Psychopharmacology

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Foreword

The use of drugs in the treatment of mental illness is far from new. Black hellebore was used in ancient Greece, and through the years many other substances, largely sedative or narcotic in action, have been employed—opium, chloral hydrate, the various barbiturates, and so on ad infinitum. Nearly all these drugs have had one feature in common, namely that they quieted the patient at the expense of clouding his consciousness or even rendering him unconscious. Indeed, the results of the various pharmacological modes have been so unsatisfactory and transient that they have been largely given up in favor of hydrotherapy, occupational therapy, and particularly in the last quarter century, psychotherapy in its numerous forms.

Within the past four years, however, two new drugs have been developed which to many of us seem to be harbingers of a new era—chlorpromazine and reserpine. Both of these substances have the unusual property of sedating the patient, reducing his overactivity, and allaying his anxiety, while at the same time he remains fully conscious and thus far more amenable to the various other therapeutic approaches of a psychological nature. Add to this the facts that the drugs are almost free from untoward side effects, and that they are non-addictive, and it is easy to see why an extraordinary enthusiasm over their possibilities has been exhibited. Whether so sweeping a term as "psychopharmacology" is warranted or not, there is no question that these substances are a valuable addition to the therapeutic armamentarium.

The ten studies presented in this volume, and the discussions thereof, should be read by all interested in hospital psychiatry. The authors are competent and careful workers who have approached this problem with a scientific attitude. Kinross-Wright, for example, warns that we have no panacea in chlorpromazine, although an extremely valuable substance which will add much

to the treatment plan, but which will not suffice alone. Hollister, too, in his comparative study of chlorpromazine and reserpine, points out that when these drugs produce improvement in a patient, "it is often not the beginning of the end of therapy, but rather the end of the beginning," and that they may well increase the burdens of the hospital staff rather than otherwise.

Throughout the volume runs the thread of caution—that even though the drugs are remarkable, there is need of much further study of their effects and dosages, alone or in combination with each other or with other drugs, of their action on the central sympathetic and autonomic nervous systems, and of the possible development of further substances of related and extended properties. New vistas are being opened for the psychiatrist, the neurologist, the physiologist, the psychologist, the pharmacologist, and the chemist.

Thanks are due THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE for making available in convenient form this group of studies.

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Preface

The present volume deals with the material presented at the first major conference on the use of several new pharmaceuticals in the field of mental disease. In the time that has elapsed since that conference a few of the questions raised have been answered, but the solution to most of the problems still lies in the future.

Fields become so rapidly systematized that the volume is also important to indicate the nature of individual thinking before communication in the area was very extensive. There is much valuable information and a certain amount of (inevitable) misinformation.

The excitement raised by the possibilities of this new pharmaceutical approach is best evidenced by the repeated self-cautions that the drugs were not panaceas. Subsequent studies have done nothing to lessen the unvoiced belief that a new door had been opened on the treatment of mental disease.

The present volume by no means represents *all* the workers in this area (even the co-chairman, Dr. Jacques Gottlieb, was snowbound in Chicago), but it does present a sampling of the early accomplishments and the hope for the future.

Gratitude is expressed to the Research Division at Central Islip State Hospital, Central Islip, New York, and to the Research Facility, Rockland State Hospital, Orangeburg, New York, for sharing the expense of stenotyping and transcribing incurred in the preparation of this volume.

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Clinical Observations with Chlorpromazine*

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Observations derived from the study of 42 unselected hospitalized patients treated with chlorpromazine for a variety of psychiatric conditions at The Langley Porter Clinic form the basis of this preliminary report.

Although there has been nearly uniform agreement that chlorpromazine is uniquely effective in controlling manic excitement, considerable uncertainty exists as to its influence upon schizophrenic phenomena, such as delusions or hallucinations. Lehmann and Hanrahan (1) found consistent improvement in manic patients, but obtained less satisfactory responses in schizophrenics. They observed no direct influence on delusional systems or hallucinatory phenomena. Winkelman (2) cited a few cases in which chlorpromazine effected reversal of psychotic symptomatology. Azima and Ogle (3) observed "no particular effect in non-excited schizophrenics" and only moderate symptomatic improvement in those who were disturbed. In a small series reported by Elkes (4) results in general were inconclusive and, although behavioral improvement was sometimes achieved, only a few patients seemed to be less disturbed by their hallucinations and delusions. Similar conclusions were reached by Anton-Stephens (5). Other studies of a more favorable nature have been reported by Kinross-Wright (6), Sigwald (7), and Baruk (8).

Although the results of this paper are based on a small series with a limited follow-up period, it is hoped they may further

* The chlorpromazine used in this study was supplied by Smith, Kline and French Laboratories under the trade name Thorazine.

clarify this issue. Moreover, these results are offered as a record of experience with a new agent, further expanding current knowledge regarding indications, dosage, and administration, the details as to what constitutes an adequate therapeutic trial, and "maintenance" therapy.

PROCEDURE

Experimental Method

The Langley Porter Clinic is a teaching, training, diagnostic, and research center, but research can rarely be given precedence over the other demands made upon the institution. The patient's treatment is paramount and cannot be sacrificed to an experimental procedure. When a new therapeutic procedure such as chlorpromazine is introduced it must fit into the overall treatment and teaching program. Patients are not selected specifically for any one type of treatment, and the psychiatrists in training are not asked to suspend their overall therapeutic efforts in order to test the efficacy of a new drug or treatment method. Because of these factors the patients selected for chlorpromazine therapy did not conform to any distinct pattern or therapeutic indication, and the administration of the drug was part of an all-inclusive treatment program. The mode of application of the treatment was highly individualized in that the residents in training were not bound to any absolute rules in this respect. A degree of consistency and continuity was maintained in that one of us (L.H.M.) had almost daily contact with both patients and therapists during the course of the study.

Case Material

Forty-two hospitalized patients were treated with chlorpromazine between May and December 1954. The ages ranged from 15 to 69 years. The diagnostic groups included schizophrenia, depressive and manic reactions, intractable pain syndromes, organic brain disorders, and a phobic reaction. Sixteen of the patients were treated on the neurosurgical service, where the emphasis was on somatic therapy. Twenty-six were on the adult in-

patient service, where chlorpromazine was added to the other elements of an intensive treatment program which emphasized psychotherapy. The salient clinical features of chlorpromazine-treated group are illustrated by the following descriptions:

9 were schizophrenics placed on treatment after failing with long trials of other types of treatment here and elsewhere.

4 were acute schizophrenics, begun on chlorpromazine within 2 weeks of admission after having been selected as candidates for somatic therapy.

3 were either less acute or recurrent schizophrenics, begun on chlorpromazine 4 to 6 weeks after admission, after having been selected as somatic therapy candidates.

4 were schizo-affective reactions—one admitted for lobotomy, the others with 31, 49, and 52 days of unsuccessful hospitalization here.

1 was a schizophrenic in remission treated essentially for an exaggeration of a pre-morbid behavioral problem.

4 were manic-like reactions, 1 in an undifferentiated psychosis, and the other 3 in manic-depressives, 2 of the latter being recent electro-convulsive therapy failures.

5 were disturbed patients with organic brain disease, including 2 post-lobotomy excitements in schizophrenics, 1 of whom later received a separate course of chlorpromazine therapy as a lobotomy failure.

4 were patients with depression, 2 referred for lobotomy, and another a failure after prolonged treatment here and elsewhere.

5 were patients with intractable pain syndromes.

1 was a phobic in whom the drug was used to help with barbiturate withdrawal.

2 were schizophrenics given the drug to observe its effect on insulin dosages while on coma therapy, along with one other patient already cited in an above group.

Evaluation of Response

Because of the limitations of the clinical sample both in respect to size and homogeneity and because it was felt that in order to

TABLE I. Clinical Data on Ten Psychotic Patients Treated with Chlorpromazine after Being Judged Failures Following Intensive In-Patient Treatment at Langley Porter Clinic

Description of Patient						Current L.P.C. course Pre-chlorpromazine				Chlorpromazine course			
No.	Age	Sex	Diagnosis	Duration, yrs.	Other factors	Duration, days	Est	Ins	Result	Duration, days	Dosage range	Result**	Comment
9	44	F	M.D. dep.	4	Contin. Rx 6 hosp.	74	18	—	(++)	91	300–600	(+)	Also failed c̄. reserpine imp. c̄. est.
11	50	M	M.D. man.	5	Contin. Rx M. & D.	162	20	—	(++)	60*	500–750	++++	Pre-morbid status
16	30	F	S.R. par.	5	Unstable since onset	85	18	—	(+)	81	300	++++	Disc. 11–6–54 pre-morbid level
19	34	M	S.R. par.	4	Hosp. since onset	179	—	49	0	98*	200–900	++++	Remission c̄. good insight
21	20	M	S.R. par.	5	Lifelong amb. schiz.	128	15	49	(+)	82*	375–600	++	Controlled visits home
27	32	M	S.R. un.	1	"Odd" near genius	193	20	50	0	88*	300–800	+++	Pre-morbid level
28	38	M	S.R. par.	4 mo.	Ob-comp. p.e. park.	100	20	—	(++)	52	600	+++	Disc. 11–4–54 remains clear
31	15	M	S.R. cat.	2 mo.	Behav. prob.	112	4	50	++	43*	1200–1600	0	Remains hyperactive aggressive
35	24	F	S.R. un.	10 day	Post partum	175	34	50	(++)	58*	500	+++	No overt symptoms
42	27	F	S.R. un.	4 day	5 mo. pregnant	144	46	—	(++)	12*	500	+++	Excitement delusions cleared

Note: Symbols in parenthesis are degrees of improvement followed by relapse.

0 No improvement
+ Slight improvement
++ Moderate improvement
+++ Marked improvement
++++ Tentatively recovered

* On Rx 12–10–54
** As of 12–10–54

Explanation of Table I

The treatment results were classified according to the following criteria:

++++ *Tentative Recovery:* The remission has not been present sufficiently long to justify the term "recovered," and for a variety of reasons the patient may yet be hospitalized, with his total course of chlorpromazine incomplete. However, he displays no overt symptoms and is described as having returned to his pre-morbid personality. He has a significant degree of insight, and is usually profiting from psychotherapy. He functions well socially. His remission appears capable of resisting stress, rather than being of the "borderline" variety.

+++ *Markedly Improved:* The patient no longer presents obvious psychotic features. If he is discharged, he is making a satisfactory, although limited, adjustment. If hospitalized, plans for discharge are being made. He may have little insight, but there is evidence of continuous progress in psychotherapy. He feels well and can face situational problems. He is socially acceptable to family and friends.

++ *Improved:* The patient is "manageable," but can make a continued adjustment only in the hospital. Most of his psychotic manifestations have cleared, but some remain. He can make home visits without difficulty and is somewhat more accessible to psychotherapy.

+ *Slightly Improved:* The patient needs continuous hospitalization and many of the presenting symptoms remain, although there has been a reduction in quantity and intensity of psychotic behavior. He may at times be a management problem but is generally more easily controlled than before treatment. His social adjustment is a tenuous one. The degree of improvement is not sufficient to warrant long-term trial of chlorpromazine.

± *Indeterminate:* Results not evaluated because of clearly inadequate course. Favorable responses may be included in this group when the relationship of chlorpromazine to the clinical response is questionable.

0 *Failure:* No essential change or worsening, despite adequate trial of the drug.

produce an adequate therapeutic effect the drug needed to be administered in sufficiently high dosage to cause unmistakable physiological side effects, attempts to provide "controls" by utilizing a sample large enough to be statistically valid or by using "blind" experimental techniques were impractical. Evaluation could be made only by having each patient serve as his own control, and by attributing only marked and definite changes to the drug. It would be especially rewarding if these changes occurred in patients previously refractory to other therapy or unchanged after considerable periods of hospitalization here (Tables I and II). Relapses occurring upon withdrawal of the drug after a

TABLE II. Duration of Hospitalization at Langley Porter Clinic of 26 Patients before Treatment with Chlorpromazine[a]

Number of days	Total cases	Hospital days per case
<30	6	7, 9, 11, 14, 20, 24
31–60	7	31, 31, 42, 43, 46, 49, 52
61–90	3	74, 81, 85
91–120	3	96, 100, 112
121–150	2	128, 144
151–180	3	126, 175, 179
181–210	2	193, 210

[a] Average hospitalization pre-chlorpromazine equals 81 days per case.

favorable response would also help "control" evaluation. Careful appraisal by the medical and nursing staff would help determine the importance of concurrent factors that might correlate with a given change. This type of evaluation does not entirely rule out the possibility of a spontaneous remission and the limited period of follow-up does not preclude the possibility of a relapse in the future.

ADMINISTRATION AND DOSAGE

Early workers using chlorpromazine were handicapped by lack of familiarity with this agent, and the attitude toward dosage and duration of treatment was a conservative one. As experience

has been gained, the trend with severely ill patients has been toward utilization of higher dosages over longer periods. Lehmann and Hanrahan (1) occasionally found it necessary to administer the drug in doses up to 800 mg in cases of acute psychomotor excitement, but continued such courses only for three days to four weeks. In less disturbed patients the duration of treatment was 2 to 3 months, but dosages for these were in the order of 50 to 200 mg. Kinross-Wright (6) observed that dosage depended upon the nature of the illness and individual response and reported amounts up to 2000 mg daily, with average requirements of 400 to 600 mg. However, high levels were limited to about 3 weeks' duration, and most patients were weaned from chlorpromazine within 2 months. Azima and Ogle (3) administered an average dose of 400 mg daily, but only for 3 weeks, and reported no particular effect in non-excited schizophrenics. These authors also used other somatic therapy in 50% of their cases "when no significant effect appeared within a few days." The papers of Elkes (4) and of Anton-Stephens (5) indicate an even more conservative approach. Their patients generally received from 100 to 200 mg daily, but trials were carried on for many weeks. Perhaps the inconclusive nature of their results is a reflection of their conservatism.

Our experience as the study has proceeded has led to the use of higher dosages over longer periods than generally reported. Proper adjustment of the two variables, time and amount, spelled the difference between success and failure in some cases.

For the most effective control of excited, disturbed, and assaultive patients, it is desirable to produce a state of drowsiness and lethargy over a period of several days, using relatively high doses administered intramuscularly. Individual tolerances vary, and for this reason the initial dose should be limited to 25 mg. Depending upon the effect, subsequent doses of 25, 50, or even 100 mg intramuscularly, may be given within 1 to 3 hours. At times, in order to institute control of extremely disturbed patients, as much as 750 mg intramuscularly or 900 mg by combined parenteral and oral routes has been used. Some patients required from 800 to 1000 mg daily by mouth, over a period of several weeks to