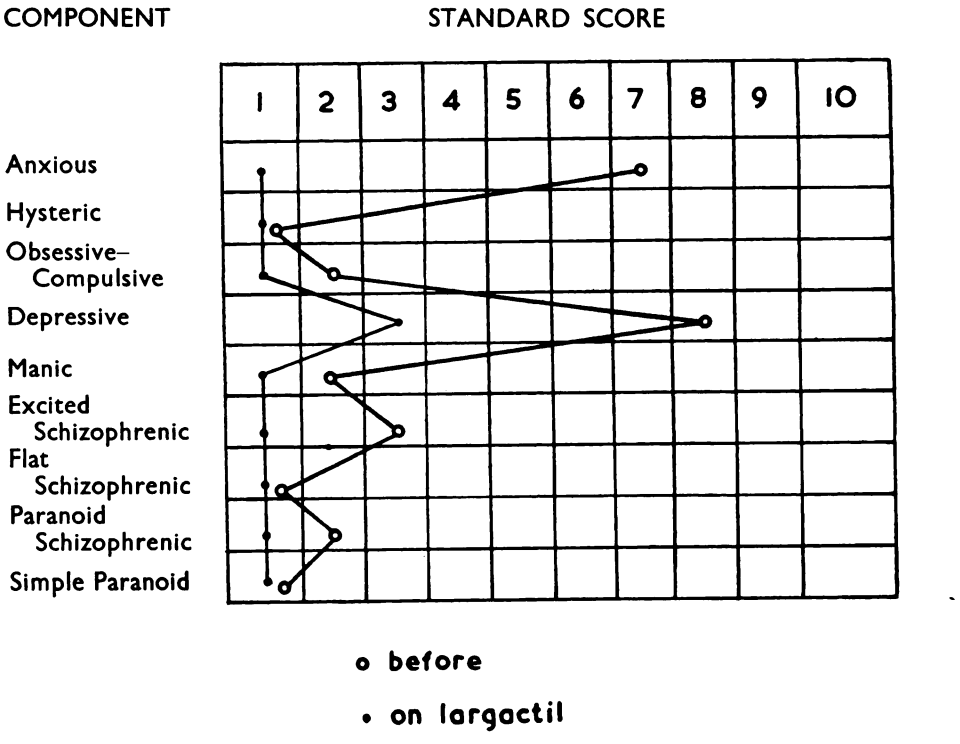
The cases of endogenous depression have all been in the involutional period and have had varying degrees of agitation. The co-operation of the patient is more readily obtained than in the two previous wildly excited groups of patients and treatment was usually commenced with oral dosage of 25 mg. 4 times daily increasing to 100 mg. 4 times daily if necessary. The usual dosage is 200 mg. daily. As with the manic patients, those who respond maintain their response while on treatment but relapse when the drug is discontinued unless recovery from the depressive phase has occurred. Careful enquiry reveals that the patients obtain good relief from agitation and the somatic symptoms of their depression but the depressive mood itself is but little affected—though the patient may complain less, it is still there. For example, early waking often remains, although the patient will lie quietly and not complain. The content of his thoughts remains depressive, even though he no longer looks so dejected,

and delusions are usually unaffected, although the patient may find it easier to ignore them or conceal them. Again a note of warning is necessary, that patients who *look* calm and contented may still be considering suicide.

The group showing the most constant response has been the senile dements with restless behaviour. If restless, the senile dement can present a difficult treatment problem. Sedation may confuse him further. E.C.T., if beneficial, is often only temporarily so and is attended by some risk in the feeble or toxic senile. If ambulant, these restless patients may injure themselves or others; in bed, develop sores and tend to scratch and pick at themselves. It has been found that Largactil is a very useful drug for these patients. Treatment starts with 25 mg. t.d.s. by mouth and rarely is more than 50 mg. t.d.s. required. The patient becomes calm and manageable, eats well and is no longer a nursing problem. Memory loss and disorientation are, of course, unaffected.

The group of anxiety states is too small to justify further comment.

As it became apparent that Largactil was likely to prove a symptomatic method of treatment it was decided that an attempt should be made to assess which symptoms or groups of symptoms responded most satisfactorily. For this purpose the Wittenborn (4) rating scale was used. This scale provides 55 symptoms for assessment. A statistical evaluation has already been made into the significance of these symptoms in each of the common psychiatric disorders. Thus, we have been able to draw a "profile" of our patients to show which components were most prominent in their illness and the response of these to Largactil. For example, the profile of a patient with an agitated depression appeared as follows.



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Thirty-four patients were scored on the first occasion after a period of observation and then a second rating made when the patient had been stabilized on the most satisfactory dosage of Largactil.

Table II shows the results of treatment on the basic components.

TABLE II

	No. of patients with no change of score	No. of patients with improvement in score	Total 34
Acute Anxiety	17	17†	
Conversion Hysteric	30	4	
Obsessive Compulsive	21	13†	
Depressive	19	15†	
Manic	12	22†	
Excited Schizophrenic	12	22†	
*Flat Schizophrenic	18	16†	
Paranoid Schizophrenic	21	13†	
Simple Paranoid	26	8†	

* Called hebephrenic in original Wittenborn articles.

† Significantly lower at 1 per cent. level.

All the components except conversion hysteria are significantly lower after treatment with Largactil as assessed by the Dixon-Mood Signs test (5).

A further analysis of each of the 55 symptom scales was prepared and those with a significant reduction are shown in Table III.

TABLE III

1.	Difficulties in sleeping	××
2.	Rapidity of change of ideas	××
7.	Over-activity	××
10.	Lack of interest in food	××
11.	Impudence or impoliteness	××
12.	Irritability	××
13.	Avoidance of people	××
14.	Loudness of voice	××
16.	Untidiness of appearance	×
18.	Feelings of foreboding	××
21.	Difficulties in carrying out plans	××
22.	Pessimistic feelings about own case	×
28.	Feelings of anxiety	××
34.	Lack of insight into own problems	×
37.	Belligerent behaviour	×
39.	Changes of mood	×
40.	Suicidal tendency	××
43.	Difficulties in making decisions	××
44.	Distortion of facts in defending opinions	×
47.	Fears of committing an abhorred act	××
48.	Irrelevancy or confusion of verbal expression	×
49.	Anxiety over tasks set or new situations	××
54.	Exaggerated affective reactions	××

Those marked × are significant at 5 per cent. level; those marked ×× are significant at the 1 per cent. level.

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TABLE IV

The following were not significantly altered:

3. Unjustified sexual beliefs
4. Obsessive thoughts
5. Delusional belief he is evil
6. Gives in easily to others
8. Unaware of others feelings
9. Use made of physical disease symptoms
15. Behaviour disrupted by phobias
17. Engrossed in plans
19. Cannot resist compulsive acts
20. Exaggeration of well being
23. Fears others misunderstand him
24. Patient's thinking clearly delusional
25. No organic basis for complaints
26. Feels systematically persecuted
27. Believes others influence him
29. Organic pathology with emotional basis
30. Concern over orderliness of surroundings
31. Dramatically attention demanding
32. Overt activity is at a minimum
33. Grandiose notions
35. Compulsive acts continuous
36. Great variation in rates of speech
38. Suspects others of homosexuality
41. Failure of affective response
42. No concern over physical handicaps
45. Hallucinations
46. Memory faults
50. Repudiates earlier insights
51. Speech is stilted
52. Shows homosexual interests
53. Lies or steals
55. Characteristically oppositional

The precise site and mode of action of Largactil are as yet unknown. Clinical observations and some special tests do provide sufficient information for speculation. It is clear that the drug does not act on any particular symptom, disease or syndrome, but leads to a reduction in the intensity of symptoms in many conditions. It is unlikely that the site of action is the cerebral cortex. Use of the Wechsler–Bellevue tests does not show evidence of "deterioration" in patients taking the drug who are still able to co-operate. Also cases of severe senile dementia respond well and in typical manner, and here presumably the cortex is severely damaged and cortical function at a minimum. All the evidence at present available suggests that it is subcortical centres which are affected. For example, we have found that the EEG record, when the patient is given intravenous Largactil, shows changes which are similar to those of normal sleep. There is considerable evidence that midbrain centres "activate" the cerebral cortex and Lindsley *et al.* (6) have shown that destruction of the reticular substance of the midbrain causes the EEG record to show a persistent sleep rhythm. Rorschach records taken before and during treatment of a number of patients who have responded favourably show "decreased energy" —as evidenced by decreased productivity and fewer "whole card" responses. The state of quiet indifference which is shown by the patient suggests a marked reduction in basic drives—or loss of "conation" as described by classical psychological theory. The indifference and lack of response to painful stimuli recalls that of patients with the condition known as Akinetic Mutism. The

latter condition is now thought to be due to a lesion of the reticular formation in the midbrain.

If it is found that Largactil acts on subcortical midbrain centres responsible for the basic drives which "activate" the cortex, it may then be possible to determine more precisely the part played by the cortex or the relevant subcortical area in mental functions and psychiatric illness.

Summary

The effects of a new drug, Largactil, on some psychiatric symptoms and illnesses are described. The evidence suggests that the drug will prove useful as a symptomatic method of treatment. The most likely uses are discussed and a brief speculation made about the site of action.

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