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Psychopharmacology Service Center

Bulletin

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Inquiries about the Psychopharmacology Service Center's program are invited. Please write to:

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*NIMH-Sponsored Collaborative Study of Phenothiazine Treatment of Acute Schizophrenic Psychoses**

The National Institute of Mental Health, through its Psychopharmacology Service Center, is sponsoring a collaborative study of phenothiazine treatment of acute schizophrenic psychoses. The comparative efficacy of thioridazine (Mellaril), fluphenazine (Permitil, Prolixin), and chlorpromazine (Thorazine) in the treatment of a large group of hospitalized acute schizophrenic patients will be evaluated at nine psychiatric institutions.

Investigators at the collaborating hospitals applied for, and have now received, NIMH research grants which will support their participation in the study, which is expected to begin in February 1961 and to continue for 2 years. The grants were awarded to the following investigators and institutions on the basis of their interest and research experience, the availability of patients, and the geographical location and type of hospital organization:

Principal Investigators	*Institutions*
Edwin M. Davidson Melvin M. Kayce	Boston State Hospital Dorchester, Mass.
Richard Steinbach Bernard Levy	Georgetown University and D.C. General Hospital, Washington, D.C.
Robert R. Knowles Edgar A. Moles	Kentucky State Hospital, Danville, Ky.
Kathleen Smith George A. Ulett	Washington University and Malcolm Bliss Mental Health Center, St. Louis, Mo.
James H. Ewing Harold H. Morris	University of Pennsylvania and Mercy-Douglass Hospital, Philadelphia, Pa.
Frederic F. Flach Charles I. Celian	Cornell University and Payne Whitney Clinic, New York, N.Y.
Guy M. Walters Christopher F. Terrence	Rochester State Hospital, Rochester, N.Y.
Martin Gross Irene L. Hitchman	Springfield State Hospital, Sykesville, Md.
John Donnelly Francis J. Braceland Bernard C. Glueck, Jr.	The Institute of Living, Hartford, Conn.

The study is under the overall supervision of Jonathan O. Cole, Chief of the Psychopharmacology Service Center. Gerald L. Klerman, PSC Research Psychiatrist, will serve as project coordinator. Other members of the PSC staff who are involved in the study are Eva Y. Deykin, Research Social Worker, Martin M. Katz, Research Psychologist, and C. Jelleff Carr, Chief of PSC's Pharmacology Unit.

The Planning Committee, composed of the principal investigators in the collaborating hospitals and the participating members of the PSC staff, provides for the coordination and execution of the specific projects. Because of the parallels with the Veterans Administration Cooperative Studies of Chemotherapy in Psychiatry, the committee maintains close liaison with the VA Central Neuro-Psychiatric Research Laboratory at Perry Point, Md.

The Committee on Clinical Psychopharmacology, a group of outside consultants appointed by the NIMH, serves as the advisory and consultative body to NIMH on this project, as well as on other aspects of the Center's clinical program. Members of this committee are Henry Brill (Chairman), Deputy Commissioner of the New York Department of Mental Hygiene, Albany, N.Y.; Sol L. Garfield, Professor of Medical Psychology, Nebraska Psychiatric Institute, Omaha, Nebr.; Goldine Gleser, Associate Professor of Psychology, Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio; Leo E. Hollister, Chief, Medical Service, Veterans Administration Hospital, Palo Alto, Calif.; and George D. Ulett, Associate Professor, Department of Psychiatry, Washington University Medical School, St. Louis. Mo.

DEVELOPMENT AND DESIGN OF THE STUDY

The Committee on Clinical Psychopharmacology and the PSC staff designed this research project during the spring of 1960. Following general approval by the National Advisory Mental Health Council of the principles of the study, the Center staff discussed it with a number of clinical investigators who had previously expressed interest in such a project. In June 1960, representatives from more than a dozen institutions met to plan and clarify the research methods and aims of the study. A number of the investigators who attended the meeting subsequently submitted applications for an NIMH research grant to support their participation in the study.

Thus the final design and methodology of the study resulted from the combined efforts of the Committee on Clinical Psychopharmacology, members of the PSC staff,

*Prepared by Gerald L. Klerman, Research Psychiatrist, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda 14, Md.

and the principal investigators. The staff of the Biometric Laboratory of George Washington University, which operates under contract to the NIMH, will provide ongoing consultation on matters of research design and statistical techniques and will analyze the data from the study.

The primary aim of the project is to evaluate the effects of two new phenothiazine derivatives, thioridazine (Mellaril) and fluphenazine (Permitil, Prolixin) on schizophrenic symptoms and behavior by comparing them with the effects of chlorpromazine (Thorazine). Each of the 9 hospitals will study 40 patients (10 in each of the 4 treatment groups). Newly admitted schizophrenic patients aged 16 to 40 will be selected for the study if they present two or more of the following types of symptoms or behavior: Thinking and speech disturbances, catatonic motor behavior, paranoid ideation, hallucinations, delusional thinking, disturbed affect and emotion, and disturbances of social behavior and interpersonal relations.

The patients will be on the prescribed research treatment regimen for 6 weeks. A double-blind procedure will be used throughout. Improvement during the hospitalization phase will be assessed by the Lorr Inpatient Multidimensional Psychiatric Scale, the Burdock Ward Behavior Rating Scale, the Clyde Mood Scale, and clinical judgments.

In addition to the primary aim, evaluating the efficacy of the drugs, the study will also allow for the followup of a large cohort of schizophrenic patients for at least 2 years. At 6-month intervals, assessments will be made of the patients' discharge status, psychopathology, social performance and adjustment, and treatment program. Social workers will interview family members for their perceptions of the patients' progress, home conditions, and attitudes toward treatment.

COLLABORATIVE AND COOPERATIVE RESEARCH

Since World War II, collaborative and cooperative research, in which a number of institutions follow a common research design, has been successful in many areas of medicine. The trials of antimalarial drugs during World War II, the extensive studies of antituberculous drugs now in their 17th year, and the British-United States research on cortisone and aspirin in acute rheumatic fever are some examples. NIH experience with cooperative research includes the current extensive cancer chemotherapy program of the National Cancer Institute and the Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurological and Sensory Disorders of Infancy and Childhood being conducted by the National Institute of Neurological Diseases and Blindness.

In psychiatry, cooperative research has been slower to develop, although the extensive studies of penicillin in CNS syphilis during the 1940's stands out as a notable early effort. In recent years the Veterans Administration has developed its Cooperative Studies of Chemotherapy in Psychiatry. The VA studies have now demonstrated the value of cooperative studies as a means of clarifying important issues in psychopharmacology.

From the scientific point of view, there are two major reasons for collaborative studies of psychiatric drug therapy. First, such studies allow one to increase the generalizability of findings. If the only question being asked is whether drug X is better than placebo, then the answer can often be obtained with groups of 20 to 40 patients. However, much larger groups of patients are necessary if one wishes (*a*) to make refined discriminations between compounds which are closely related chemically and pharmacologically, such as the phenothiazines; (*b*) to increase knowledge of predictors of drug response; or (*c*) to define the specific types of patients for whom a particular drug is best suited.

Multihospital studies allow for comparisons among institutions. In the mental health field there has been much discussion of the possible differences in the effectiveness of drugs given in varying hospital and clinical settings. A multihospital study provides both the number of hospitals and the number of patients needed to clarify these complex drug-environment interactions.

The pros and cons of conducting large-scale, multihospital cooperative studies of psychopharmacological agents have been carefully weighed by NIMH and its advisory groups during the 4 years of the Institute's program in psychopharmacology, administered by the PSC. The NIMH first developed a wide program of basic and clinical studies in psychopharmacology, and has until now centered its major efforts upon the stimulation and support of individual research projects. While this program has resulted in a great deal of clinical drug research, it has not met the need for large-scale evaluation of widely prescribed psychiatric drugs.

The several Cooperative Studies of Chemotherapy in Psychiatry which have been developed by the Veterans Administration in recent years have provided a great deal of useful information about some of the newer psychiatric drugs. The generalizability of these findings has, however, been limited by the special characteristics of the clinical material available to the Veterans Administration. The NIMH Collaborative Study of Phenothiazine Treatment of Acute Schizophrenic Psychoses has been designed to provide information on the effectiveness of new drugs in a population which will include female patients. The patients will, in general, be more acutely ill and will be treated in a wider range of hospital milieus than could be the case within the Veterans Administration. In addition, the study is designed specifically to explore possible interactions between hospital milieu and drug response in a more systematic manner than has

been possible in the earlier studies conducted by the Veterans Administration.

The success of the Collaborative Study, a complex research endeavor, will depend upon close and continuing cooperation and collaboration between the research teams in the participating hospitals, the staff of the Psychopharmacology Service Center, and the advisory bodies of the National Institute of Mental Health. As this project develops, it is hoped that the participating groups will undertake a continuing series of investigations of the treatment of acute schizophrenic psychoses.

NIMH Grant Support for Early Clinical Drug Evaluation Units

In November 1960, the National Institute of Mental Health announced the establishment of special grants for early clinical investigations of psychiatric drugs. The primary purpose of the grants is to broaden the present scope of early clinical trials of promising new compounds and to make it possible to screen more new drugs for effectiveness in the treatment of psychiatric disorders.

The grants will be awarded to a limited number of carefully selected clinical units to support trials of promising compounds in patients to determine the safety, appropriate dose ranges, and side effects of the drugs, preliminary studies of their clinical effectiveness in the treatment of particular symptoms or syndromes, and small controlled comparisons of new drugs with known standard drugs or placebo. Because of the need for flexibility in tailoring a clinical research design to fit the types of drugs and types of patients under study, an attempt will be made to achieve an adequate balance between careful observational studies and small-scale comparative and controlled studies.

This particular area was chosen for expansion because NIMH considered it to be more seriously in need of further support than either of the other two major stages of new drug development; i.e., (*a*) preliminary screening of new drugs in animals to determine safety and pharmacological activity, which is being adequately supported by the drug industry and by National Institutes of Health grants for basic research, and (*b*) definitive clinical drug research (controlled clinical trials and hypothesis-oriented clinical investigations), which is amply provided for by the existing NIMH research grant program in psychopharmacology.

Expansion of support for early clinical drug evaluation was therefore recommended by the Advisory Committee on Psychopharmacology and by the National Advisory Mental Health Council, and the Congress subsequently provided funds for the establishment of special grants in this area. The program will be administered by the Psychopharmacology Service Center.

*NIMH-PSC Outpatient Study of Drug-Set Interaction**

The National Institute of Mental Health has recently awarded research grants to Karl Rickels, of the University of Pennsylvania, Philadelphia, Pa., and E. H. Uhlenhuth, of the Johns Hopkins University, Baltimore, Md., to support their participation in a special research project initiated by the Psychopharmacology Service Center. The study is a double-blind, placebo-controlled investigation of the effects of an active psychopharmacological agent (meprobamate) and physicians' attitudes on a carefully defined sample of neurotic outpatients. It is one of the first known attempts to control experimentally the communication of differential attitudes by physicians when administering medication. The project is to be conducted at three clinics simultaneously, the Henry Phipps Psychiatric Clinic of the Johns Hopkins University, the Functional Clinic of the Hospital of the University of Pennsylvania, and the Neuropsychiatric Clinic of the Philadelphia General Hospital.

The study was designed by the staff of PSC's Special Studies Unit in collaboration with the two principal investigators, Drs. Rickels and Uhlenhuth, and was approved by the Committee on Clinical Psychopharmacology and the Advisory Committee on Psychopharmacology, both of which are appointed groups of consultants who serve the National Institute of Mental Health in an advisory capacity. The two principal investigators subsequently applied for and received, on recommendation of the National Advisory Mental Health Council, research grants to carry out the study. Coordination of the project will be handled by the Center's Special Studies Unit, whose members are Seymour Fisher, Seymour H. Baron, Mitchell B. Balter, and Elizabeth Hackett. Under contract with the National Institute of Mental Health, the Biometric Laboratory of George Washington University, Washington, D.C., will assist in the analysis of the data.

RESEARCH DESIGN AND METHODS

The Outpatient Study of Drug-Set Interaction is part of a larger special program which is concerned with the effects of psychological set and social interaction upon drug response in both patients and normal subjects. The study has three main purposes:

1. To determine whether meprobamate, administered for a 6-week period at a fixed dosage, is more effective than an inert placebo in the treatment of neurotic outpatients. (See Laties and Weiss, 1958.)

2. To determine whether patients' expectations or set (as induced by contrasting behavioral roles by the doctors participating in the project) have a significant effect upon treatment course. Set will be varied by training one group of doctors (the "T" group) to maintain a positive, consistent, enthusiastic, "therapeutic" approach to their patients; another group (the "E" group) will be trained to manifest a more aloof, uncertain, "experimental" approach in relating to their patients. The "T" therapists will attempt to convey the belief that they are treating the patient with a known, efficacious agent; the "E" therapists will attempt to convey the belief that they are evaluating the agent.

3. To determine whether a significant drug-set interaction exists; i.e., to test the hypothesis that a "T" set will potentiate response to the active drug.

Following a pilot study of 24 patients, a total of 200 patients will be treated for a 6-week period, 50 patients being assigned to each of the following 4 treatments: Meprobamate combined with "therapeutic" set; meprobamate combined with "experimental" set; placebo combined with "therapeutic" set; and placebo combined with "experimental" set. The basic research design is in the form of a 2 x 2 factorial analysis, with each of the two independent variables being varied in two ways. Table 1 shows the four-cell design, which permits an exact statistical test (by analysis of covariance) of the three hypotheses.

Patients will be seen biweekly for 6 weeks. In order to rule out the effects of the personality characteristics of the doctors in the study, a total of 12 physicians will participate, 4 psychiatric residents at each of the 3 clinics. Thus, interclinic comparisons will be possible. An attempt will also be made to validate the role behaviors in the doctors.

TABLE 1.—*Research Design*

Set	Medication (N=200 patients)	
	Meprobamate	Placebo
"Therapeutic"	50 patients	50 patients.
"Experimental"	50 patients	50 patients.

*Prepared by Seymour Fisher, Chief, Special Studies Unit, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda 14, Md.

The dependent variables are ratings—patients' self-ratings as well as doctors' ratings—on a symptom-distress checklist, on the Clyde Mood Scale, and of overall change. Dropout rate will also be considered.

BACKGROUND OF THE STUDY

The impetus for this study stems from the Psychopharmacology Service Center's interest in various methodological problems involved in the clinical evaluation of psychiatric drugs, in particular the problem of attitudinal variables and their effect upon drug response. The basic thinking underlying this approach was presented in a draft paper prepared some months ago (Fisher, 1960). That paper also pointed out the kinds of specific research designs which would test for any unique interactive effects between medication and set (i.e., attitudes and expectations).

A review of the literature has revealed much clinical suspicion that patients' expectations may interact with medication to produce differential clinical effects, but supporting evidence for such speculations is rather tenuous. Sabshin and Ramot (1956) note that: "Often the patient may interpret a change in his internal milieu in the context of being a change in the expected direction. It is thus possible for a subtle type of communication to take place . . . and this may potentiate the drug effects. Hence a relatively specific effect can be geometrically increased." However, the investigators do not present empirical evidence.

That a particular drug can have one effect under one psychological condition and a quite different effect under another psychological condition is well documented experimentally. This holds for animals (e.g., Brown, 1958; Chance, 1946; Gunn and Gurd, 1940) and for humans. In an elegantly designed experiment, Hill, Belleville, and Wikler (1957) clearly demonstrated a significant interaction between incentive conditions and drug response in human subjects. Nowlis and Nowlis (1956) and Starkweather (1959), in studies of normals, report complex interactions between drug response and the subject's perception of other subjects' behavior.

In the clinical setting, Feldman's paper (1956) indicated that the physician's attitude toward medication is reflected in his report of degree of improvement in psychiatric patients. However, that is not conclusive evidence for an interaction effect, since placebos were not employed for comparison, and evaluation of the patients was badly contaminated by the fact that each of the participating physicians made his own overall estimate of change.

The latter comment also applies to a clinical study reported by Kast and Loesch (1959), who similarly argue that the action of a psychopharmacological agent can be made disproportionately more effective than an inactive placebo when the medication is administered within the context of a positive set (i.e., a given set can potentiate drug response). While their theoretical formulation is quite ingenious and heuristic, their experimental design does not afford a valid test of their hypothesis.

A more dramatic study concerned with potentiation was published by Uhlenhuth et al. (1959). In a double-blind, cross-over design using meprobamate, phenobarbital, and placebo, two physicians obtained significantly different rates of drug-related improvement in their patients. One physician (who was "therapeutic" and enthusiastic) obtained significant differences between the active drugs and placebo, while the other physician (who was more skeptical and "experimental") found no significant differences among the three agents. The results of this study are certainly suggestive, but they are difficult to interpret since one cannot state definitively what the effective differentiating characteristic(s) between the two physicians was (i.e., in addition to "attitude," they obviously differed in an infinite number of ways), and because of the complication introduced by using a three-way cross-over of drugs.

In March 1960, Irvin S. Wolf, of Denison University, and PSC's Special Studies Unit tested the interaction hypothesis on normal subjects who were given dextroamphetamine and placebo under three different attitudinal sets (consistent, uncertain, and inconsistent expectations). Analysis of covariance for a 3 x 2 factorial design on subjective and psychomotor dependent variables revealed a number of significant or near-significant trends (all in the anticipated direction) suggesting a drug-set interaction.

The significance of this research approach is perhaps revealed in the following considerations. When reference is made to a "placebo response," it is evident that the concept is a complex one. In a placebo-controlled experiment, not only is there a *general* set of expectations associated with the symbolic value of receiving medication from a prestige authority, but there are also undoubtedly *specific* expectations about the nature, purpose, and action of the medication. These different kinds of expectations have been discussed elsewhere (Fisher, 1960), but one important implication is worth repeating here.

The most frequently used model in controlled evaluations of drugs assumes that the "placebo response" (i.e., the amount of change attributed to nonpharmacological factors) is a type of "error" involved in assessing the pharmacological effects of the active drug: If one can accurately measure the degree of placebo response, that effect can be subtracted from the total effect, thus giving the pharmacological component. This assumes that the psychological (i.e., general and specific expectations) and the pharmacological components are *additive* in nature. As shown in figure 1, specific expectations

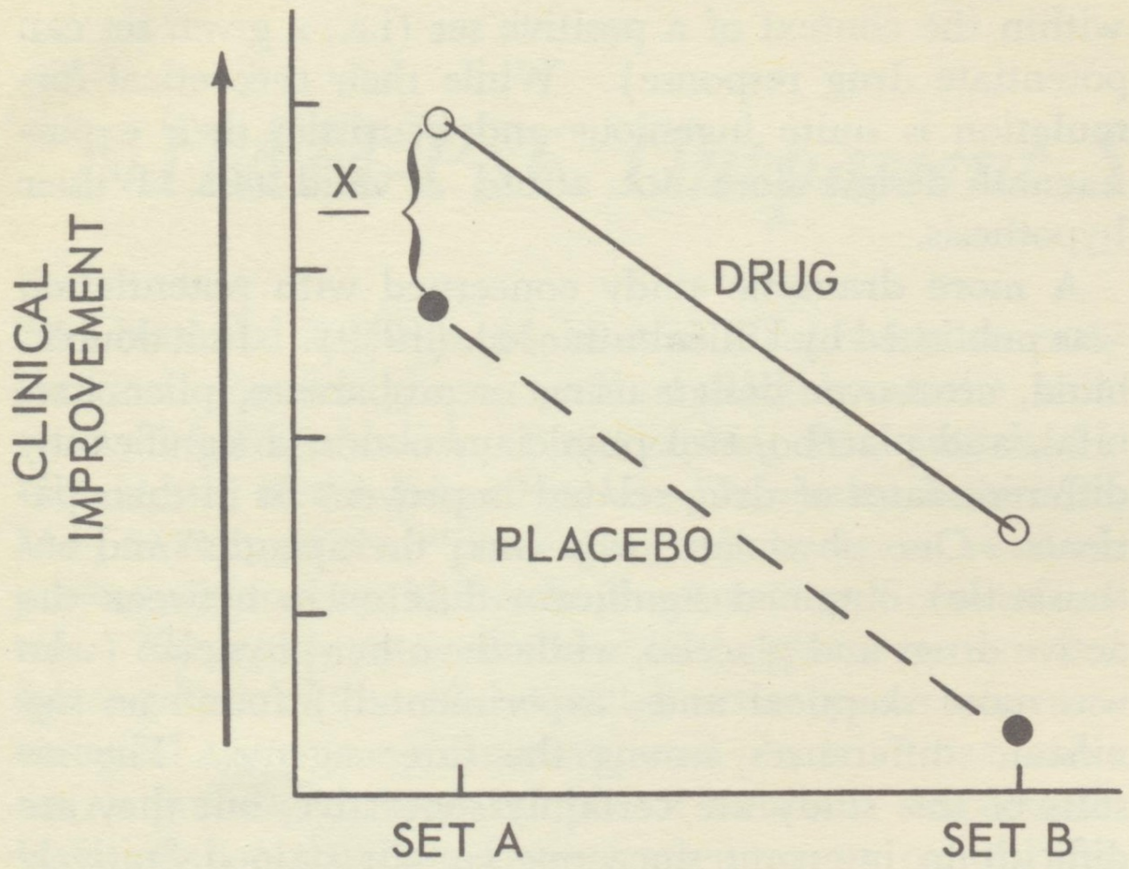

FIGURE 1. *Hypothetical Data Illustrating Additive Model.*

(sets A and B) do affect the response, but essentially equally for subjects who receive the active drug and for those who receive placebo. Irrespective of the set under which the drug is evaluated, the conclusion is the same—the drug is X units more effective than placebo.

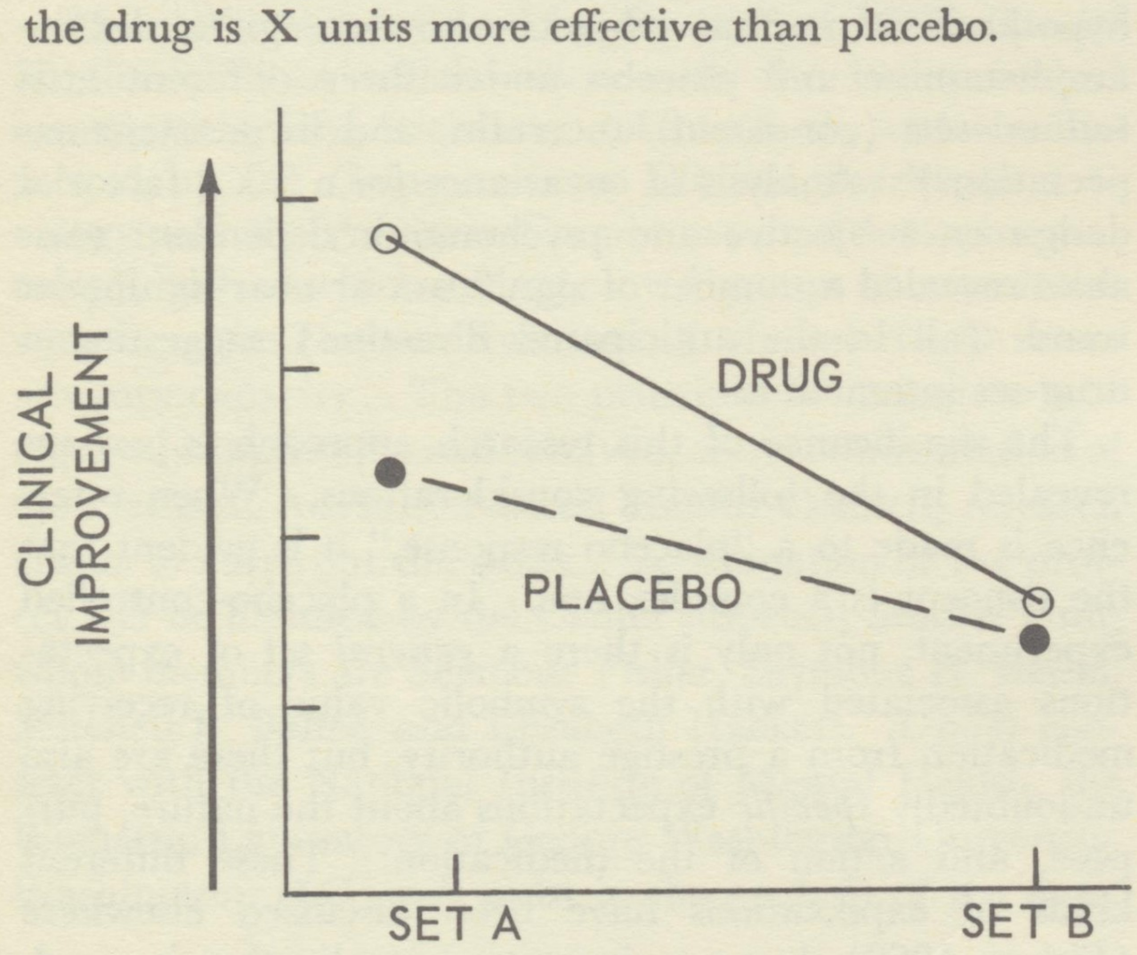

FIGURE 2. *Hypothetical Data Illustrating Interactive Model.*

A quite different possible model, however, can be built on the assumption that the pharmacological and psychological components are interactive. As shown in figure 2, the specific expectations in set A *potentiate* the drug response, and one cannot generalize the effect of the drug without taking into account the set under which it was administered. Note in figure 2 that if the drug were evaluated in an experiment in which only set B was operative, one would conclude that the drug was no more effective than placebo—a conclusion which, though correct, would have to be limited to the conditions of the experiment. Figure 2 also shows, however, that under set A the drug was obviously superior to the placebo—an equally correct conclusion for the given conditions. Thus, if it were established that the interactive model is more appropriate for certain kinds of clinical evaluation, one would run the risk of rejecting as ineffective a treatment which really does have an effect (type II error) whenever the clinical trial is conducted under inappropriate conditions of set.

A great deal has been written about the need for controls in clinical research. It has often been noted that new forms of therapy are enthusiastically received on the basis of early uncontrolled clinical impressions, only to be laid to rest by subsequent controlled evaluation (Cornell Conference, 1954). Recent papers by Foulds (1958) and Astin and Ross (1960) show that a significantly greater number of uncontrolled studies in psychopharmacology yield positive results than do controlled experiments. Undoubtedly, this difference can be partly attributed to such factors as lack of controls, faulty or biased measurement, faulty design, etc., in the uncontrolled studies, or to insufficient dosage or duration of medication, or sampling bias, in the controlled experiments. On the other hand, it is possible that this difference is *not* all due to various kinds of "error." If some genuine interaction effect should exist between physician-milieu and drug action, that would go a long way in accounting for many of the apparent discrepancies between the findings of hardheaded researchers and those of equally hardheaded clinicians. In uncontrolled clinical trials, the patients may be exposed to a quite different "attitudinal" atmosphere: They more often see themselves as being "treated" rather than "researched," and that might provide a quite different setting for drug action. In many controlled experiments, the patients are definitely aware that they are participating in a research project (implying "Let's see if the drugs will help you"), and such a perception is probably reinforced whenever patients find themselves periodically being observed, tested, and probed.

The overall aim of the Outpatient Study of Drug-Set Interaction is to attempt to create experimentally these two contrasting attitudinal sets within the context of a controlled clinical evaluation.

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*Research Conference on Drugs and Community Care**

In September, the Psychopharmacology Service Center sponsored a "Research Conference on Drugs and Community Care" to bring a number of investigators together to discuss problems of research on the use of drug therapy in the care of psychiatric patients living in the community. The conference, held in Washington, D.C., dealt with studies of both acute and chronic patients, evaluations of home-treatment or day-hospital care, maintenance therapy, treatment specifically designed to prevent relapse in previously hospitalized patients or to treat relapsed patients in the community, and followup studies.

The primary objectives of the conference were (*a*) to permit investigators whose research in this area is supported by NIMH to discuss problems and to exchange ideas and experiences related to solutions to problems; (*b*) to provide the Center, its consultants, and the participating research investigators with an overview of the nature of the research now being supported; (*c*) to determine what has been learned from these studies about the role of drugs in the community care of psychotics; and (*d*) to assess progress in dealing with the technical aspects of these kinds of research; e.g., the establishment of criteria and the development of methods for classifying patients and for evaluating change and adjustment.

In addition to NIMH grantees conducting research on drug therapy in the community, the participants included investigators whose interests and experience were compatible with the aims of the conference and several who are just entering research related to this general field.

The conference was organized by Martin M. Katz, PSC research psychologist. The formal participants were Dean J. Clyde, Washington, D.C.; Jonathan O. Cole, PSC; Joel J. Elkes, Bethesda, Md.; David M. Engelhardt, Brooklyn, N.Y.; Leon Epstein, Sacramento, Calif.; Seymour Fisher, Houston, Tex.; Norbert Freedman, Brooklyn, N.Y.; Sol L. Garfield, Omaha, Nebr.; Goldine Gleser, Cincinnati, Ohio; Bernard Glueck, Hartford, Conn.; Milton Greenblatt, Boston, Mass.; Martin Gross, Sykesville, Md.; Leo E. Hollister, Palo Alto, Calif.; Martin M. Katz, PSC; Else B. Kris, New York, N.Y.; Jordan Lawrence, Sykesville, Md.; Mark Lefton, Columbus, Ohio; Samuel B. Lyerly, Washington, D.C.; David Mann, Brooklyn, N.Y.; Richard D. Morgan, Sacramento, Calif.; Benjamin Pasamanick, Columbus, Ohio; Leonard Pearlin, Bethesda, Md.; Seymour Perlin, New York, N.Y.; George A. Ulett, St. Louis, Mo.; and Joseph Zubin, New York, N.Y.

The first half of the program was devoted to reports on six research projects, each of which was related to some aspect of drugs and community care. The papers reporting the projects emphasized aims and general research design, methodological and operational problems, and plans for future work. The second half of the conference was devoted to theoretical and practical problems of methodology. In many cases, new methods and methodological problems mentioned briefly in the research reports were presented in greater detail and discussed more fully during the second half of the meeting.

Some of the points made in each paper are summarized in the following paragraphs. These summaries do not, of course, cover all of the points covered by the speakers, but it is hoped that they will provide at least enough information to convey some impression of the overall content of the meeting and of the major issues which were considered.

*Prepared by Martin M. Katz, Research Psychologist, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda 14, Md.

SIX RESEARCH PROJECTS

Home Versus Hospital Care for Schizophrenics. Presented by Benjamin Pasamanick, Department of Psychiatry, Ohio State University Medical School, Columbus, Ohio. This study is designed to test the hypothesis that acute schizophrenic patients can be treated at home when proper public health care is combined with appropriate drug therapy. All first-admission schizophrenic patients referred to the Columbus Psychiatric Institute are to be considered for the study. Those who are suicidal, homicidal, or so violently disturbed that it would be impossible to keep them in the home will be dropped from further consideration. The remaining patients will then be randomly assigned to one of the following three treatment groups: (*a*) A group treated at home with drugs plus frequent visits by a public health nurse; (*b*) a group treated at home with placebo plus frequent visits by a public health nurse; and (*c*) a hospitalized group treated with the usual methods of the hospital. The three groups are to be evaluated before treatment, after 1 year, and after 2 years by psychiatric and psychological examinations, and by reports and ratings from nurses and social workers (including interview data from patients and their families). Quality of housing and general home environment of all three groups will also be rated.

A public health nurse, working in consultation with the psychiatrist and social worker, will frequently visit each home-care patient to give nursing guidance and counsel to the patient and his family. Patients in the home-care groups will be hospitalized when that is recommended, on the basis of previously established criteria, by a diagnostic council from the Institute.

The hospitalized group and the home-treatment groups are to be compared for total length of hospitalization, psychiatric condition, and family reaction and receptivity. The two home-care groups—one on placebo, one on drug—will be compared for rate of hospital admission.

Discussion of this study was devoted to such matters as control of medication in the home-care groups, degree of comparability of the hospitalized and home-treatment groups, and problems related to hospitalization of patients assigned to home treatment. Later in the conference, Lefton, also from the Columbus Psychiatric Institute, presented a detailed discussion of the interview schedules which will be used in the study.

A Study of Ataractics in Outpatient Schizophrenia. Presented by David M. Englehardt and Norbert Freedman, State University of New York, Downstate Medical Center, Brooklyn, N.Y. This project was described as a longitudinal study of the effects of tranquilizers on the community adaptation of schizophrenic outpatients. Questions of interest in the study are whether continuation of medication after an initial gain will prevent relapse, whether further improvement is noted when medication is continued, and, when there has been no initial gain, whether improvement will occur after prolonged administration of drug. Changes in symptomatology and in social behavior associated with drug therapy will be assessed after a brief time and after sustained administration of drug. The following criteria of outpatient adaptation are being used: Maintenance of outpatient status (i.e., avoidance of hospitalization), reduction in psychopathology, freedom from functional decrement, reduction in social dysfunctioning, concordance between social adaptation and psychopathological changes, and stability of clinic course during a prolonged period (up to 24 months) of continuous treatment with drug or placebo.

Baseline psychiatric and psychological data are obtained during the first week. The patient is then placed on promazine, chlorpromazine, or placebo. Dosage levels are flexible and medication is administered double-blind. Supportive psychotherapy is given, but the emphasis is on medication. Patients are seen in the clinic at frequent intervals. Detailed re-evaluations are conducted after 3 months and at the end of 1 year.

Preliminary findings reported by Engelhardt show that the rehospitalization rate is significantly lower in the drug groups than in the placebo group. Also, the number of patients showing clinical improvement at 6 months is much higher in the drug groups than in patients on placebo, as is the rate of improvement of a group of patients who demonstrate severe thought disturbance on initial evaluation. Further, the amount of social dysfunctioning as reported by the relative has been found to be greater in the placebo group than in the patients on chlorpromazine.

A detailed report on the accumulation and analysis of the data on social behavior was presented later in the meeting by Mann and Freedman, participating investigators in the study.

Freedman also discussed the problem of dropout, which has been one of the major difficulties thus far. Attempts to distinguish clear-cut differences in personality or psychopathological features in the patients who drop out have not been successful, though the speculation is that there may be a complex interaction between the patient's expectation concerning treatment and what he actually experiences in the clinic.

Discussion of this project centered around the specific kinds of information obtained from the patient's relatives, the handling of such data, problems of following up patients who drop out of the study, possible reasons for dropping out, side effects (which have not been a problem), the ethics of using placebos, and the possible relation between degree of social dysfunction and level of drug dosage.

Drug Therapy in a Daycare Facility for Relapse Control. Presented by Else B. Kris, Manhattan Aftercare Clinic, New York, N.Y. The aims of this project are to evaluate

day hospital care plus drug therapy as a means of controlling relapse and preventing rehospitalization of formerly hospitalized psychotics, primarily schizophrenics. Acutely disturbed (relapsed) patients who would ordinarily be rehospitalized are randomly assigned to one of two treatments: (*a*) Rehospitalization and usual hospital care, or (*b*) drug therapy in a special day hospital affiliated with the Research Unit of the Manhattan Aftercare Clinic. At the time of assignment to a treatment group, the psychotic condition of each patient is determined by use of the Wittenborn Psychiatric Rating Scales. Patients assigned to the day hospital are immediately started on intensive pharmacotherapy, with drug dosage individualized according to patients' needs.

Length of time between onset of relapse and subsequent remission in the two treatment groups, and community adaptation following remission, are being compared. After patients are released from either the hospital or the day hospital, the investigators will study the patients further to determine whether remission achieved in the day hospital is temporary or lasting.

Community adaptation is being measured by a set of scales developed by Katz, who described them more fully later in the conference.

Kris reported that the most remarkable finding thus far has been the rapid achievement of remission in the day hospital patients, who return to their jobs far sooner than patients who were rehospitalized. She also noted that treatment in the day hospital seems to promote better community adjustment and that patients seen in the day hospital seem to have learned that they can discuss recurrence of symptoms without fear of being rehospitalized.

Questions about the details of handling patients at the day hospital were discussed, along with comments about the liaison betwen the day hospital and employment agencies or vocational rehabilitation centers, possibilities of using the center as a training facility for physicians and psychiatrists in private practice, criteria for admission to the study, and the staffing and physical layout of the day hospital.

Termination of Treatment With Ataractic Drugs. Presented by Martin Gross, Springfield State Hospital, Sykesville, Md. This project, begun in 1958, investigated the importance of continuing chronic psychotic patients on medication after their release from the hospital. All patients in the study were first stabilized on one of six drugs and then randomly assigned to either (*a*) a control group which was continued on active medication, or (*b*) an experimental group which was gradually transferred from drug to placebo under double-blind conditions. Patients who relapsed were removed from the study and placed on medication if they had been receiving placebo or were rehospitalized. The criterion for relapse was the clinical judgment of the treating psychiatrist. A rating scale developed to permit objective determination of the psychiatric condition and social adjustment of the patients was described by Lawrence during the second half of the conference.

During the preliminary phase of the study, and at intervals thereafter, patients were evaluated by psychological tests, and their families or the people with whom they were living were interviewed by the social workers. Frequency of relapse while on active medication was compared with that which occurred while patients were on placebo.

Summarizing some of the findings from the study, Gross reported that relapse occurred significantly more frequently during the withdrawal or placebo period, the relapse rate being approximately three times as high during the placebo period as during the period on medication. He also noted that three-fourths of the patients who relapsed while on placebo did not require rehospitalization but were able to regain stability after medication was resumed.

Among the problems of methodology and design which Gross enumerated were the difficulties experienced in dealing with six different drugs rather than with a single drug. He noted also that the generalizability of the findings was limited in that patients in the project—chronic psychotics who were free from alcoholism and organic brain damage and who were able to attend the clinic regularly—could not be considered representative of the general outpatient clinic population.

In reply to a question, Gross stated that he felt the low incidence of dropout was due to the personal contact between the patients and the social worker and physician. Other points discussed were the difficulties of maintaining double-blind conditions and of objectively determining the point of relapse, procedures for determining whether the patients took their medication, and techniques for switching patients from drug to placebo.

Drugs and Social Therapy in Chronic Schizophrenia. Presented by Milton Greenblatt, Massachusetts Mental Health Center, Boston, Mass. This study was initiated to determine (*a*) how much of drug effectiveness is due to the drug per se and how much to other causes, and (*b*) whether there are significant social and environmental differences between hospitals which may account for the differences between drug effects in one setting and another.

Sixty chronic schizophrenics were transferred from a State hospital to an intensive treatment center (the Massachusetts Mental Health Center), where 33 received drug in addition to other therapy and 27 were not given drug. Comparison groups were composed of 55 patients remaining at the State hospital, of whom 25 were assigned to drug treatment and 20 were not. In neither setting were the patients assigned to "research wards." The criteria on which patients in the four groups were compared were clinical improvement and discharge rate.

Findings reported by Greenblatt showed only slight differences between the State hospital groups and the MMHC groups after 6 months. At 18 months, however, there were differences which suggested the possibility of a beneficial carryover of milieu effects in patients who had originally been transferred to the MMHC.

In commenting on discharge rate, Greenblatt indicated that the State hospital criteria for discharge are much more stringent than those of the MMHC. He also noted that discharge rate was affected by the availability of a family or a transitional facility to which the patients could be released. Among other special problems which he discussed were the difficulties of incorporating chronic schizophrenic patients into MMHC treatment routines without changing the environment of the Center, the reasons for having decided not to attempt double-blind administration of drugs, and the possible significance of any effects of "transfer trauma" in patients moved from one setting to another.

The Effect of Ataractic Drugs on Hospital Release Rates. Presented by Richard D. Morgan and Leon Epstein, California State Department of Mental Hygiene, Sacramento, Calif. This project is one aspect of a much broader study of population movement in the California State mental hospitals. Morgan's paper was devoted to the overall study, and Epstein's to the parts of it which are specifically concerned with drug therapy.

Morgan first briefly explained the system of cohort followup analysis which is being used, noting that it is essentially the application of individual followup analysis techniques to a group of patients who have one or more characteristics in common—e.g., age, year of admission, sex, diagnosis, etc. Having set July 1948 as the beginning point for the collection of data, the California State Department of Mental Hygiene is now systematically coding and punching onto IBM cards detailed information on all first-admission patients in the State's 11-hospital system. The records are not restricted to the period of first admission, but cover residence during subsequent readmissions in the same hospital or in a different one within the State system. A wealth of information is collected for each patient: Vital statistics, diagnosis and details of treatment, and data covering current hospital entry, previous hospitalizations, leaves, etc. Thus, a patient's complete record of hospitalization can be examined in great detail at any point during the followup period, and cohorts can be constructed on the basis of any combination of a large number of descriptive characteristics.

Morgan observed that this technique permits analysis of the frequency or the likelihood of occurrence of changes in status during any specified interval in the followup. The status of a given cohort of patients can be examined for any period of time. Data being collected in this study are proving valuable in studies of current administrative policies and investigations of the effectiveness of new or expanded programs. This system is also valuable in providing retrospective control data which may be used in lieu of a control group in evaluations of specific programs.

Following Morgan's report, Epstein discussed a particular set of analyses of these data in which the aim is to evaluate the role of tranquilizing drugs in the recent decline in State mental hospital populations, a decline which has occurred in California as well as in other States.

For the period from July 1, 1955, through December 31, 1957, additional information (i.e., additional to that routinely obtained for all patients) on details of drug therapy was recorded for each patient in the State system who had received treatment with drugs. Name of the drug, total amount of drug administered, number of days on drug, and the reason for stopping drug treatment were among the additional data recorded. By looking at significant subgroups—for example, first-admission male schizophrenics between the ages of 25 and 44—the investigators hope to be able to draw certain conclusions about shortened periods of hospitalization and their association with drug therapy. Data concerning drug usage during the period of the study are now being analyzed.

Epstein stated that investigators participating in this study are "painfully aware" that the data involve a variety of physicians, drugs, settings, and timings of drug treatment in relation to admission, as well as a variety of discharge policies among the 11 different hospitals. Despite such problems, the data do provide some reflection of what may be associated with drugs as they are used in a total system.

A number of the conference participants were particularly interested in certain specific applications of data being recorded in the California studies or of cohort analysis techniques generally. Others expressed concern about the use of release rates as a criterion in studies such as these, questioned the comparability of present-day schizophrenics with those of a few decades ago, or asked whether the current "decline" in certain hospital populations might not be in part a reflection of the decline in birth rate which occurred during the depression.

RESEARCH METHODS

The section of the conference which dealt specifically with methods was devoted to technical and theoretical problems which arise in carrying out research on drugs and community care. In accord with evidence that drugs in combination with other psychiatric treatments are contributing significantly toward maintaining formerly hospitalized patients in the community, investigations have been initiated which are aimed at specifying the nature of these treatments and their effects.

For purposes of the conference, the question of specificity was seen as having two major parts. The first was concerned with the problems of specifying the kinds of

patients who are helped by a given treatment, identifying the clinical, personal, and social characteristics of patients which are associated with response to treatment, and identifying the "types" of patients who are most likely to respond to a given treatment. In addition to the question of types of variables which merit study with regard to this problem, the technical problems which arise here, such as coding and the application of multivariate analysis procedures, were also considered in separate papers.

The second part of the section on methods was concerned with the problems of specifying the effects of a given treatment, of measuring clinical change and the various aspects of adjustment. Several approaches to these problems were described.

Population Specification

Three papers were concerned with the search for significant variables in clinical history, sociological characteristics, or personality of the patients.

Clinical history was discussed by Bernard Glueck, of the Institute of Living, Hartford, Conn. Although several clinical and social variables have demonstrated some general predictive value in studies of response to treatment, Glueck observed that the search for specific prognostic factors in these areas has not been very successful. He reviewed some of the clinical history variables which have been linked to response to insulin therapy, electroshock, and lobotomy, and commented to the scarcity of such information in relation to treatment with drugs. His major criticism was aimed at the continuing lack of a common language to describe psychiatric conditions. Following a description of Q-sort techniques which he and his associates are applying to this problem, Glueck suggested that Q-sort methods provide a means of standardizing language and making comparable the findings from different clinics or hospitals.

Sociological variables were covered by Leonard Pearlin, of the National Institute of Mental Health, Bethesda, Md. Arguing for greater specificity in this area, Pearlin observed that generic variables such as social class, age, and sex role are too global to be of much value in understanding the relations among variables. The need, he maintained, is for greater emphasis on description of the social context—i.e., the family, the community—and a descriptive system in which the "social characteristic in context" is the unit of analysis.

The role of personality in the prediction of response to treatment was the topic of the paper by Seymour Fisher, of Baylor Medical School, Houston, Tex. His review of previous work in the personality area and his own experience led him to the opinion that the more simple personality variables have not been very helpful in the past as predictors and are not likely to be too helpful in the future. Increased emphasis should, he felt, be placed on theoretically derived configural measures of personality. Several possible conceptual dimensions were described. He acknowledeged, however, that the linking of personality variables to response to treatment is subject to a number of pitfalls, some of which he enumerated.

The discussion which followed focused upon the issue of the single variable versus the configural approaches in attempts to relate personality and treatment response, and resulted in some clarification of the roles of each. The issue, however, was not resolved.

Methods for dealing with population variables were discussed by Samuel B. Lyerly, of the Society for Investigation of Human Ecology, Washington, D.C., and Dean J. Clyde, of the Biometric Laboratory of George Washington University, Washington, D.C.

Lyerly, in a paper entitled "Interview Data: Coding, Scaling, and Selection of Potentially Useful Variables," emphasized the differences in hospital and community situations which affect the collection and analysis of data, the characteristics of information which are essential to statistical analysis of data, and the importance of insuring that information collected is comparable from subject to subject. With regard to coding, he discussed different types of data and classification systems, the role of the pilot study, ways of handling of "free responses," and the application of simple mathematical procedures to patterning problems. Problems of weighting, suggestions for dealing with "does not apply" responses, and the application of different types of validity models were also considered.

Clyde's paper, "Multivariate Problems: Clustering Variables and Classifying Patients into Types," focused on the role of multivariate models in drug research. He described the following three approaches and presented examples of the application of each: (*a*) Analysis of covariance, whose use was exemplified in a study in which control of the pretreatment level of severity of illness was required; (*b*) factor analysis, which was used, in the example presented, to reduce a large number of items in a rating scale to two independent dimensions and thus served to clarify the composition and meaning of the instrument; and (*c*) discriminant function, which was applied to a problem of separating out groups of patients on the basis of their differential response to drug treatment. The relevance of the latter procedure to the problem of etiology was also considered.

In discussing these papers, Goldine Gleser, of the University of Cincinnati, Cincinnati, Ohio, elaborated upon several approaches to separating subjects into meaningful groups. Three statistical models for accomplishing this kind of separation were described. She stressed that the state of knowledge in the field is not sufficiently advanced to permit the prediction beforehand of the best way of separating groups, but pointed out that study

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of the outcome of such empirical separation can yield hypotheses which can then be cross-validated in other studies.

Methods for Measuring Improvement

Papers presented in this section of the conference described methods which are being used or developed to evaluate the adjustment of the patient and to specify ways in which improvement is manifested.

Norbert Freedman and David Mann, of the State University of New York, Downstate Medical Center, Brooklyn, N.Y., described the manner in which they are attempting to measure psychopathology and social behavior. Emphasis within the clinic is on the psychiatric rating scale approach, and in their community studies emphasis is on a "naturalistic" approach. They have, through preliminary analysis of their psychopathology ratings, identified factors which improve with drug treatment and which predict drug response to treatment. In the area of social behavior, development of an extensive interview schedule covering such areas as family history, work history, and social pathology was described by Mann. He also discussed in some detail their coding procedures, the progress of their approach to studying the "typical day in the patient's life," and the dimensions of classification which have been derived from the social data and which will contribute toward defining "social remission." It was pointed out that the definition of social remission is one of the central aims of the project.

The details of a rating scale for measuring the improvement of outpatient psychotics treated with drug and placebo were discussed by Jordan Lawrence, formerly of Springfield State Hospital, Sykesville, Md. The scale, which is completed by a psychiatrist or psychologist and a social worker following an interview with the patient, has three sections, one covering major psychopathology, one describing neurotic symptoms, and one concerned with social adjustment. Lawrence reported that the more reliable items in the scale have been factored and have yielded tentative dimensions of "schizophrenia" and "depression." He also indicated that the three subscores and the total score have been found to discriminate well between pre-relapse and relapse conditions, but noted that further, better controlled validational studies need to be carried out.

Progress on the development of a set of inventories designed to assess clinical and social adjustment was reported by Martin M. Katz, of the Psychopharmacology Service Center. He noted that the instruments are based on the need to integrate two points of view, the patient's and the relative's, in assessing the adjustment and performance of the patient. The inventories represent attempts to obtain objective estimates of (*a*) the amount and kind of home and free-time activity in which the patient is involved, and (*b*) the patient's and the relative's level of satisfaction with the patient's functioning in the clinical, work, social behavior, and free-time-activity areas. A validity study was described in which relatives were shown to be in very high agreement with psychiatric assessment (based on intensive clinical study of the patient) with regard to the level of psychopathology present and the extent of home, social, and free-time activities of the patient. Several trends in the data were noted: The relative is capable of providing accurate, objective information in certain areas; the sheer quantity of activity as reported by patient and relative reflects the level of adjustment; and the relative's level of expectations at the time of assessment correlate highly with adjustment. More detailed study of the composition of the instruments and their general applicability is in progress.

Mark Lefton, of Ohio State University, Columbus, Ohio, described his implementation of the interview-schedule approach, which had some similarity to others with regard to the areas of functioning sampled. Separate schedules were designed for the patient and the relative. The variables of prime interest in Lefton's assessment of community adjustment are social participation, work performance, psychological functioning as measured by a relative's ratings on a list of psychopathological indices, performance as a homemaker, and measures of the relative's expectations and tolerance of deviation. He reported that several measures have been found to discriminate between patients who were returned to the hospital within 6 months and those who remained in the community, as well as between patients who function well and those who function poorly in the community.

During the discussion of these papers, one participant commented on the salutary effect that commitment to a particular approach has in this area, but he cautioned against inflexibility at this early stage in the development of the field. The use of clinical judgment as a criterion has its advantages, but it was noted that areas of disagreement among raters can be just as important for understanding the nature of the problem.

In an area that has seen only scattered attention in the past, the conference participants agreed that the diversity and extent of efforts now being directed toward assessing the clinical and social effects of various psychiatric treatments are very promising developments.

Conference on Information Needs of Psychopharmacologists

A conference on scientists' need for information, sponsored by the Psychopharmacology Service Center under contract wtih the Matrix Corp., of Arlington, Va., was held on November 25 and 26 in Washington, D.C. It was a small, invitational conference of scientists active in research in psychopharmacology, documentalists, and other information storage and retrieval specialists. The aims of the conference were several: To learn whether the conference method of face-to-face interchange would reveal more relevant data about scientists' needs in the field of information and communication than has hitherto been revealed in questionnaire and interview studies; to learn whether bringing the generators and users of information into direct contact with the experts in documentation would yield information of value to both; to obtain specific information about needs of scientists working in psychopharmacology; and, as a byproduct, to help the PSC's Scientific Information Unit plan its future activities.

The meeting was very informal. There was no prearranged agenda, nor was any attempt made to arrive at specific recommendations. Under the chairmanship of Roger W. Russell, of Indiana University, Bloomington, Ind., three speakers presented papers as starting points for the discussion. Robert J. Hayes, of the Electrada Corp., Los Angeles, Calif., reviewed the whole field of information storage and retrieval, emphasing new methods and machines. He brought out that there are now machines that can be applied to almost any problem or situation in the field of information storage and retrieval. Emphasizing the team approach to the problem, the cooperative efforts of users, operators, and machine experts, he observed that the application of machine methods to information problems is successful only when the machine specialists and documentalists have a clear understanding of the users' requirements.

Daniel X. Freedman, of Yale University, New Haven, Conn., discussed the use of information in his own research, reviewed the development of his research program and the role of information in the program, and mentioned ways in which information could be more useful.

Murray E. Jarvik, of Yeshiva University, New York, N.Y., also reviewed the sources of information that he employs, including journals, monographs, books, reprints, review articles, conferences, the public press, science writers, drug company literature, textbooks, and other materials.

In addition to these three speakers, several other participants described their uses of information, covering kinds of information used, how it is used, and ways in which they would like to have it improved.

Interspersed among the papers was lively and varied discussion from most of the participants. The following summary attempts to convey some of the ideas presented in the discussions, but it does not cover all the points that were made.

Throughout the meeting one recurring theme was concern about the quality of scientific information. Commenting on the many problems of so-called scientific writing, one participant observed that much scientific writing occludes more than it illuminates. Most participants felt that many experiments were poor to begin with and should never have been published. They pointed to the need for editors of scientific journals to evaluate work more carefully and more critically before accepting it for publication. On the other side of the question were emphatic comments that strong efforts in this direction could lead to stultifying and untenable orthodoxy in science.

One of the participants maintained that the problem was too much information, and that steps should be taken to cut it off at the source; i.e., to induce the scientist himself to be more selective in reporting his work. Another took the opposite point of view, saying that, as with farm surpluses, the real problem is not that of having too much information but of distributing and using information more effectively.

A frequently recurring generalization was that scientists do not make maximal, or even good use of the many sources of information available to them. As each participant mentioned kinds of information he used, others remarked that they did not know of those sources. Similarly, when specific needs were mentioned, other participants often retorted that such needs were now being satisfied and the scientist had only to take advantage of available services.

One of the questions raised was whether centralized, or even decentralized, information services could ever serve all the needs of scientists. One participant suggested that much of the seeming dissatisfaction with present information and communication is due to the unrealistic expectations of scientists, who often want answers to research questions that they themselves should submit to research. Information at the forefront of knowledge must be obtained by the scientist; readymade answers do not exist. A related comment was that information needs differ from one stage of research to another.

A point that could be generalized from the discussion was that scientists perhaps do not know what they want

in the way of information, and that it is, therefore, the duty of specialists in the information area to provide scientists with a wide variety of information presented in many different forms. If that were done, the scientists could then select what they need from what is offered to them.

The usefulness of critical reviews of the literature was discussed in some detail. Although all agreed that critical reviews are valuable, they noted that finding really eminent scientists to write the reviews constitutes a major problem.

Handbooks and other compilations of factual information that would be of particular value to the applied scientist were also felt to be of great importance. Many participants cited reprints, rather than journals, as one of the most useful forms of information, and felt that much could be done to make distribution of individual articles more feasible and more effective.

In discussions of systems of handling information, it was noted that a scientific discipline is itself an informational system, and that some disciplines are, at different times, much more tightly organized systems than others. Physics and chemistry, for example, are at present relatively more "organized" than the biological sciences and, therefore, in a sense, present fewer information and communication problems. This discussion, which occasionally bordered on excursions into the philosophy of science, brought out the paradoxical observation that as a body of knowledge or science develops and overthrows old concepts and formulations, it is in a continuous cycle of creating chaos out of order and then creating order out of chaos.

In general, the conference participants agreed that the most important and effective means of disseminating and exchanging new information are by personal contacts at scientific meetings, by the "first" type of scientific communication—the letter—and by visits with other scientists. In discussing the value of this kind of direct, personal interchange, it was suggested that tape recorders, which are now available in most laboratories and university departments, might be used to simplify and speed up the informal exchange of information. The practical value of directories of scientists and of indexed compilations of films and other audiovisual aids was also stressed.

*The Psychopharmacology Research Unit State University of New York Downstate Medical Center**

The Psychopharmacology Research and Treatment Unit of the Department of Psychiatry, State University of New York, Downstate Medical Center, Brooklyn, N.Y., was established in October 1957. From its inception, the Unit has been concerned with the study of the effects of long-term psychopharmacological treatment on the community adaptation of schizophrenic outpatients. In the selection of ambulatory schizophrenic patients as our study population we were guided by the wide use to which psychopharmacological treatment is put with such patients. By setting community adaptation as the criterion of treatment outcome we hope to emphasize that change in these patients must be defined in terms of performance at home, at work, and in the community, as well as in terms of the usual criteria of psychological and psychiatric functioning. By assessing the effects of long-term, sustained drug action (1 to 5 years of continuous drug administration) we expect to determine to what extent such treatment may prevent relapse or lead to further improvement after an initial stabilization has been attained.

The Unit thus focuses on the behavioral (i.e., psychological as well as social behavioral) correlates of drug treatment and tries to apply the method of controlled investigation to the clinical setting. Considerable effort is also being extended to the methodology of outpatient drug assessment and to the basic research task of developing objective assessment techniques which will allow for the tracing of changes in the qualities of community adaptation. These overall research objectives are discriminated into the seven specific studies outlined below. The overall project is in part supported by Public Health Service grant MY–1983. In addition to these long-term studies of chronic schizophrenic outpatients, a section of the Research Unit is specifically concerned with the testing of new drugs. In the course of the short-term studies we have an opportunity to test the validity of some of the assessment techniques developed in the long-term studies. Finally, the staff of the Research Unit also engages in teaching psychopharmacology to undergraduate medical students and psychiatric residents. A research fellowship program is carried out by the Research Unit with second- and third-year medical students who are expected to conduct their own experiments in psychopharmacology.

The present staff of the Unit includes David M. Englehardt, Director, Norbert Freedman, Associate Director, Leon D. Hankoff, Research Psychiatrist and Director of the Treatment Unit, David Mann, Research Social Psychologist, and Reuben Margolis, Research Clinical Psychologist.

The research design of the principal (long-term) project has the following essential features: (*a*) A free-clinic population of chronic schizophrenic patients is studied. Some patients come with a history of prolonged hospitalization, some with a history of brief recurrent hospitalization, some without previous hospitalization. The population is ethnically heterogeneous, evenly divided between males and females, and draws upon the lower socioeconomic groups. (*b*) Patients are given one of three commonly used agents, chlorpromazine, promazine, and placebo, and are seen in a setting which emphasizes a supportive doctor-patient relationship. The drugs are given under double-blind conditions, and drug assignment is made randomly. (*c*) Assessment of treatment effects is made by psychiatric ratings and psychological tests, as well as by detailed social behavior interviews administered to key relatives of the patient according to a predetermined schedule. Psychopathology and social behavior are thus independently evaluated, the former in the clinic by a psychiatrist and psychologist and the latter by the report of a relative. It is planned to assemble a cohort of 500 patients who have completed 3 months of treatment and a smaller number of patients who have completed 1 to 2 years of treatment under these relatively standard conditions.

Study 1: The Role of Ataractic Treatment in the Maintenance of Community Status

Treatment may affect both incidence of hospitalization and clinic dropout. Preliminary findings show that drug treatment (chlorpromazine) is associated with lower incidence of hospitalization. Our next goal is to determine the role of drug treatment in preventing hospitalization by separately studying certain criterion groups.

*Prepared on request by David M. Engelhardt and Norbert Freedman, Psychopharmacology Research Unit, State University of New York, Downstate Medical Center, Brooklyn, N.Y.

Thus, we hope to define incidence of hospitalization on the basis of diagnosis, socioeconomic status, the relative's tolerance for the patient, and previous hospitalizations, and to ascertain the probability of hospitalization for each of these criterion groups separately, for drug and placebo conditions.

Clinic attrition for reasons other than hospitalization is also being studied systematically. Analysis of dropout patients relative to patients remaining represents an important methodological task because of the potential bias that early attrition may introduce in the interpretation of results of change. Drug treatment does not appear to affect dropout rate. Instead, dropout appears to be affected by factors in the patient's motivation toward treatment and certain factors in the treatment situation. Social (group membership) determinants also appear to be implicated.

Study 2: The Measurement of Social Behavior and Social Behavior Change

Emphasis is placed on the development of quantitative and qualitative indices of community adaptation. The instrument used is a detailed focused interview. This interview elicits from a relative a reportorial description of the patient's activities at home and at work, covering a specified timespan. These detailed reportorial accounts by the relatives provide measures predictive of change as well as measures denoting changes per se over the course of drug treatment.

Preliminary data have shown that the effects of drug treatment can be discriminated by a relative reporting on the patient's behavior. This preliminary study has involved the use of a simple checklist of social dysfunctioning filled out by the relative. Patients on drug showed greater reductions in dysfunctional social behavior than did the patients receiving a placebo. Relatives having no awareness of the specific treatment the patient was receiving were able to make this discrimination. The meaning of these differential changes must await the detailed coding of qualitative behavioral descriptions.

Study 3: Changes in Psychopathology and their Concordance with Social Behavior Changes

Changes in psychopathology are evaluated by the coding of the doctors' clinical judgments (progress notes), a detailed psychiatric rating scale, and certain psychological test performances. Psychological tests are used primarily to elucidate the meaning of changes observed on psychiatric and social behavior indices. A cluster analysis of psychiatric ratings suggests that psychiatric changes may be described in terms of two relatively independent dimensions of change, a cluster called thought disorder and a cluster called change in anxiety and treatment contact. There is a trend for patients on chlorpromazine to show greater reduction of thought disorder than for patients on placebo.

Once the social behavior indices of change are sufficiently developed, we expect to determine the degree to which psychiatric judgment and relatives' observations concur or diverge. Specifically, we expect to inquire whether relatives and psychiatrists concur on specific aspects of the patient's behavior (i.e., belligerence) or whether both concur that change has taken place but are in fact referring to different areas of change. Preliminary data so far indicate greater concordance of change on certain specific variables for patients on drug than for patients on placebo. Basically, this study seeks to attack the question of generality of the treatment effect. Is the treatment effect limited to change observed in the doctor's office, or does it extend to the patient's functioning in the community as this is perceived by a representative of the community? Implicitly, we are studying variations in the conceptions of mental health and illness as these are held by different observers.

Study 4: Freedom from Functional Decrement

The possibility that sustained treatment with psychopharmacological agents may bring about a decrement in the effectiveness of the patient's functioning is especially important for outpatients, on whom the demands for effective performance in a community are greater than for inpatients. Psychiatric ratings and relatives' reports on such variables as sluggishness, apathy, inertia, etc., are especially relevant here. Equally cogent in determining functional decrement are psychological test performances on measures of inertia and perseveration* and the Porteus Maze Test. Data on about 100 patients treated with drug or placebo for a 3-month period have been analyzed for changes in maze performance; so far we have not been able to substantiate Porteus' general findings of a decrement with chlorpromazine treatment, but we have observed a decrement in one specific subgroup. The subgroup was characterized by a "more complex" level of cognitive organization. (See the following description of study 5.)

Study 5: Prediction of Clinical Course

Underlying our studies of the community adaptation of a heterogeneous group of schizophrenic patients being treated with drugs is the assumption that outcome is modified by factors within the patient and within his social mileu. Preliminary data suggest that several parameters other than drug must be considered in predicting clinical outcome: (*a*) The patient's motivation toward treatment, (*b*) his cognitive organization, and (*c*) the attitude of the family toward the patient's illness. The patient's cognitive organization as gleaned from

*See Cattell, R. B. On the measurement of perseveration. *British Journal of Educational Psychology,* 1935, 5, 76–92.

Rorschach responses (based on a scoring derived from Werner's concepts) has been especially helpful in elucidating a "pattern of drug effects": the direction of change in response to a given medication depended upon the patient's cognitive organization.

Study 6: Incidental (Nondrug) Treatment Factors

In addition to the prognostic indices just enumerated, the role of several nondrug factors within the treatment situation has been observed. We have explored the significance of the initial response to placebo and the doctor-patient relationship as they may affect the patient's clinic attendance (dropout or hospitalization), as well as qualitative changes observed by the psychiatrist. Scoring procedures for the assessment of both doctor-patient relationship during the initial interview and response to placebo have been devised. These studies have emphasized the importance of nonverbal communication in the psychopharmacological treatment of schizophrenic outpatients. They have also delineated the contributions of the active agents to the treatment effect in some patients, but have suggested that in other patient groups the nondrug factor was prepotent.

Study 7: Long-Term Drug Action

Patients remaining in treatment for 12 to 24 months under drug and placebo conditions are observed at monthly intervals and their progress is then graphically charted. Our approach to long-term studies has been to select one of the more reliable change indices (psychoticism) and trace the patient's status at successive intervals. In analyzing the time trends we have found it useful to distinguish two baselines, one at intake and a second after approximately 3 months of treatment. This second baseline permits the comparison of any further improvement or worsening in the patient's adaptation after allowance for the initial drug effect has been made. It must be emphasized, however, that this study is always limited to patients willing and able to remain in treatment for such a long period of time. We are continually assessing differences between remainers and dropouts, so as to be in a position to detect bias introduced by the selective attrition of the sample. These long-term studies will also be corroborated by intensive case studies.

Study 8: New Drug Testing

The major efforts of the Unit are devoted to the study of long-term drug responses of chronic schizophrenic outpatients. Three relatively commonly used agents are employed. However, one section of the Unit is concerned with exploring the suitability of newer psychopharmacological agents, specifically as they may be applicable to outpatients. Assessment methods which have proved to be useful in the larger study are also employed with the relatively brief trials of new drugs for outpatient use. With the study of new drugs we also hope to extend our information about the behavioral changes among outpatients in different diagnostic groups such as depressed patients. Studies of the following compounds have been completed or are in progress: fluphenazine (Prolixin), isocarboxazid (Marplan), imipramine (Tofranil), and pyrbenzindole (IN–461, or 4-(1-benzyl-3-indolylethyl) pyridine hydrochloride).

In the course of conducting these studies we are accumulating a body of information about the methodology of outpatient drug testing; i.e., we are beginning to delineate the relative advantages and limitations of double-blind procedures in long-term assessment, the merits of simultaneous appraisal of an agent by the multiple clinic-community-member criteria, the utility of at least two baselines in the study of long-term trends, and the advantages of a drug spectrum of chemically similar agents which vary in presumed clinical intensity.

Future Plans

The findings so far support the view that the hospitalization rate tends to be lower for schizophrenic patients on active medication than for those on placebo; that psychotic symptomatology among these patients tends to be reduced by the drug; and that the adequacy of social behavior as judged by the relative appears improved, although we are not able to specify the quality of behavioral changes implicated here. Preliminary data on such variables as "psychotic thinking" also suggest that with prolonged administration of medication there tends to be less relapse with drug than with placebo. Furthermore, the data suggest that significant variations in the effectiveness of drugs depend on the patient's cognitive organization and his motivation toward treatment. In certain criterion groups, incidence of remission tends to be high regardless of drug treatment. In other criterion groups whose improvement is lower, the remission rate for patients on active drug exceeds the expectancy of improvement attributable to nondrug factors.

Our next step in the project is to place these findings on a more solid foundation: We expect to study a sample of 500 patients who have received 3 months of treatment; we expect to cross-validate some of the specific predictions drawn from the initial sample; we expect to specify the meaning of the qualities of treatment outcome, particularly in the area of community behavior, through qualitative coding of behavioral descriptions by the relative; we expect to conduct certain control studies on the source of dropout, the patient's condition after separation from the clinic, and changes in a sample of "isolated" schizophrenic patients, i.e., those not living with relatives. Finally, we hope to describe changes in subjective experiences among those patients judged by

psychiatrists and relatives to be in remission. Thus, we hope to describe improvement from three vantage points, the community's, the psychiatrist's, and the patient's.

In most general terms, it is hoped that our Unit can contribute to the knowledge of the effectiveness of psychopharmacological treatment of schizophrenic outpatients by developing and delineating criteria of treatment outcome, by specifying expectancies of clinical change for specific patient groups, by indicating the role of the drug and nondrug factors in outcome, and by tracing the long-term consequences of treatment. Once this information has been derived from a large heterogeneous group of schizophrenic patients under relatively standard treatment conditions, it is hoped that newer agents can be tested more effectively; i.e., that the larger sample can be used as a reference group and that inferences can be drawn from smaller patient groups seen over briefer periods of observation.

Finally, we hope that the accumulated data will increase our knowledge of the schizophrenic outpatient.

*Experimental Psychiatric Programs at Hillside Hospital**

Hillside Hospital, located in Glen Oaks, Long Island, N.Y., is a nonprofit, philanthropically supported psychiatric institution to which patients are admitted voluntarily for extensive psychotherapeutic treatment. Patients are from a predominantly middle-class, urban population, and most have high educational attainment. The programs of the Department of Experimental Psychiatry are a cluster of interrelated studies focused on common population samples. Other research laboratories in biochemistry and in medicine are active, and laboratories in psychodynamic psychiatry are being developed.

The programs of the Department of Experimental Psychiatry have developed over 6 years, and are devoted to understanding of the mode of action of psychiatric therapies through studies of brain function. The principal techniques have been adapted from descriptive psychiatry, neuropsychology, electroencephalography, linguistics, pharmacology, and sociology. Members of the staff, representing various disciplines, are Max Fink, Director, Karl Andermann, Ira Belmont, Martin A. Green, Abraham A. Kaplan, Eric Karp, Donald F. Klein, George Krauthamer, Joseph Jaffe, John C. Kramer, Max Pollack, and Nathaniel Siegel. Former associates who contributed to these programs are Harold Esecover, Robert L. Kahn, Hyman Korin, and Henry J. Lefkowits.

In initial studies of convulsive therapy, changes in brain function were found to relate both to evaluations of improvement and to pretreatment psychological variables. As our understanding of convulsive therapy developed, a general neurophysiological-adaptive view of somatic therapies emerged. In this view, psychiatric treatments are therapeutically effective to the degree that brain function is measurably altered. While change in brain function is necessary for behavioral change, the type of adaptation varies, depending upon pretreatment psychological and sociological characteristics of the subject. Thus, the mode of action is not seen as either "organic" or "psychological," but rather as the interaction of diffuse neurophysiological changes and adaptive mechanisms. Further, while behavioral change is related to changes in brain function, and the adaptive pattern to pretreatment psychological characteristics, evaluations of "improvement"—being special types of evaluation of change—are derivative judgments based on staff and family expectations and tolerances.

This hypothesis was developed and sustained in a series of studies of convulsive therapy. Concurrent studies of insulin coma indicated that behavioral change here, too, was related to the onset and degree of prolonged coma or repeated seizures, these being the principal manifestations of prolonged neurophysiological change in this therapy.

The mode of action of the new psychotropic agents was also expressed within this hypothesis. It was suggested that these agents would be effective to the degree that they induced persistent changes in brain function, and that the type of behavioral response would be related to the type of brain change and to premorbid psychological (personality) patterns. The present programs in the Department are designed to study these relationships in detail.

Convulsive Therapy Process

Of various measures of brain function, the amount of slow wave activity in the electroencephalogram and confabulatory and denial language patterns after amobarbital were the most sensitive indices in convulsive therapy subjects. In one experiment, improvement ratings were correlated with the appearance of high degrees of change in these indices.

These observations were tested in a double-blind study in which patients referred for electroshock were randomly assigned to courses of either convulsive or sub-

*Prepared on request by Max Fink, Department of Experimental Psychiatry, Hillside Hospital, Glen Oaks, Long Island, N.Y.

convulsive therapy under thiopental (Pentothal) premedication. High degrees of neurophysiological change were observed only in the convulsive group; improvement rates were significantly higher in this group; and when subconvulsive subjects were re-treated by convulsive applications, the improvement rate was similar to the original convulsive group.

In the subjects given subconvulsive treatment considerable amounts of electric current passed between the bitemporal electrodes. It appeared that the therapeutic agent was not the total electrical current per se, but an all-or-none quality manifested by the grand mal seizure. The significance of the grand mal seizure was examined in studies of the inhalant convulsant hexafluorodiethylether (Indoklon). Similar degrees of electrographic change, improvement rates, types of behavioral change, and changes in neuropsychological task behavior were observed in the Indoklon group and in the electrically treated group.

It was soon apparent that not all subjects manifesting high degrees of physiological change were rated as "improved." In a descriptive typological study, five patterns were described, empirically termed "euphoric," "hypomanic," "somatization," "paranoid-withdrawal," and "panic." While the first two of these adaptive modes were rated as "much improved," the latter two were seen as "unimproved" or "worse."

In studies of psychological variables, it was reported that patients rated as much improved and recovered frequently manifested personality patterns similar to that described by Weinstein and Kahn as the "explicit verbal denial personality." In language patterns, patients expressed the "language of denial" when diffuse brain change was induced, exhibiting such aspects as explicit denial, minimization, displacement, cliches, etc., more frequently than unimproved subjects. Other indices related to favorable outcome were high scores on the California F Scale, and Rorschach determinants of pure color, absent movement, and absent form-color. In this population, also, favorable outcome was associated with low educational achievement and foreign birth.

Anticholinergic Compounds and Convulsive Therapy

Seeking a way to augment the degree of postconvulsive EEG slow wave activitiy, an anticholinergic compound, diethazine, was given intravenously at various stages of the convulsive therapy process. Contrary to expectations, diethazine caused an immediate and sustained decrease in EEG slowing. Patients with denial language patterns relinquished them. Instead of feeling euphoric and experiencing a sense of well-being, the subjects became irritable, anxious, and showed symptoms expressive of pretreatment patterns. Prior to convulsive or drug therapy, diethazine induced excitement, tension, anxiety, and illusory sensations.

Subsequent studies with other central anticholinergic compounds—WIN–2299 (2-diethylaminoethyl-α-cyclopentyl-α-(2-thienyl)-glycolate HCl), JB–318 (1-ethyl-3-piperidyl benzilate HCl), JB–336 (N-methyl-3-piperidyl benzilate), and benactyzine—showed behavioral and electrographic patterns similar to those of diethazine. Similar desynchronization of postconvulsive EEG slowing was also noted with central sympathomimetic hallucinogens (amphetamine, mescaline, LSD–25), and has been reported for antihistamines (diphenylhydramine). These observations led to the suggestion that an increase in central cholinergic activity was a biochemical basis for the convulsive therapy process.

Psychopharmacological Agents and EEG

During this period, the mode of action of newer psychopharmacological agents aroused interest. Following the concepts derived from convulsive therapy, the neurophysiological changes induced by drugs were tested within the same acute experimental framework of the EEG setting. It was observed that phenothiazines (chlorpromazine, promazine, triflupromazine) induced EEG synchronization and a shifting of the spectrum to the slow frequencies; meprobamate and barbiturates induced an increased synchronization and a shift of spectrum to fast frequencies; reserpine induced an increased slowing with synchronization at low dosages and desynchronization at higher levels; and imipramine induced desynchronization with a shift of frequencies to the slow bands.

Other experimental compounds tested included BL–MI88 (which is 4-dimethylamino-3,4,5-trimethoxybenzanilide) and phenyltoloxamine, deanol and its various congeners, WY–2149 (which is tropin-4-chlorbenzhydryl ether HC1), and azacyclonol. No consistent electrographic pattern was recorded for any of these compounds.

It was suggested that psychopharmacological agents provide a means for eliciting a variety of neurophysiological patterns in contrast to the single pattern of induced convulsions. Furthermore, the type of neurophysiological alteration, as reflected in EEG synchrony and frequency patterns, was related to specified types of behavioral adaptation. Increasing EEG synchrony and a shift to slow frequencies were associated with tranquilization, sedation, and decreasing agitation, while desynchronization and a shift to fast frequencies were associated with excitement, illusions, and delusional ideation. These observations are consistent with hypotheses of Wikler. The advantages of EEG techniques for the assay of new psychiatric drugs have already been reported.*

Psychopharmacology Evaluation Program

The present psychopharmacology program, instituted in October 1959, was based on the studies described in the

*See Fink, M. EEG and behavioral effects of psychopharmacological agents. In P. B. Bradley, P. Deniker, and C. Radouco-Thomas (Eds.), *Neuro-psychopharmacology*. New York: Elsevier Publishing Co., 1959. Pp. 441–446.

preceding paragraphs. It is designed to answer the following questions:

Is there a relation between measurable alteration in brain function and behavioral change with psychotropic drugs on chronic administration?

Are there pretreatment clusters of psychiatric physiological and psychological variables related to the type of behavioral adaptation?

And, are such clusters related to the type and degree of physiological change?

Method. As an initial approximation, a double-blind drug study was undertaken in which subjects were randomly assigned to a fixed-dosage schedule. On the basis of our clinical experiences with various psychotropic compounds from 1954 to 1959, we selected three classes of drugs according to their patterns of EEG response. The agents selected were those with either predominant desynchronizing patterns, synchronizing and slowing, or minimal or no effect. After medical examination and after all other medications have been discontinued, patients referred for drug therapy are randomly assigned to treatment with a compound in one of these three classes.

Convulsive and drug therapies are prescribed by staff psychiatrists on referral to the Department of Experimental Psychiatry. All treatment is administered by the Department staff, so that the experimental variables of drug dosage, route of administration, assignment to groups, etc., are readily controlled. All patients in the hospital are available for study. The mean duration of stay for patients is 7 months.

After a testing period, all patients receive 40 cc. of liquid medication daily from individually labeled bottles. Dosages are increased in fixed weekly steps until a maximum dosage is achieved at 4 weeks. After 2 weeks on maximum dosage, retesting occurs.

To date, 140 subjects have been referred, and 110 have completed the study period. Preliminary analyses of the data are now in progress.

Behavioral Change. In a survey of the behavioral adaptations of patients receiving various agents during 1958–59 a number of clusters of behaviors were developed. The typologies were based on the treatment response and on pretreatment psychiatric profiles. In the present study, the typologies are being tested and various measures of behavioral change are being studied. These include therapist referral questionnaires and 6-week evaluations; therapist's ratings of patients on the Clyde Mood Scale; the Multidimensional Scale for Rating Psychiatric Patients, used for evaluations in interview by two research psychiatrists; the Lorr Psychiatric Behavior Rating Scales for ward behavior (AAMI: Level of Anxiety, Level of Activity, Mental Disorganization and Interpersonal Relationships); and patients' self-ratings on the Johns Hopkins symptom checklist, the Chicago Attitude Scales (self-perceptual scales devised to elicit attitudes of dependency, fight, flight, and pairing), and the Clyde Mood Scale.

Neuropsychology. Psychological tasks have been viewed both as change variables and predictive variables. In convulsive therapy, changes in memory tasks, tactile perception, Wechsler-Bellevue, critical flicker frequency, figure-ground tasks, and tachistoscopic recognition of figures were related to the degree of induced neurophysiological change. For each task, the degree of decrement in task performance was found to be positively correlated with the amount of EEG slowing. Following treatment completion, with the return of physiological indices to pretreatment levels, performance on these psychological tasks also returned to pretreatment levels or higher, a betterment of performance ascribed to practice effect.

Denial scores on interview, Rorschach determinants, F scale scores, language patterns after amobarbital, auditory feedback, and perception of the visual upright have been viewed as predictive indices of the behavioral changes following ECT.

Psychopharmacological agents are now being used to assess these various tasks, their capacity to change with various agents, or their capacity to predict change.

Electroencephalography. In the studies of convulsive therapy, the degree of EEG slowing was measured by counting the consecutive waves in selected samples. When the more subtle changes of drug effects are studied, it is necessary to apply less tedious techniques. Electronic frequency analysis was introduced in August 1959. By measuring the pen deflection for various frequencies from 3 to 33 c.p.s. in 10-second epochs, rapid measurement of apparently small changes in total activity and frequency spectra are now obtained and applied.

Other physiological variables studied in this program include the response of EEG to intravenous chlorpromazine, blood-pressure response to Mecholyl, the EKG, radioactive iodine uptake, and analyses of various blood and urine elements.

Psycholinguistics

Another series of studies in the Department has been devoted to formal language patterns.

Following the studies of syntactic language patterns in convulsive therapy, other aspects of language were studied as indices of change in interpersonal behavior. Jaffe, after considerable exploration with various linguistic measures, suggested that type-token-ratios (TTR) of consecutive samples of dyadic speech might be a useful index. While TTR had previously been applied to written texts or to the language samples of individuals, Jaffee indicated that the two-person communication (dyad) was a more significant index of the state of the

interaction than were analyses of separate samples from the participants.

Applying this technique to patients receiving convulsive therapy, changes in TTR mean and standard deviations were related both to the degree of induced EEG slow wave activity and to syntactic language patterns obtained in independent structured interviews. Speech became more repetitive (lowered mean TTR) and more variable in consecutive samples (increased standard deviation). In interviews before and after the intravenous administration of centrally active agents, similar changes were observed. Agents with a predominant synchronization pattern on the EEG exhibited a decrease in mean TTR and an increase in standard deviation of scores, while desynchronizing compounds elicited greater variability in speech patterns (increase in TTR mean) and a decrease in variability of consecutive scores (decrease in standard deviation).

Other language measures studied included distress-relief quotients, self-reference, and alteration in tense and person. It was suggested that these psycholinguistic measures are potent techniques for the operational analyses of physiological and psychological effects of psychopharmacological agents.

Sociological Studies

In the course of these psychiatric programs, considerable interest was engendered in the family organization to which patients were returning. Also, the general problem of the relation of social factors to choice and results of psychiatric treatment, and the specific problem of the relation of these factors to the referral patterns, led to a series of population studies. In one study, education, age, place of birth, and score on the California F scale were significantly related to the type of therapy received and the utilization of adjunctive hospital services. Thus, patients who were older, poorly educated, had higher F scores, and were foreign born, particularly those born in Eastern Europe, were most likely to be referred for electroshock. These relationships were independent of diagnosis. Within the group of electroshock patients, the time of referral for ECT was also related to these factors.

In a second study, duration of hospitalization, discharge evaluation, and diagnosis were related to the same social factors. For example, patients hospitalized for the shortest period were oldest, had the least education, were most likely to have been foreign born, and had the higher F scale scores. Younger, native-born, better educated patients who had lower F scale scores were hospitalized the longest. These relationships held true within treatment type and within diagnostic class. On discharge, older patients had the most favorable ratings. In ECT, patients rated as recovered or much improved had the highest F scores, least education, and were most likely to be foreign born. In another study of patient refusal of ECT, similar relationships were observed.

These relationships are now under study in the Outpatient Department and in a trihospital comparative study. This study is assessing the populations of three hospitals, each of which has a prevailing patient population which differs from that of the other two. In each of the three hospitals, all therapies are equally available to all patients. The participating hospitals are the Menninger Foundation Hospital, whose population is primarily upper class and Protestant; the Massachusetts Mental Health Center, whose population is primarily lower class and Catholic; and the Hillside Hospital, whose population is predominantly middle class and Jewish. It has been postulated that the relationships mentioned in the preceding paragraphs reflect the influence of social background on psychological processes, such as habitual patterns of communication and modes of expression. The contribution of these factors to the pattern of mental illness and to the patient-therapist interaction are being investigated.

Plans for Future Work

Further growth and the direction of ensuing studies will depend upon the results of the investigations described here, as well as upon the growing institutional awareness that research is as much an integral part of the hospital's operation and budgets as are patient treatment and staff training.

*Coca-Leaf Chewing in the Andes**

For many centuries, at least as far back as 1000 B.C., the inhabitants of the highlands in the Andean region have been habituated to the consumption of the leaves of Erythroxilon coca, a shrub growing in the Andean mountainsides at an altitude between 1,500 and 6,000 feet above sea level. At present, the production of coca leaves in Peru is estimated at 10 million kg. per year; approximately 40,000 acres of cultivated land are used, employing 25,000 workers (approximately 2 percent of the population devoted to agricultural tasks).

The leaves of this shrub may be cropped on the second or third life-year, and the plant continues to produce for 20 years, yielding from three to six crops per year. The leaves are dried in the sun for several hours and then kept in cool, shadowed places until sold for human consumption. Marketing is essentially free, being only under the necessary controls for proper taxation and to avoid illegal exportation. Coca leaves are sold all over Peru, in any requested amount, from a few grams to several thousand kilograms. Human consumption of the leaves, as such, is unrestricted. Industrial processing for the production of cocaine is forbidden by law, although frequent disclosure of illegal factories and cocaine rings calls for improved methods of fiscal control.

Coca leaves contain 0.60 to 1.80 percent of cocaine and 0.03 to 0.90 percent of ecgonine, according to calculations from different laboratories and varying also with the region and method of cultivation. Mention is also frequently made of the fact that coca leaves contain vitamin B_1 (6 to 8 mg. per kg.), riboflavin (10 mg. per kg.) and vitamin C (150 to 200 mg. per kg.).

The high content of cocaine in the coca leaves becomes more meaningful if one realizes that the Peruvian people consume an estimated 9 million kg. of coca leaves per year, representing an average of 90,000 kg. of cocaine per year. The legally approved medical requirements of all the rest of the world amount only to 2,500 to 3,000 kg. per year. (This does not include the legally approved consumption in the United States. According to official information from Peruvian sources, the Coca-Cola Co. imports from Peru 140,000 kg. of coca leaves per year. These coca leaves are decocainized and the decocainized product is used in the manufacture of the Coca-Cola beverage. The cocaine obtained as a subproduct is turned over to the proper authorities for legally approved consumption, the surplus being incinerated. The United States, thus, does not import or export cocaine.)

The 90,000 kg. of cocaine contained in the 9 million kg. of coca leaves are consumed by approximately 2 million of the total 10 million inhabitants of Peru. These 2 million people represent 90 percent of all adult males in the highlands, 20 percent of all adult women in the highlands, and a large, but undetermined, percentage of male children over 12 years of age in the highlands. Consumption of coca leaves at lower altitudes is exceptional.

The amount of coca leaf taken daily per individual varies from 10 to 100 gm. The average adult man takes approximately 30 gm. daily, but there are exceptional chewers who will take as much as 200 to 300 gm. every day. Although one speaks usually of "coca chewing," the act of consumption may not properly be called chewing, at least in its complete process. The habitual chewer usually takes a handful of coca leaves and carefully cleans it from dirt, debris, and the main nerves of the leaf. He puts the clean leaves into his mouth and chews on them for 3 or 4 minutes until a bolus is well formed. Then he takes the bolus in his fingers and pricks it deeply and repeatedly with a pointed stick which carries an alkaline powder, to be described below. The bolus is thereafter put back in the mouth and kept there, under the cheek, without chewing, for about 1 or 2 hours, during which the "chewer" sucks on it while he goes about his business. Finally, the bolus is either discarded or swallowed.

Usually, this process is repeated with 10 gm. of leaves every 3 to 4 hours, with interruption of current activities for about 45 minutes in order to prepare the bolus, in what might be called a "coca break." It is exceptional to find "chain chewing," which brings up daily consumption to about 300 gm. per person.

The addition of an alkaline substance to the bolus is a rather intriguing subject. The composition of this powder varies from region to region, ranging from plain quicklime to ground seashells or ashes of different plants. In exceptional cases, chewers do not use the alkaline substance, but there is archeological evidence to show that in one way or another it has been used for as long as coca has been known to man.

One might speculate that this procedure increases the yield of alkaloid in the mouth, but there is conflicting evidence that this is a real fact. Gutierrez Noriega, one of the authorities on this subject, claims that the yield is increased by only 4 percent. Other explanations have been offered—improvement of taste, breaking up of the cellular membrane, etc.—but there is an obvious need for further research in this direction.

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It is generally accepted that cocaine is liberated in the mouth, being extracted from the bolus. Actually, that should not be a very difficult point to settle, but nonetheless different observers have reported very conflicting data. The actual yield, which should result from subtracting the amount of cocaine in the discarded bolus from the content of a similar amount of leaves, is difficult to obtain because of the rather frequent spitting, the swallowing of part or all of the bolus, and the different methods of titration. Published results vary from a 10- to a 90-percent yield. Also, whether the saliva contains free or bound alkaloid is not well known. At any rate, some form of cocaine is swallowed and, again, not much is known about its fate on reaching the stomach and intestine. How much of it is destroyed or further activated by the digestive juices is also in question. Furthermore, we have no information about how much is absorbed into the bloodstream or about the behavior of the gastric and intestinal mucosa exposed to bound or free cocaine.

Cocaine absorbed into the bloodstream reaches the liver through the portal system, but no one really knows much about its metabolism at this level. There is some evidence that liver tissue will detoxify cocaine in vitro, and this has led to the thought that only a minimal amount of the ingested alkaloid actually reaches the general circulation. Here, again, careful evaluation is needed, since it seems that blood itself will partly destroy cocaine added to it in vitro. And, to complicate matters further, the results of determinations of cocaine blood levels in coca-leaf chewers are riddled with very difficult problems of interpretation, mainly because of the lack of appropriate methods of titration. Even if this information were available, absolute figures on cocaine blood levels would have but little meaning, owing to the lack of information on the level of neural toxicity of this substance. How high a blood level of cocaine can be tolerated without nervous effects in a normal individual, in a cocaine addict, and in a coca-leaf chewer is thus unknown.

In spite of all these important questions, it is quite evident that some cocaine, or a cocainelike substance, reaches the nervous system of the coca-leaf chewers. This is easily concluded from clinical observation. Cocaine is perhaps the best antifatigue substance known to man. And it is a well proved fact that coca-leaf chewing is an excellent means of combating fatigue, both in industrial work and under experimental conditions.

The possible differences between the effects of parenterally or orally administered cocaine and those obtained by chewing coca leaves, in normal as well as in habituated persons, and the action of cocaine and coca leaves on different types of fatigue remain to be experimentally evaluated.

Cocaine decreases hunger sensation, admittedly through its central action. And this is also a very well known effect of chewing coca leaves, brought about either through a similar mechanism or, as commonly assumed, through local anesthetic action on the digestive tract. Whatever the mechanism is, coca-leaf chewing kills hunger. And this effect has an obvious social implication. It is said, on the one hand, that because of this action coca chewing leads to malnutrition. Other groups of sociologists claim the opposite; that malnutrition leads to coca chewing. And a third factor is brought into play when one is reminded that the coca leaves contain a fair amount of certain vitamins which are ordinarily lacking in other constituents of the usual diet of the dwellers of the high Andes. A pharmacological problem thus becomes a problem of socioeconomics and of social anthropology. Malnutrition, poverty, low culture, and coca chewing all go together, and at times it becomes almost impossible to disentangle one from the other.

And if to this mixture we add high altitude, the problem becomes more and more intriguing and complicated. One cannot but wonder why, if the coca tree is only cultivated at altitudes lower than 6,000 feet, the habit of chewing coca leaves is found mainly above that level. Very few communities in the coastal area show the habit, which is mainly concentrated in the high altitudes. Futhermore, the habit of chewing coca leaves, a habit carried on continuously for many years, is usually abandoned when the individual is permanently transferred to lower geographical levels. And one cannot dismiss the frequent claims of travelers and of cultured dwellers of the highlands regarding the beneficial effects of coca tea or coca chewing against the acute symptoms of mountain sickness. Unfortunately, no experimental evaluation has been made of these observations, which have been subject to much literary discussion in years past. It is true, of course, that high altitude is only one of the factors of a very complicated problem seen through the narrow light of an off-habit, on-habit proposition. But only a careful experimental approach will tell us what the real importance of this factor is, especially in the presence of a drug with as many unpredictable pharmacological actions as cocaine.

It is commonly accepted that cocaine has a deleterious effect on the central nervous system when taken chronically. And it is only logical that this concept has been used in the interpretation of the mental functions of the coca-leaf chewers. This assumption, however, may not be entirely justified, since most of the alleged "facts" lack experimental verification. The so-called effects of chronic consumption of coca leaves are always related to the other factors of the socioeconomic complex surrounding the coca habit; poverty, malnutrition, low culture, poor educational facilities, high altitude, etc. And although coca may be an important determining cause, the alleged low mental output of the Andean dweller should not be blamed only on this factor, as it frequently is. The appraisal of chronic coca-leaf consumption com-

pletely separated from its socioeconomic constellation is, however, very difficult to achieve.

The acute action of coca-leaf chewing on mental processes also lacks sound and thorough experimental evaluation. A few experiments suggest that the effects are quite different in habituated and nonhabituated individuals, as would logically be expected. The extent and mechanism of these differences remain to be determined.

There is also some indication that muscular activity during the process of coca chewing basically alters its mental effects. It is said that if the individual is resting, daydreaming and pseudohallucinations ensue, but that these mental effects can be prevented by physical activity. These observations need further experimental study, but this type of psychopharmacological study would meet with great obstacles in the markedly introvert personality of the Peruvian Indian, his resistance to participation in experimental studies of this type, the frequent language difficulties, and the lack of basic psychological and social anthropological studies in the Andean milieu.

It is thus evident that there are many questions to be answered concerning the pharmacology of coca leaves and the socioanthropological aspects of this widespread habit. Differences between the chronic or acute effects of parenterally administered cocaine (a subject on which much remains to be settled) and the chronic or acute effects of coca-leaf chewing should be investigated. The former leads to a rather well known condition: *cocainism,* i.e., addiction to cocaine. The latter leads to a habit, *cocaism,* which apparently does not follow the same psychopharmacological pattern, since a simple change in socioeconomic status or a change in geographical milieu leads to its spontaneous discontinuance; there is not a clear tendency to increase the dosage, as there is in cocainism, nor are there any evident withdrawal symptoms.

Are these differences due only to the route of administration of cocaine? One certainly can provoke a clear syndrome of cocaine addiction in experimental animals (dogs, monkeys) by chronically administering cocaine by the parenteral route. But so far it has not been possible to obtain similar results by oral administration of this drug.

Research Opportunities

There are many stimulating areas for research on coca-leaf chewing. Facilities for research in this field are potentially available at the Brain Research Center of the Armed Forces of Peru, of which I am director, and at the American Hospital in Lima, which has a good neurological and neurosurgical service. Investigators who wish to explore the possibility of conducting research related to coca-leaf chewing, or who wish to obtain further information, are invited to write to me at the following address: Dr. Fernando Cabieses, Talara 655, Lima, Peru.

Publications

Tranquilizing and Anti-Depressant Drugs. Veterans Administration Department of Medicine and Surgery Medical Bulletin MB–6, September 12, 1960. Washington, D.C.: U.S. Government Printing Office. This 19-page bulletin is by Eugene M. Caffey, Jr., Leo E. Hollister, Alex D. Pokorny, and Jesse L. Bennett, all of whom are members of the Executive Committee of the Veterans Administration Cooperative Chemotherapy Studies in Psychiatry. It presents a general summary of current practices in the use of tranquilizers and antidepressives in psychiatry and in nonpsychiatric practice, and includes tabulations of generic names, trade names, and range of total daily dosage of drugs for outpatients and for hospitalized patients. The price of the publication is $0.15. Copies should be ordered from the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C.

Agressologie, an International Review of Physio-Biology and Pharmacology Applied to the Effects of Agression, is a recently established journal that should be of interest to psychopharmacologists. In the preface to the first issue, the title of the journal is explained: The commonly understood meaning of the word aggression is applied to the action of agents which harm the living organism by attacking it abruptly (from the outside or from the inside), including cold, heat, lack of air, surgery, disease, poisoning, and other causes of physiobiological disequilibrium which results in "more or less profound and lasting disturbances" in cellular metabolism. The purpose of the journal is to synthesize and integrate contributions which many basic disciplines are making to the study of the effects of "aggression" as previously defined, and to the prevention and treatment of such effects. The journal is being published and edited by Henri Laborit, of the Hôpital Boucicaut, 78 rue de la Convention, Paris 15, France, and P. Huguenard, of the Hôpital de Vaugirard, Paris 15, France.

Metabolism of, and Analytical Methods for, Phenothiazine Derivatives Used in Psychopharmacology; A Selected Annotated Reference List, compiled by the Scientific Information Unit of the Psychopharmacology Service Center. This list of approximately 65 references is made up primarily of articles concerned with analytical methods for the detection of phenothiazine derivatives used in psychopharmacology, together with a few more general articles on the metabolism of these agents. The annotations are factual summaries of the articles, and are not evaluative or critical. The list is arranged chronologically. Copies may be obtained by writing to: Dr. Lorraine Bouthilet, Head, Scientific Information Unit, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda 14, Md.

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