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CLINICAL AND HEURISTIC VALUE OF CLINICAL DRUG RESEARCH

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The development of modern psychopharmacology has been associated with striking changes in the principles and practice of psychiatry. There are now numerous psychopharmacologist-psychiatrists, a continuing proliferation of new drugs, and an enormous amount of federal money for drug research. However, the authors, who together have had extensive experience in both psychopharmacological research and the private practice of psychiatry, have felt that there is a gulf between their experiences as researchers and as clinicians seeking to apply research findings to the treatment of individual patients. In order to examine carefully the factors involved in this problem, they have exhaustively reviewed the methodology and findings of controlled clinical psychopharmacological research. In presenting their analysis of the literature, they have detailed findings of practical use for the clinician, divided according to the psychopharmacologists' categories of "drug factors" and "nondrug factors."

It was found that as far as practical applicability is concerned, clinical drug research has not added very much to what has been learned through clinical experience, which is rather striking in view of the fact that the expressed main purpose of such research is to increase our capability as practitioners using drugs. On the other hand, the heuristic value of drug research has been great in terms of opening new approaches to understanding and influencing mental functioning and psychopathology, and in the development of research methodology for the behavioral sciences. Considered in historical perspective, perhaps the greatest clinical value of the age of drug research has been that it has catalyzed the study of directive approaches to psychotherapy. From a "preventive medicine" point of view, the frequently contradictory research results, in spite of careful control of variables, encourage more caution in theoretical formulations.

The authors discuss the terms "nondrug" and "nonspecific factors," which are frequently used by psychopharmacologists to cover in blanket fashion various critical psychotherapeutic factors in patient improvement not particularly valued by their theoretical approach. The authors point out that this narrow view has prevented adequate study of simultaneous psychotherapy and pharmacotherapy and has been reflected in the lack of applicability of research findings for the practitioner. Psychotherapy variables relating to drug therapy are discussed.

At the conclusion of the paper, the authors give general guidelines for the clinical use of psychotropic drugs, based on integration of current research and clinical knowledge.

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With the advent of psychopharmacology and, later, "community psychiatry," there has been a change in the principles and practice of our specialty that has been as striking as developments in medicine following the introduction of chemotherapeutic agents in the treatment of infectious disease. This has been particularly evident in the treatment of psychotically disturbed patients subsequent to the discovery of the major tranquilizers (19), which allowed the turning of so much of our attention from managing disturbed hospitalized patients to their active rehabilitation. In this setting, the community began to show less fear of these patients, to the point that programs were developed in which housewives and college and high school students could work with hospitalized patients.

At the 1967 annual meeting of the American College of Neuropsychopharmacology in Puerto Rico, a panel of prominent clinical psychopharmacologists (Cole, Elkes, Kinross-Wright, Kline, Lehmann) discussed the development of the drug age of American psychiatry and pointed out the difficulties they had encountered with the psychiatric "establishment" (13). The resistance or inertia of much of the psychiatric community to the introduction of drug therapy is now all but forgotten, but many of us still recall the great caution with which drugs were prescribed during our residency training. Much instruction time was involved warning us that drugs only diminished disturbed behavior and had no meaningful effect on the illness itself.

Now the situation has changed dramatically. A new establishment has come into being, one that involves many psychopharmacologists, a continuing proliferation of new drugs, and an enormous amount of federal money for drug research. Psychopharmacological research has expanded to involve not only disturbed hospitalized patients but the great mass of functioning neurotic individuals. In the latter situation particularly, a good deal of excitement associated with the term "drug effects" is being transferred to "nondrug effects" or "nondrug factors" or "nonspecific factors in drug therapy." All of these developments bring a glow of approval from other medical specialists and basic scientists, who, in the past, have regarded psychiatry as a nonscience.

In the following section we review the methodology and findings of controlled or carefully conducted clinical psychopharmacological research, with special reference to relevance for the practitioner of psychiatry.[2] There are two general groups with whom we wish to communicate. First, as psychopharmacological researchers we will attempt to weed out from the plethora of research data those findings which can be of use to practitioners. Second, as practitioners, we hope to make useful comments and suggestions to psychopharmacological researchers concerning limitations and assets of their concepts, methods, and results in terms of applicability to patients seen in practice. We have asked ourselves such questions as the following: Has this research greatly increased our capabilities as practitioners using drugs, which is the expressed main purpose of such research? How specific can we be in selecting a given drug for a given patient? What are major methodological flaws in clinical drug research as far as the practitioner is concerned? What is the relationship between psychotherapy and pharmacotherapy? Is psychopharmacological research taking a comprehensive approach to the study of factors influencing mental illness or only narrowly focusing on that which can be most easily studied? When are drugs contraindicated for psychological as opposed to medical reasons?

In the "Discussion" section, the heuristic significance of clinical drug research is discussed. Practical guidelines are offered for

[2] No attempt will be made to include an exhaustive bibliography, but a representative one will be presented for the benefit of readers who wish to review the subject.

the practitioner, integrating what has been learned from research and from clinical experience.

FINDINGS OF CLINICAL DRUG RESEARCH, WITH PARTICULAR REFERENCE TO METHODOLOGY AND TO APPLICABILITY FOR THERAPY

Drug Effectiveness

Are there findings from controlled clinical drug research which can be of significant help to the practitioner of psychiatry *in selecting the appropriate drug in his day-to-day work with individual patients?*

SCHIZOPHRENIA

One major class of drugs, the phenothiazines, has been found significantly effective in the treatment of schizophrenia in controlled studies of large populations of patients. Recent studies indicate that butyrophenones and thioxanthenes, with similar pharmacological profiles to the phenothiazines (46), also have antipsychotic effects, but so far they do not seem to add significantly to pharmacotherapy of mental illness, with the exception of a possible specificity of haloperidol for Gilles de la Tourette's syndrome (9).

The early experiences with phenothiazines seemed to promise that drugs might be found which would introduce a Utopian age of mental health. There was also cautioning that drugs only controlled superficial behavior in schizophrenics and did not alter mental processes, but subsequent work indicated that phenothiazines may tend selectively to affect Bleuler's "fundamental" symptoms of schizophrenia (5, 30). In his recent book, May (63) presented findings which suggest that phenothiazines are so effective with hospitalized schizophrenics that such patients do not respond significantly better to individual therapy plus drugs than to milieu therapy plus drugs and show significantly less improvement in response to individual therapy without drugs.

Evaluation of these recent findings must be tempered with the thought that some doctors may function better as therapists with one type of treatment or patient than another (97, 101). Further, one must consider experimenter bias (48), since investigators have tended to find what they expected. Controlled, double blind studies do not necessarily eliminate experimenter bias, which can be facilitated through appearance of drug side effects, and also through unintentionally biased methodology and data analysis. For example, in one study (71) we asked 72 patients in a structured interview at evaluation to estimate on a 4-point scale how much help they expected from treatment, giving them two negative choices and two positive choices. Sixteen patients indicated negative expectations. Two questions later they were asked to estimate on a 5-point scale how much improvement they expected ("no improvement," "not much better," "a little better," "a good deal better," and "complete cure"). Only 1 patient indicated "no improvement," no patients indicated "not much better," 7 patients expected "a little better," and all the rest gave the two most positive responses. One possible explanation for these results is that the second scale indicated to the patients that expected improvement was the right answer in that only one out of five choices allowed a completely negative answer.

Furthermore, an observer's bias that a drug is no better than a placebo is not necessarily eliminated in his ratings of improvement by unawareness of the contents of the pills prescribed, since a negativistic, uninterested or careless rater can make the same low scoring from patient to patient; likewise, an exceptionally enthusiastic rater can blur data through consistently overenthusiastic ratings. A therapeutic milieu indicating that strong positive or negative results are expected can also tend to complicate results from patient self-ratings (61). However, biased expectation does not *nec-*

essarily mean biased observer judgment, since conscious awareness of one's predjudices, along with intellectual honesty, can together act as powerful "controls." These are but a few of many problem areas indicating further need for careful study of methodology in controlled drug research. Thus, in an evaluation of the effects of conscious expectation on judgment, the former could be measured by a questionnaire, but the latter can be measured only by observing the researcher or comparing his judgments with those of others. Up to now, the short cut way to handle such methodological problems has routinely been to control a situation to death, so to speak, rather than to study what kind of control is needed.

Even when taking bias into consideration, however, the preponderance of results from various studies leads to the conclusion that phenothiazines should be administered in the treatment of most schizophrenics, and in particular of those requiring hospitalization. Prescriptions of phenothiazine combinations (*e.g.*, chlorpromazine-trifluoperazine), as well as periodic short term withdrawal of phenothiazines (72), have not yet been proven of significant value. However, recent data suggest that there are complex interactions between phenothiazine dosage, prior medication with phenothiazines, and length of hospitalization (73).

In the treatment of schizophrenia, are certain phenothiazines more effective than others? Does one drug influence certain manifestations of the illness, such as apathy, more than another? Pharmaceutical houses have furnished us with all sorts of phenothiazines with different kinds of chemical tails and attachments, with company brochures suggesting differential effectiveness. For instance, piperazines such as trifluoperazine and fluphenazine have been thought more effective for withdrawn, apathetic patients than chlorpromazine, an aliphatic phenothiazine. Yet a study reported by the National Institute of Mental Health Collaborative Study Group (66) would suggest, if anything, a reverse trend with chlorpromazine more effective for "core" symptoms such as apathy and retardation. This group of researchers has also presented suggestive evidence that piperazine phenothiazines may be particularly effective with delusional-hallucinatory patients and that schizophrenics showing "simple excitement" do especially well on thioridazine, a piperidine phenothiazine (31, 32). However, indications of differential therapeutic benefits are conflicting, such that it appears we are dealing at the most with only minor differences above and beyond the immense common effect of the phenothiazines (17, 31, 32, 53). The phenothiazines do differ in intensity of certain side effects, predictable to some extent by chemical structure, and a prime factor in choosing a specific phenothiazine for a particular patient remains the consideration of extrapyramidal (piperazines) and sedative (aliphatics) side effects rather than therapeutic effects. Cole and Davis (12, p. 1058) stated recently with regard to research results: "All this has, one feels, convinced almost everyone in creation that many phenothiazines are effective, generally, in the treatment of both acute and chronic schizophrenics. It is far less clear that any of them, with the exception of promazine and mepazine [both less effective] are significantly more or less effective than chlorpromazine." Again, Cole stated (11, p. 514), "Specific differential indications for one or another of these drugs in individual subgroups of schizophrenic patients may yet be evolved, but have not been clearly demonstrated to date."

MAJOR MOOD DISORDERS

Research has supported the clinical impression that imipramine and related tricyclic agents, sometimes in combination with phenothiazines for agitated and guilt-ridden patients, are effective drugs in the treatment of depression, and that lithium

and phenothiazines are effective in the treatment of mania (18, 33, 88, 89). As with phenothiazines, antidepressant drugs differ in side effects, a point to be considered in selecting a specific drug for a specific patient. Thus, amitriptyline is reported to have more of a sedative side effect than imipramine or the desmethyl and other derivatives. Recent evidence suggests that the effects of imipramine may be enhanced by thyroid hormones. Monoamine oxidase inhibitors also appear effective for depression, although less so than tricyclics (88), and they are not as safe. The possibility is being studied currently that lithium say serve as a prophylactic for depressive episodes (33). There is still doubt that any of the presently known antidepressants are usually more than mildly effective (88).

As with drug treatment of schizophrenia, more detailed findings, including those regarding differential effectiveness for the various tricyclics and duration of time from ingestion to effectiveness, tend to be contradictory from study to study (18, 88). Major problems in studying drug treatment of depressive disorders are: 1) Mood tends to fluctuate a great deal "spontaneously." 2) Disturbance of affect is "only" a symptom, and groups of "depressives" in various studies differ remarkably in personality characteristics, ego strength, history of mania, and degree of depression, *e.g.*, "reactive" *vs.* "endogenous" (105). Even the definitions of "endogenous" and "reactive" depression have not been clear, and despite much written comment, differential drug therapy for these is not worked out (74). Reactive depressions are likely to "respond" to all kinds of influence, so that any safe, new drug can be found "effective" in an uncontrolled study. 3) Depression is often disguised as something else (45). For instance, there are reports that antidepressants are effective in "atypical depression" which can present with phobic symptoms predominating (50, 82).

NEUROSES

Research has supported the commonly held clinical impression that drugs are not of major benefit in the treatment of the neuroses as opposed to "nondrug" or "placebo" factors such as interpersonal and environmental influences. In fact, often only refined statistical techniques reveal significant differences between "minor" tranquilizers and placebo in double blind studies. Statistically unsophisticated persons may not realize that a mathematically highly significant difference between a drug and placebo reported in a journal article does not necessarily mean a big difference for the patient (88). For instance, if almost all of 50 patients showed 1 to 2 points more improvement on certain symptom scales in response to a drug than another 50 patients did when taking placebo, the significance might be very high mathematically but not clinically if most of the patients improved about 10 points regardless of medication. The requirement of refined statistics to demonstrate beneficial effects of a minor tranquilizer over placebo indicates in itself that the drug is only one of many factors causing improvement, and not an especially outstanding one at that. Some studies indicate that certain of these drugs may be more useful than others, for instance, diazepam and chlordiazepoxide *vs.* meprobamate, but we are not certain that even this example is of really meaningful clinical significance. Minor tranquilizers more effective than placebo in a number of controlled studies are diazepam, chlordiazepoxide, oxazepam, tybamate, and meprobamate, listed in the generally considered approximate decreasing order of effectiveness. Other drugs also have their advocates. In lieu of a valid scientific basis for selecting one minor tranquilizer over another, most clinicians simply have one or two favorites that they believe to be mildly helpful in the treatment of their anxious, neurotic patients. Phenothiazines are still considered of

little use in psychoneurosis except with borderline, highly distressed, or impulse-ridden patients, where they are also of diagnostic value. Also, phenothiazines and certain minor tranquilizers, especially diazepam and chlordiazepoxide, have been noted clinically and in a number of studies to ease the symptoms of the alcohol withdrawal syndrome.

The effects of minor tranquilizers and antidepressants on neurotic outpatients have been found clinically and in research studies to cross over classical diagnostic categories (59, 78, 96, 104). The finding that "antianxiety" drugs seem to help depressive symptoms and vice versa, above and beyond a general placebo effect, supports a flexible approach to prescribing drugs and a willingness to change to or add a different kind of medicine if the first one tried does not seem to help. Further, drug research has suggested that if one replaces habituating tranquilizers, such as diazepam, chlordiazepoxide, and meprobamate, with other tranquilizers or antidepressants, it may be wise to deviate from the general medical principle of discontinuing one drug before starting another, but rather to leave a patient briefly on the original drugs to avoid withdrawal effects and a resulting biased clinical impression that the second drug is not of potential benefit (2, 16).

In addition to tranquilizers and antidepressants, clinical reports and research studies suggest possible therapeutic value of psychotomimetics (1, 57, 62) and diphenylhydantoin (8, 47, 92) for various conditions. Further investigation is required to elucidate possible specific benefits of these agents. It also appears that amphetamine has a paradoxically tranquilizing effect on many behaviorally disturbed children (6, 23, 25).

Nonspecific Factors

"Nonspecific" or "nondrug" factors in drug therapy are terms which have not been consistently defined. On the one hand, they have been defined (75) simply as all those factors influencing patient responses while receiving drugs which are not pharmacological (definition A). However, the term can also be applied more narrowly to findings from drug research which are not specifically applicable to drug therapy but which apply to all kinds of psychological treatment and/or are only of theoretical interest (definition B). Research reports of nondrug factors have been particularly apparent in studies of neurotic populations, where it is clear that most patients improve symptomatically regardless of which drug is used and even when given placebo—sometimes even if informed they are getting placebo (69).

DEFINITION A

Factors influencing patient responses while receiving drugs but which are not inherent in the drugs themselves: Are there findings from clinical drug research which can be of significant help to the practitioner of psychiatry in *deciding if, when, and with which approach he should prescribe the appropriate drug in his day-to-day work with individual patients?*

Characteristics of the therapist: There are controlled research findings which suggest that the more experienced or effective the therapist, the less important it is whether drugs are used with neurotic patients (104), and this may also be the case to a lesser degree with schizophrenic patients (100).

Several clinical studies with neurotics have supported the idea that manifest enthusiasm by the therapist concerning his treatment can sometimes increase specific drug effects (26, 76, 95, 97), and there are a few studies relating therapist enthusiasm to improvement on drugs in schizophrenia (36, 44). There are also data indicating that drugs may be of special benefit if the patient is not appealing to the therapist (95).

Combined drug therapy and psychotherapy: One might expect to find in

the literature a multitude of controlled studies grappling with the complex issues involved in combining psychotherapy with drug therapy, especially in the treatment of neuroses, evaluating such factors as the therapist's theoretical orientation and practical approach, his length of experience, attitudes, feelings, warmth, empathy; the patient's wish or need for advice, insight, and a relationship as contrasted with his need for pharmacotherapy plus the vague "supportive" therapy; and the interactive match between various doctor and patient characteristics in a specific therapeutic relationship (59, 69, 70, 86, 93, 97, 100). However, there has been minimal effort in even major studies to define and measure "psychotherapy" components (28, 81, 90), as compared with the effort to define and measure "pharmacotherapy" variables (34, 94); rather, much drug research seems to handle "psychotherapy" as the outmoded, unifactorial approach of a relatively dark age of psychiatry. There has not even been adequate effort in clinical drug research to determine whether intensive psychotherapy of schizophrenics, with or without drugs, although more time-consuming than supportive pharmacotherapy alone, is more likely to re-educate a patient so that he can avoid repeated difficulties in the future; whether pharmacotherapy alone offers neurotic individuals as much chance of symptomatic improvement as psychotherapy alone over more than brief drug study periods (79); whether pharmacotherapy for such patients enhances only occasionally or frequently the effects of simultaneous psychotherapy (60).

There are a number of obvious factors behind this naive approach. For instance, whereas the practicing psychiatrist is usually not in a position scientifically to test hypotheses derived from his clinical impressions, the clinical psychopharmacologist is in an equally poor position to immerse himself sufficiently in the emotional strains and subtleties of intense and long term psychotherapeutic relationships to develop a feeling for treatment models other than those more appropriate for time-limited physical illness. The result is a confusing babble of voices and a lack of integration of major areas of clinical experience, which is not a new problem in the behavioral sciences (21, 35, 55).

Careful studies of individual patients (rather than just statistical analyses of large groups) treated with psychotherapy plus drugs, particularly their subjective experiences (71), could generate a wealth of testable hypotheses. Interestingly, we tend to hear reports of individual patient response chiefly when there is a *negative* symptomatic response to drug prescription. Sarwer-Foner (83) has listed various causes for such "paradoxical" responses, on the assumption that they often reflect the *meaning* to the patient of the prescription or of the physiological effects of the medicine rather than simply being adverse drug reactions. We will present here categories of such situations which are of importance to the clinician, with illustrations from our own experience. One factor which can bring about a patient's negative response to prescription of a medicine is his prior attitude concerning drug therapy or drug effects (84). In one of our pilot projects (59), a small group of staff members took atropine for a period of a week to test dosage and safety. There was considerable "humorous" discussion in the planning stage that the trial paralleled such heroic situations as self-inoculation with yellow fever and malaria, and that the danger of drug-induced psychosis was being ruled out. A psychiatrist and a nurse, although quite aware of atropine effects, developed severe diarrhea, requiring one of them to discontinue the drug. In another project, patients responded beneficially to placebo according to their "certainty" of the specific nature of the pills (69).

A second factor which can result in a "paradoxical" response to drug prescription

is the patient's negative feelings toward the therapist, toward the therapeutic approach, or toward the clinical or hospital milieu. Along this line, a middle-aged female patient recently sought consultation because of the return of symptoms of depression. She had previously experienced two episodes of severe depression that had responded to imipramine prescribed by one of the authors, in whom she had expressed much confidence. Upon the return of her symptoms for the third time, she initially consulted her internist as she had done on the earlier occasions, and he prescribed amitriptyline in the approximate dosage which had been found effective for her and suggested that she let him know how things went but offered no regularly scheduled visits. The patient's symptoms proliferated and, because of the apparent ineffectiveness of the medicine, she had discontinued it by the time of her arrival at the psychiatrist's office. Weekly visits were planned, and the therapist expressed the opinion that another trial of amitriptyline was worthwhile in view of her earlier responses to such treatment. Within 2 weeks the patient began to respond and eventually made an excellent symptomatic recovery. She herself was impressed by such a response to the same drug which had been utterly ineffective a few weeks earlier. How much of the drug's usefulness depended on its pharmacology remains problematic.

Third, negative feelings by the therapist toward his patient and/or toward prescription of medicine should be considered as possibly promoting negative response to drugs. Fourth, patients for whom control of their own psychic and bodily functions is part of the problem which brings them to treatment may often respond negatively to real or imagined control by drugs. Needing a drug may imply to the patient that he is "sick," and this may sometimes be unacceptable, especially to the schizophrenic patient. We all have had pseudoneurotic or overtly schizophrenic patients who require hospitalization before they can take drugs without serious "side effects" and/or negativism, and it may be that such patients cannot give up their rigid avoidance of outside control until placed in a safe, supportive setting where certain broad controls are imposed. Along this line, there is a state hospital study indicating that some schizophrenic patients, delineated by statistical analysis of drug response, do less well on phenothiazine than on placebo (31). Such patients tend to show more "insight," in that they are more likely to have been hospitalized on a voluntary basis and show lower scores on observer ratings of "irritable" and "resistive" behavior. It was hypothesized that these patients may "feel a further loss of mental control" on active drugs. Fifth, drugs are rather ineffective or can even have a negative effect where secondary gains of illness are high. Sixth, a change of drugs may have a poor result if the patient attaches symbolic meaning to the initial drug. The authors have had two patients referred from other physicians for whom they wished to prescribe new medicines. Both patients had been very attached to the referring physicians and to their treatments, such that they became distressed (more than simply physiological withdrawal symptoms) each time new medicines were tried. In the end, through allowing the patients to take the new and the old drugs together, the weaning was effected, followed by significant improvement. Seventh, the meaning of side effects may have an effect on individual responses. The timing of interpretation of side effects may be significant. Thus, in one study patients who were told prior to prescription of drugs that an unpleasant side effect (dry mouth) was correlated with improvement did less well than patients not given any side effect interpretation (59), whereas in a pilot study in which correlation was made to patients after such side effects occurred, patients appeared to have a positive response. Eighth, there are patients who respond to sympto-

matic improvement from drugs by self-destructive acting out, such as leaving treatment prematurely, getting even with the family, leaving one's spouse, telling off the boss, etc. On the other hand, there is evidence that some action-oriented individuals feel more distressed if tranquilized with drugs which have considerable sedative side effects (20, 83). Finally, some basically very anxious or fearful patients, such as many schizophrenic patients, may become more disturbed when given energizers for depression, and a few reports have suggested that some passive patients may simply become more passive when given tranquilizers for relief of therapeutically necessary anxiety. These negative drug response factors indicate just one area in need of careful evaluation in combined drug-psychotherapy research.

There are innumerable research findings of drug-related variables which may be of great interest to the psychopharmacologist but of little help to the practicing psychiatrist in prescribing drugs. For instance, studies of neurotics have suggested that various patient characteristics, such as chronicity of illness and a patient's past experience with psychoactive drugs, are correlated with drug response (69, 77). Social class of the doctor and patient may play a role in response to drugs (97). Some studies have produced very precise statistical findings; for instance, in one study it was found that the heavier, male, married, anxious, neurotic patient who was less well liked by his doctor responded better to meprobamate than to placebo, as compared with the slim, single, anxious, neurotic woman who was well liked by her doctor (95). No attempt is made here to summarize the mass of such research findings, too often contradictory, which, however, may be slowly building up a significant body of knowledge for the theoretician and the practitioner of the future.

DEFINITION B

Are there findings from controlled drug studies which are of *major day-to-day usefulness to the practitioner regardless of the kind of treatment, that is, independent of drug therapy?*

For neurotic outpatients, the "law of initial value" has been demonstrated (93, 96, 103). Thus, we find that the initially more anxious patients tend to show more symptomatic improvement than initially less distressed patients (although still tending to retain a higher general level of tension than the patients who were initially less distressed), regardless of prescription of drug or placebo, or no pill at all. This confirms the authors' clinical impressions, who have found the law of initial value particularly noticeable at the Johns Hopkins University Psychological Clinic where dramatically distressed college students often improve markedly after their first visit. This is a very hopeful finding concerning such patients, which is of help not only in working with them but in advising and reassuring residents who evaluate and treat them. Shaffer[3] confirmed the usefulness of this concept in working with young adults. It must be added, however, that this principle is relatively unreliable with clearly schizophrenic patients.

There are indications from research that the clearer a patient is concerning the nature and meaning of the treatment approach, the more rapidly he improves (27, 41, 69, 70). If this is true, it behooves us all to explain carefully our treatment approach and plans to our patients unless there are specific indications not to do so.

Evaluations of therapist characteristics in drug studies indicate that genuinely confident, positive feelings by the therapist

[3] Shaffer, G. W., Director of the Psychological Clinic and Retired Dean of the Homewood Schools, Johns Hopkins University. Personal communications, 1967.

for his treatment and warmth[4] for his patient have a beneficial effect regardless of whether drugs are prescribed (69, 93). This reinforces the general principle that in all treatments, even brief drug therapy, the therapist should carefully and honestly consider his feelings for his patient.

DISCUSSION

If the findings from controlled drug research are summarized, what do we have with regard to clinical applicability for the practitioner using drugs? It would appear that such research has made significant contributions to the pharmacotherapy of schizophrenia and severe mood disorders. However, has all the controlled drug research in recent years done much more than *reassured* us, particularly the skeptics among us, that certain gross clinical impressions are valid, that drug therapy is applicable to mental illness, that phenothiazines and similar compounds significantly affect the symptomatology of psychotic patients, that the tricyclic drugs and lithium are useful for major mood disorders, that if one drug does not seem to work we should often try another rather than stop drug therapy, and that all kinds of pills are symptomatically welcomed by neurotic patients? One might add that pharmacological research has been of help in evaluating drug metabolism, dosage levels, response times, dangers and medical contraindications, and addiction problems, yet we still do not know how these drugs work, just as we still do not know how electroconvulsive therapy works. We are not in a position to prescribe a specific drug by the ideal method of evaluating its biochemical activity in relation to the patient's metabolism, but rather we must choose the phenothiazine, tricyclic antidepressant, or minor tranquilizer we believe in, know best, or which has minimal side effect problems for the individual patient. Then we change to or add another drug if the first prescription is ineffective or produces unexpected side effects. We may, however, be approaching biochemical specificity in the area of mood and amine metabolism (22).

There are heroic efforts by some careful researchers (32, 51, 52, 88, 104) to evaluate drug study data with the necessary fine-toothed comb, aiming toward the day when we can select just that subtype of drug which will be best for the specific patient. Likewise, the development of a program by the Psychopharmacology Research Branch of NIMH to pool data from large numbers of divergent studies will facilitate clarification of subtle effects of innumerable variables which require tremendous numbers of patients (56). At the other extreme, there is developing more interest and sophistication in studying single individuals or small groups longitudinally, as well as cross-sections of large groups (10, 22, 85). Such studies hold great promise of bringing factors into focus that would be washed out in more gross populations. The objectivity and care involved in some of these projects give us hope concerning the future applicability of research results for the practitioner.

It is our conclusion, however, that the mushrooming of clinical drug research in the past 15 years has had a heuristic significance above and beyond the overt goal of finding "the right drug for the right patient" (54). Considered in historical perspective, perhaps the greatest value of this age of drug research has been that it has helped break the fixation on the nondirective approach to psychotherapy as the only one of real value. Only those of us in the field prior to the use of drugs know how passive we tended to be in residency training, trying to apply psychoanalytic meth-

[4] Rickels, K., Lipman, R. S., Park, L. C., Covi, L., Uhlenhuth, E. H. and Mock, J. E. Drug, doctor warmth and clinic setting in the symptomatic response to pharmacotherapy. Unpublished manuscript, 1970.

ods to hospitalized psychotic or other patients who couldn't respond to such an approach.

From the point of view of research methodology, the idea that medicine is of use in the treatment of mental illness has allowed the introduction into psychiatric research of a marvelous variable, the "pill." This is so solid, so specific, so easy to quantify and control. It even allows us to study "dummy" treatment. Drug research has impressed upon us the therapeutic significance of the doctor's belief in himself and his treatment, and the importance of double blind and other methods to control for this influence when trying to compare treatments, not only in psychopharmacology but in all areas of research concerned with factors influencing patient symptoms and adjustment. Psychopharmacologists have taken a leading role in developing the use of refined statistical techniques and computers in psychiatric research. The sometimes dehumanizing approach of psychopharmacological research methods has even had its recent constructive reverberations in provoking a fresh concern for the patient's rights (70). Along this line, psychiatric research and treatment are finally departing from the mystery-shrouded hocus pocus which began with the primitive medicine man and has continued as a tradition until finally the patient can know what is going on because the professional has effective treatments based on scientific principles (87). This is a particularly important issue in working with psychiatric patients, since it is clearly antipsychotherapeutic to use deceptive research procedures with someone who is likely to be coming for help in the first place because of problems in relationships involving such things as distorted communications, deceit, being used, fear of being honest, etc. (15).

From a "preventive medicine" point of view, the frequently contradictory research results, despite careful control of variables, remind us of our ignorance and caution us against flowery advertisements or too certain opinions that different phenothiazines do this or that terribly important different thing or that minor tranquilizers are tremendously more effective than placebo, and so forth. We would so much like to believe all this, that it is important to have good research and cool heads to bring us back to cold reality time and again. Thus, Beecher (3) recently indicated the resistance to the repeated proof of the powerful effect of placebo factors. If we do so well with "nothing pills," completely separate from all our carefully laid scientific plans, are we "brilliant" scientists or do we fear we are just additional bit players in the human scene (80, 102)?

Finally, the findings of drug research are helping us to learn more about the functioning of the normal and disturbed mind and various factors which influence it, stimulating good research beyond the scope of applied psychopharmacology. Studies of doctor and patient variables which influence drug response contribute to theories of human behavior, and interaction. For instance, studies of responses of schizophrenics to phenothiazines have not only supported the perspicacity of Bleuler (30), who had to work without statistically refined methods and computers, but are also leading us into a new Kraepelinian-like descriptive period of computer-grouped, drug-influenced patient variables which may hopefully be conceptualized into an increased understanding of schizophrenia by the Bleulers among us if they search beyond the narrow confines of statistics and methodologies (32, 67). Similar responses to certain drugs by neurotics of different diagnostic labels and different symptoms may lead to groupings of factors by drug response which enlarge our view of neurotic illness. Wittenborn (104) discussed the importance for drug research of developing symptom subscales to evaluate anxiety of different types, degrees, causes, and expressions, and he indicated the broad implications of such work for development of anxiety theory. Animal and human meta-

bolic studies of actions of psychoactive drugs have opened new avenues for learning how the central nervous system functions at a neurochemical level (22, 24).

Thus, it appears that controlled drug research may paradoxically make some of its greatest contributions in the area of nondrug factors or nonspecific factors. However, to apply these terms to what we learn about people as opposed to what we learn about chemicals is to be questioned. Relegating complex psychological issues to the category of nondrug factors would be analogous to dividing human beings into Eskimos and non-Eskimos. This notion can be carried to amazing extremes. Thus, because drug effects are relatively so important in the treatment of schizophrenia, it has been suggested that nonspecific factors are only important for "small treatments with small illnesses," citing, for example, that there has never been any research on such factors in the treatment of general paresis with penicillin (39). However, one could argue (equally unrealistically) that since acutely suicidal patients represent the major psychiatric emergency and require concerned communication and protection but do not respond with immediate hope to a handful of pills, drugs are only important for "small treatments with small illnesses."

"Nondrug factor" seems analogous to the "transference cure" expression of psychoanalytic writers, another phrase more timely than timeless, which tended to cover in blanket fashion and sometimes to demean various critical factors in patient improvement not valued by that group's theoretical treatment approach (68). "Placebo effect" is another related term which has been found to cover a wealth of critical factors in human behavior (29, 42, 43, 69, 80, 87, 99). It is intriguing that "nondrug factors" and "placebo effect" have had among their various definitions the identical one of indicating those factors in patient response which are not pharmacological drug effects. These terms can blind us to an eclectic approach and to integrating knowledge gained in other ways and in other times. It is our contention that "nondrug factors" is a term concerned with much more than psychopharmacology and beckons not just to the present and future but to Pinel, Kraepelin, Bleuler, Freud, Meyer, Sullivan, and other giants of the past.

Considered in historical perspective, psychiatry has had its cycles, periods, and fads, varying in meaningfulness. The 19th century had its earlier wave of moral therapy for the neglected and untreated psychotic patient, followed in the latter half of that century by a mechanistic period (106). Freud brought us into the 20th century with a psychodynamic approach again, but the development of means to study biochemical factors has ushered basic science into current prominence in psychiatry. At the same time, our social conscience has been rearoused to bring "moral therapy" to neglected, underprivileged groups with a new term, "community psychiatry." These "cycles" have obviously not been purely cyclical but have brought new knowledge to us. However, there is the tendency in such a process for new knowledge to be at first rejected and then for old knowledge to be discarded as the new period gains competitive status. For instance, we have "discovered" community psychiatry, which, as has been pointed out by Elkes,[5] was an approach urged by Adolph Meyer (64) in 1913 but which was all but forgotten because it did not have status in that period. We have witnessed also the early struggle of psychopharmacologists for a fair hearing in an era which was hostile to direct intervention as opposed to insight therapy, followed by the current psychodynamically naive drug literature.

A mature approach to new periods of development of an idea or a science is to avoid this natural human failing to consider

[5] Elkes, J., Chairman, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine. Personal communication, 1966.

ourselves so unique as to have discovered something completely new which warrants discarding the past (48, 49, 91), as Laotzu (7, pp. 25–26)[6] suggested approximately 600 years B.C.:

> People through finding something beautiful
> Think something else unbeautiful,
> Through finding one man fit
> Judge another unfit.
> Life and death, though stemming from each other, seem to conflict as stages of change,
> Difficult and easy as phases of achievement,
> Long and short as measures of contrast,
> High and low as degrees of relation;
> But, since the varying of tones gives music to a voice,
> And what is is the was of what shall be,
> The sanest man
> Sets up no deed,
> Lays down no law,
> Takes everything that happens as it comes,
> As something to animate, not to appropriate,
> To earn, not to own,
> To accept naturally without self-importance:
> If you never assume importance
> You never lose it.

Practical guidelines: If we consider drug treatment as an approach of proven usefulness which must be integrated with other approaches, then we can apply what we have learned about drugs to individual patients. First of all, it is clear that drugs are to be prescribed for relief of symptoms, along with alteration of behavior and certain pathological thoughts, but are not to be considered magical agents for instant erasure of intense feelings of loneliness or emptiness, or for immediate relearning of faulty habits and inappropriate patterns in relating to oneself or others; for the individual who cannot initiate his own relearning, the latter can only come either through "corrective" interpersonal emotional experiences, which can sometimes be facilitated by drugs, or by communication to him of new ideas. Drugs in themselves cannot re-educate, retrain or rehabilitate. For instance, pharmacotherapy seems particularly impotent when used in the absence of psychotherapy and/or family therapy in children and adolescents, and antidepressants seem particularly inadequate when used without intensive psychotherapy for treating depressed late adolescents and young adults (37). On the other hand, certain motivated patients can show good therapeutic response when drugs decrease severe symptoms and/or disordered thinking to the point that they can conceptualize and deal effectively, on their own, with family or other interpersonal difficulties (58).

We should keep foremost in mind that all patients have problems in relationships, and that most patients of all social classes these days want to work on these problems, hoping for something more meaningful and lasting than only some relief of symptomatology (14, 65), although they do often want drugs in crisis situations or when first starting treatment. This not only is our general clinical experience, but is indicated even when lower socioeconomic drug study subjects are carefully questioned (71). Further, there are many patients for whom a nondirective, psychoanalytically oriented approach is optimal and for whom a prescription of medication could represent a lazy or ignorant approach by the therapist which can be resented by the perceptive patient.

Following are general guidelines for clinical use of psychoactive drugs, based on an integration of current research and clinical experience.[7] *Selecting the right*

[6] Copyright © 1944 by Witter Bynner. Reprinted from *The Way of Life According to Laotzu*, translated by Witter Bynner, by permission of The John Day Company, Inc., publisher.

[7] It is not our purpose here to discuss use of sedatives for sleep, dosages, physiological dangers including addiction, or general pharmacotherapeutic principles such as the safety of withdrawing one drug before prescribing another, giving as few drugs as possible, etc.

drug: Research has not as yet demonstrated the value of trying to select a specific drug uniquely effective for a specific patient. Rather, it is usually important only to select the right category of drugs, with special attention being paid to side effects and medical contraindications. There are, in addition to lithium, three proven major categories of psychoactive agents at present: phenothiazines, tricyclics, and minor tranquilizers. Other antipsychotic and mood-altering agents are either less or only equally effective or are less safe. If the patient is schizophrenic, a popular phenothiazine should be selected, usually the one with which the therapist is most familiar regarding effective dosages. Sedative *vs.* extrapyramidal side effects of the phenothiazine should be considered in relation to the patient's needs, along with indications for anti-Parkinson medication. The inconstant side effects of thioridazine on sexual functions might be specific consideration for certain patients. If the patient is depressed, a popular tricyclic drug is indicated; if such a patient is also agitated, a phenothiazine should be considered in combination with the antidepressant. If the seriously depressed patient is unresponsive to a tricyclic, other somatic therapies to be considered are monoamine oxidase inhibitors and electro- or inhalant (Indoklon) convulsive treatment. If the patient is manic, a phenothiazine and/or lithium would be the drugs of choice, with the possible addition of an antidepressant for a cyclical major mood disorder. If the patient presents with anxious neurotic symptomatology, any one of many minor tranquilizers can be considered as probably better than placebo. If such a patient does not experience relief with psychotherapy and minor tranquilizers, a phenothiazine or antidepressant should be considered in a diagnostic-therapeutic approach.

Thus, it is rather easy in the present state of knowledge to choose *which* medication to use according to the diagnostic picture presented by a patient. It is more difficult to determine *when* and *with what approach* to prescribe a drug for a given patient.

When to prescribe a drug: We should generally use drugs for patients with severely disturbed affect, thought processes, and/or behavior, especially those patients so incapacitated as to require hospitalization. Before hospitalizing a patient because of decompensation or suicidal risk, we should consider the possibility that immediate institution of drug therapy might allow continuation of outpatient status, if the family can cooperate through extra assistance at home. We should consider drugs with the seriously distressed neurotic patient, to tide him over the initial period of therapy until the distress level abates somewhat and/or to reduce distress to a level that allows him to participate effectively in psychotherapy. We should, however, try to rule out the possibility that relief of distress by drugs will result in a conviction the problem is only physical, in a "flight to health" and a premature termination of therapy, in other forms of "acting out," or in development of other inappropriate defenses. Drugs should be considered when there is no improvement on psychotherapy alone and/or if the patient cannot make adequate use of verbal experience. We should also think of drugs if we do not have the time or capability to help the patient find out or act on the problems producing his symptoms. This will often be a factor in a busy clinic situation. This would also be the case with the general practitioner or internist who might not have the time, interest, or experience required for psychotherapeutic intervention, yet who would feel that the patient did not require the attention of a psychiatrist.

A physician who does not like a patient but who is unable or reluctant to arrange a change in doctors might consider drugs to add a positive factor in such an unhappy situation. Research data suggest that drugs would be particularly helpful here if the doctor has some natural enthusiasm for pharmacotherapy.

Drugs should also be considered if there is difficulty communicating with or relating to an autistic or withdrawn patient, with the prescription carefully treasured as one of the few chances to communicate to the patient that we will not hurt and that we do care. The timing can be very important here. Thus, sometimes it is helpful to wait a few sessions to conceptualize such a patient's problems before prescribing a drug, so that he can be given a specific therapeutic reason for the drug; for instance, a schizophrenic patient with a fear of the doctor might be told that the drug will help settle him down *and* enable him to communicate more comfortably.

In general, the more serious the illness, the longer the patient will require medication, with many psychotic patients on maintenance dosages indefinitely. Decision to discontinue medication also requires careful thought, with symptomatic improvement being only one of many factors to be considered.

With what approach should a drug be prescribed? Research data have reinforced clinical knowledge that the prescription of a pill to a psychiatric patient involves a great deal more than a mechanical procedure. The patient responds to the pill even before he swallows it, just as so many individuals respond to a Bufferin advertisement long before the pill reaches the blood stream, as pharmaceutical advertisers are well aware. The patient responds on the basis of his own preconceived expectations interacting with the therapists's manifest attitudes. He is more likely to respond positively if the therapist takes a reasonably warm, genuine, and hopeful approach.

Further, in the section of the paper discussing psychotherapy in relation to pharmacotherapy, various examples of contraindications to drug therapy were presented. Before prescribing a drug, even if the category of drugs can be selected and if the timing appears appropriate, the *meaning* to the patient of prescribing a drug should be explored as an essential step in psychotherapeutic intervention. The meaning as far as the therapist is concerned should be explained and likely side effects presented for discussion along with mutual evaluation of the patient's past experience with drugs. If a patient still appears likely to respond with a paradoxically negative meaning of his own, and if drug therapy is not acutely necessary, it often should be postponed. If he is an outpatient, he cannot be forced to take the drug properly anyhow. Furthermore, in some cases it is therapeutic to rely somewhat on the patient's judgment in self-management of dosage. Of course, the issue of the patient trying to control therapy should be considered in this situation. Along this line, a reason for prescribing drugs can be that the patient indicates he is medically oriented and wants medicine—and a reason for not prescribing drugs can be that the patient doesn't want medicine. On the other hand, we might hesitate to prescribe a drug for a patient if it is felt that the patient is mainly seeking passive-dependency and/or is addiction-prone, and we might insist on medication even if a psychotic patient is resistive on a delusional basis. However, there should be the greatest attempt to maintain the therapeutic relationship on a democratic, consultative, evocative-leadership basis (4, 15, 37, 38, 40, 98). How the therapist approaches drug prescription can often be a major chapter in the patient's learning about the therapist's interpersonal, leadership, and intuitive patterns and capabilities.

SUMMARY

A review of psychopharmacological research methodology and findings has been presented, with special attention to clinical applicability *vs.* heuristic value. From the point of view of practical clinical applicability, we have not learned a great deal more through research than we have learned through clinical experience. On the other hand, the heuristic value of drug re-

search has been great in terms of opening new approaches to understanding and influencing mental functioning and psychopathology, and in the development of research methodology for the behavioral sciences. Viewing pharmacotherapy in appropriate clinical context and perspective, we can apply what we have learned about drugs to the individual patient. Specific suggestions along this line are discussed.

REFERENCES

1. Abramson, H. A. *The Use of LSD in Psychotherapy and Alcoholism.* Bobbs-Merrill, New York, 1967.
2. Bakewell, W. E., Jr. and Wickler, A. The incidence of non-narcotic drug addiction in a university hospital psychiatric ward. Paper read in part at the Annual Meeting of the A.M.A. in Atlantic City, N. J., June 22, 1965.
3. Beecher, H. K. Some remarks on quantitative studies of subjective responses to drugs. In Efron, D. H., Cole, J. O., Levine, J. and Wittenborn, J. R., eds. *Psychopharmacology: A Review of Progress, 1957–1967,* pp. 973–977. PHS Publication No. 1836, U.S. Government Printing Office, Washington, D.C., 1968.
4. Betz, B. J. A study of tactics for resolving the autistic barrier in the psychotherapy of the schizophrenic personality. Amer. J. Psychiat., *104:* 267–273, 1847.
5. Bleuler, E. [Zinkin, J., trans.] *Dementia Praecox or The Group of Schizophrenias.* International Universities Press, New York, 1950.
6. Bradley, C. and Bowen, M. Amphetamine therapy of children's behavior disorders. Amer. J. Orthopsychiat., *11:* 92–103, 1941.
7. Bynner, W. Ed. *The Way of Life According to Laotzu.* John Day, New York, 1944.
8. Case, W. G., Rickels, K. and Bazilian, S. Diphenylhydantoin in neurotic anxiety. Amer. J. Psychiat., *126:* 254–255, 1969.
9. Challas, G., Chapel, J. L. and Jenkins, R. L. Tourette's disease: Control of symptoms and its clinical course. Int. J. Neuropsychiat. [Suppl. 1], *3:* 95–104, 1967.
10. Chassan, J. B. *Research Design in Clinical Psychology and Psychiatry.* Appleton-Century-Crofts, New York, 1967.
11. Cole, J. O. Are there significant differences between the phenothiazines in their effectiveness in the treatment of schizophrenia? In Rinkel, M., ed. *Biological Treatment of Mental Illness,* pp. 507–522. Farrar, Straus and Girous, New York, 1966.
12. Cole, J. O. and Davis, J. M. Clinical efficacy of phenothiazines as antipsychotic agents. In Efron, D. H., Cole, J. O., Levine, J. and Wittenborn, J. R., eds. *Psychopharmacology: A Reviw of Progress, 1957–1967,* pp. 1057–1064. PHS Publication No. 1836, U.S. Government Printing Office, Washington, D.C., 1968.
13. Cole, J. O. and Gerard, R. W., eds. *Psychopharmacology.* National Academy of Sciences, National Research Council, Publication No. 583, Washington, D.C., 1959.
14. Cole, N. J., Branch, C. H. and Allison, R. B. Some relationships between social class and the practice of dynamic psychotherapy. Amer. J. Psychiat., *118:* 1004–1011, 1962.
15. Coleman, J. V. Aims and conduct of psychotherapy. Arch. Gen. Psychiat., *18:* 1–6, 1968.
16. Covi, L., Park, L. C., Lipman, R. S., Uhlenhuth, E. H. and Rickels, K. Factors affecting withdrawal response to certain tranquilizers. In Cole, J. O. and Wittenborn, J. R., eds. *Drug Abuse: Social and Psychopharmacological Aspects,* pp. 93–108. Charles C Thomas, Springfield, Ill., 1969.
17. Davis, J. M. Efficacy of tranquilizing and antidepressant drugs. Arch. Gen. Psychiat., *13:* 552–572, 1965.
18. Davis, J. M., Klerman, G. L. and Schildkraut, J. J. Drugs used in the treatment of depression. In Efron, D. H., Cole, J. O., Levine, J., and Wittenborn, J. R., eds. *Psychopharmacology: A Review of Progress 1957–1967,* pp. 719–747. PHS Publication No. 1836, U.S. Government Printing Office, Washington, D.C., 1968.
19. Delay, J. and Deniker, P. Le traitement des psychoses par une methode neurolytique dérivée de l'hibernotherapie. Congres des Medicins Alienistes et Neurologistes, Luxembourg, 1952, pp. 497–502.
20. Di Mascio, A. Personality and variability of response to psychotropic drugs. In Rickels, K., ed. *Non-Specific Factors in Drug Therapy,* pp. 40–49. Charles C Thomas, Springfield, Ill., 1968.
21. Dubos, R. *So Human an Animal.* Charles Scribner's Sons, New York, 1968.
22. Durell, J. and Schildkraut, J. J. Biochemical studies of the schizophrenic and affective disorders. In Arieti, S., ed. *American Handbook of Psychiatry,* vol. 3, pp. 423–457. Basic Books, New York, 1966.
23. Eisenberg, L., Lachman, R., Molling, P. A., Lockner, A., Mizelle, J. D. and Connors, K. A psychopharmacologic experiment in a training school for delinquent boys. Amer. J. Psychiat. *33:* 431–447, 1963.
24. Elkes, J. Psychoactive drugs: Some problems and approaches. In Solomon, P., ed. *Psychiatric Drugs,* pp. 4–21. Grune & Stratton, New York, 1966.
25. Epstein, L., Lasagna, L., Connors, C. K. and Rodriquez, A. Correlation of dextroamphetamine excretion and drug response in hy-

perkinetic children. J. Nerv. Ment. Dis., *146:* 136–146, 1968.
26. Fisher, S., Cole, J. O., Rickels, K. and Uhlenhuth, E. H. Drug-set interaction: effect of expectations on drug response in outpatients. In Bradley, P. B., Flügel, F. and Hoch, P., eds. *Neuro-Psychopharmacology,* vol. 3, pp. 149–156. Elsevier, Amsterdam, 1964.
27. Frank, J. D. The influence of patients' and therapists' expectations on the outcome of psychotherapy. Brit. J. Med. Psychol., *41:* 349–356, 1968.
28. Frank, J. D. *Persuasion and Healing.* Johns Hopkins Press, Baltimore, 1961.
29. Gliedman, L. H., Nash, E. H., Imber, S. D., Stone, A. R. and Frank, J. D. Reduction of symptoms by pharmacologically inert substances and by short-term psychotherapy. A.M.A. Arch. Neurol. Psychiat., *79:* 345–351, 1968.
30. Goldberg, S. C., Klerman, G. L. and Cole, J. O. Changes in schizophrenic psychopathology and ward behavior as a function of phenothiazine treatment. Brit. J. Psychiat., *111:* 120–133, 1965.
31. Goldberg S. C. and Mattsson, N. B. Schizophrenic subtypes defined by response to drugs and placebo. Dis. Nerv. Syst., *29:* 153–158, 1968.
32. Goldberg, S. C., Mattsson, N. B., Cole, J. O. and Klerman, G. L. Prediction of improvement in schizophrenia under four phenothiazines. Arch. Gen. Psychiat., *16:* 107–117, 1967.
33. Goodwin, F. K., Murphy, D. L. and Bunney, W. E., Jr. Lithium-carbonate treatment in depression and mania. Arch. Gen. Psychiat., *21:* 486–496, 1969.
34. Gottschalk, L. A. Some problems in the evaluating of psychoactive drugs, with or without psychotherapy, in the treatment of non-psychotic personality disorders. In Efron, D. H., Cole, J. O., Levine, J. and Wittenborn, J. R., eds. *Psychopharmacology: A Review of Progress 1957–1967,* pp. 255–269. PHS Publication No. 1836, U.S. Government Printing Office, Washington, D.C., 1968.
35. Grinker, R. R. An essay on schizophrenia and science. Arch. Gen. Psychiat., *20:* 1–24, 1969.
36. Haefner, D. P., Sacks, J. J. and Mason, A. S. Physicians' attitudes toward chemotherapy as a factor in psychiatric patients' responses to medication. J. Nerv. Ment. Dis., *131:* 64–69, 1960.
37. Halleck, S. L. Psychiatric treatment of the alienated college student. Amer. J. Psychiat., *124:* 642–650, 1967.
38. Halmos, P. *The Faith of Counselors.* Basic Books, New York, 1968.
39. Hamilton, M. Discussion. In Rickels, K., ed. *Non-Specific Factors in Drug Therapy,* pp. 133–135. Charles C Thomas, Springfield, Ill., 1968.
40. Hill, L. B. *Psychotherapeutic Intervention in Schizophrenia.* University of Chicago Press, Chicago, 1955.
41. Hoehn-Saric, R., Frank, J. D., Imber, S. D., Nash, E. H., Stone, A. R. and Battle, C. C. Systematic preparation of patients for psychotherapy. I: Effects on therapy behavior and outcome. J. Psyciat. Res., *2:* 267–281, 1964.
42. Honigfeld, G. Non-specific factors in treatment: I. Review of placebo reactions and placebo reactors. Dis. Nerv. Syst., *25:* 145–156, 1964.
43. Honigfeld, G. Non-specific factors in treatment. II. Review of social-psychological factors. Dis. Nerv. Syst., *25:* 225–239, 1964.
44. Honigfeld, G. Relationships among physicians' attitudes and response to drugs. Psychol. Rep. *11:* 683–690, 1962.
45. Imboden, J. B., Canter, A., Cluff, L. E. and Trever, R. W. Brucellosis: III. Psychological aspects of delayed convalescence. Arch. Intern. Med., *103:* 406–414, 1959.
46. Janssen, P. A. J. Applied pharmacology and the butyrophenones. In Efron, D. H., Cole, J. O., Levine, J. and Wittenborn, J. R., eds. *Psychopharmacology: A Review of Progress, 1957–1967,* pp. 1083–1084. PHS Publication No. 1836, U.S. Government Printing Office, Washington, D. C. 1968.
47. Jonas, A. D. The diagnostic and therapeutic use of diphenylhydantoin in the subictal state and non-epileptic dysphoria. Int. J. Neuropsychiat. [suppl. 2], *3:* 21–29, 1967.
48. Kety, S. S. The heuristic value of psychiatry. Amer. J. Psychiat., *118:* 385–397, 1961.
49. Klee, G. A. Research in psychotherapy: A background leap into the future. Amer. J. Psychother., *22:* 674–683, 1968.
50. Klein, D. F. Delineation of two drug-responsive anxiety syndromes. Psychopharmacologia, *5:* 397–403, 1964.
51. Klein, D. F. and Davis, J. M. *Diagnosis and Drug Treatment of Psychiatric Disorders.* Williams & Wilkins, Baltimore, 1969.
52. Klein, D. F., Honigfeld, G., and Feldman, J. Prediction of drug effect by a successive screening, decision tree diagnostic technique. In May, P. R. A. and Wittenborn, J. R., eds. *Psychotropic Drug Response: Advances in Prediction,* pp. 45–91. Charles C Thomas, Springfield, Ill., 1969.
53. Klerman, G. L. Comments from the viewpoint of a clinical psychiatrist. In Wittenborn, J. R. and May, P. R. A., eds. *Prediction of Response to Pharmacotherapy,* pp. 183–200. Charles C Thomas, Springfield, Ill., 1966.
54. Klett, C. J. and Moseley, E. C. The right drug for the right patient. J. Consult. Psychol. *29:* 546–551, 1965.

55. Kruse, H. D., ed. *Integrating the Approaches to Mental Disease.* Hoeber-Harper, New York, 1957.
56. Leeds, A. A. Reorganization: Psychopharmacology research branch. Psychopharmacol. Bull., *5:* 1–2, 1969.
57. Levine, J. and Ludwig, A. M. The LSD controversy. Compr. Psychiat., *5:* 314–321, 1965.
58. Lipman, R. S., Hammer, H. M., Bernardes, J. F., Park, L. C. and Cole, J. O. Patient report of significant life situation events: Methodological implications for outpatient drug evaluations. Dis. Nerv. Syst., *26:* 586–590, 1965.
59. Lipman, R. S., Park, L. C. and Rickels, K. Paradoxical influence of a therapeutic side-effect interpretation. Arch. Gen. Psychiat., *15:* 462–474, 1966.
60. Lorr, M., McNair, D. M. and Weinstein, G. J. Early effects of chlordiazepoxide used with psychotherapy. J. Psychiat. Res., *1:* 257–270, 1963.
61. Lowinger, P. and Dobie, S. What makes the placebo work? Arch. Gen. Psychiat., *20:* 84–88, 1969.
62. Ludwig, A., Levine, J., Stark, L. and Lazar, R. A clinical study of LSD treatment in alcoholism. Amer. J. Psychiat., *126:* 97–107, 1969.
63. May, P. R. A. *Treatment of schizophrenia.* Science House, New York, 1968.
64. Meyer, A. The purpose of the psychiatric clinic. Amer. J. Insanity, *69:* 857–860, 1913.
65. Meyer, E., Spiro, H. R., Slaughter, R., Pollack, I. W., Weingartner, H. and Novey, S. Contractually time-limited psychotherapy in an outpatient psychosomatic clinic. Amer. J. Psychiat., *124:* 57–68, 1967.
66. National Institute of Mental Health Psychopharmacology Research Branch Collaborative Study Group. Differences in clinical effects of three phenothiazines in "acute" schizophrenia. Dis. Nerv. Syst., *28:* 369–383, 1967.
67. National Institute of Mental Health Psychopharmacology Research Branch Collaborative Study Group. Short-term improvement in schizophrenia: The contribution of background factors. Amer. J. Psychiat., *124:* 900–909, 1968.
68. Oberndorf, C. P. *A History of Psychoanalysis.* Grune & Stratton, New York, 1953.
69. Park, L. C., and Covi, L. Nonblind placebo trial: An exploration of neurotic patients' responses to placebo when its inert content is disclosed. Arch. Gen. Psychiat., *12:* 336–345, 1965.
70. Park, L. C., Covi, L. and Uhlenhuth, E. H. Effects of informed consent on research patients and study results. J. Nerv. Ment. Dis., *145:* 349–357, 1967.
71. Park, L. C., Slaughter, R. S., Covi, L. and Kniffin, H. G., Jr. The subjective experience of the research patient: An investigation of psychiatric outpatients' reactions to the research treatment situation. J. Nerv. Ment. Dis., *143:* 199–206, 1966.
72. Prien, R. F. and Cole, J. O. High dose chlorpromazine therapy in chronic schizophrenia. Arch. Gen. Psychiat., *18:* 482–495, 1968.
73. Prien, R. F., Levine, J. and Cole, J. O. High dose trifluoperazine therapy in chronic schizophrenia. Amer. J. Psychiat., *126:* 53–61, 1969.
74. Raskin, A. The prediction of antidepressant drug effects: Review and critique. In Efron, D. H., Cole, J. O., Levine, J. and Wittenborn, J. R., eds. *Psychopharmacology. A Review of Progress, 1957–1967,* pp. 757–765. PHS Publication No. 1836, U.S. Government Printing Office, Washington, D. C., 1968.
75. Rickels, K., ed. *Non-Specific Factors in Drug Therapy.* Charles C Thomas, Springfield, Ill., 1968.
76. Rickels, K. and Cattell, R. B. Drug and placebo response as a function of doctor and patient type. In May, P. R. A. and Wittenborn, J. R., eds. *Psychotropic Drug Response: Advances in Prediction,* pp. 126–140. Charles C Thomas, Springfield, Ill., 1969.
77. Rickels, K., Lipman, R. and Raab, E. Previous medication, duration of illness and placebo response. J. Nerv. Ment. Dis., *142:* 548–554, 1966.
78. Rickels, K., Raab, E., DeSilverio, R. and Etemad, B. Drug treatment in depression: Antidepressant or tranquilizer? J.A.M.A. *201:* 675–681, 1967.
79. Roth, I., Rhudick, P. J., Shaskan, D. A., Slobin, M. S., Wilkinson, A. E. and Young, H. H. Long-term effects on psychotherapy of initial treatment conditions. J. Psychiat. Res., *2:* 283–297, 1964.
80. Roueché, B. Placebo. New Yorker, pp. 85–102, Oct. 15, 1960.
81. Rubenstein, E. A. and Parloff, M. B., eds. *Research in Psychotherapy,* vol. 1. National Publishing, Washington, D. C., 1959.
82. Sargant, W. The treatment of anxiety states and atypical depressions by the monoamine exhibitor drugs. J. Neuropsychiat. [suppl.], 96–102, 1962.
83. Sarwer-Foner, C. Recognition and management of drug-induced extra-pyramidal reactions and "paradoxical" behavior reactions in psychiatry. Canad. Med. Ass. J., *83:* 312–318, 1960.
84. Schachter, S. and Wheeler, L. Epinephrine, chlorpromazine and amusement. J. Abnorm. Soc. Psychol., *65:* 121–128, 1962.
85. Schooler, N. R., Goldberg, S. C., Boothe, H. and Cole, J. O. One year after discharge: Community adjustment of schizophrenic

patients. Amer. J. Psychiat., *123:* 986–995, 1967.

86. Shaffer, G. W. Suggestion and hypnosis. In Gibson, R. W., ed. *Crosscurrents in Psychiatry and Psychoanalysis,* pp. 89–99. Lippincott, Philadelphia, 1967.
87. Shapiro, A. K. The placebo effect in the history of medical treatment: Implications for psychiatry. Amer. J. Psychiat., *116:* 298–304, 1959.
88. Smith, A., Traganza, E. and Harrison, G. Studies on the effectiveness of antidepressant drugs. Psychopharmacol. Bull., [Special Issue], pp. 1–53, March, 1969.
89. Special Section, Lithium Carbonate (10 articles). Amer. J. Psychiat., *125:* 487–555, 1968.
90. Strupp, H. H. and Luborsky, L., eds. *Research in Psychotherapy,* vol. 2. French-Bray Printing, Baltimore, 1962.
91. Tower, S. S. Discussion. In Gibson, R. W., ed. *Crosscurrents in Psychiatry and Psychoanalysis,* pp. 219–221. Lippincott, Philadelphia, 1967.
92. Turner, W. J. The usefulness of diphenylhydantoin in the treatment of non-epileptic emotional disorders. Int. J. Neuropsychiat. [suppl. 2], 8–20, 1967.
93. Uhlenhuth, E. H., Covi, L., Rickels, K., Lipman, R. S. and Park, L. C. Predicting the relief of anxiety with meprobmate: An attempt at replication. In Wittenborn, J. R., Goldberg, S. C. and May, P. R. A., eds. *Advances in Biochemical Psychopharmacology.* Raven Press, New York. In press.
94. Uhlenhuth, E. H., Lipman, R. S. and Covi, L. Combined pharmacotherapy and psychotherapy: Controlled studies. J. Nerv. Ment. Dis., *148:* 52–64, 1969.
95. Uhlenhuth, E. H., Lipman, R. S., Rickels, K., Fisher, S., Covi, L. and Park, L. C. Predicting the relief of anxiety and meprobamate: Non-drug factors in the response of psychoneurotic outpatients. Arch. Gen. Psychiat., *19:* 619–630, 1968.
96. Uhlenhuth, E. H. and Park, L. C. The influence of medication (imipramine) and doctor in relieving depressed psychoneurotic outpatients. J. Psychiat. Res., *2:* 101–122, 1964.
97. Uhlenhuth, E. H., Rickels, K., Fisher, S., Park, L. C., Lipman, R. S. and Mock, J. Drug, doctor's verbal attitude and clinic setting in the symptomatic response to pharmacotherapy. Psychopharmacologia, *9:* 392–418, 1966.
98. Whitehorn, J. C. Alienation and leadership. Psychiatry, *24:* 1–6, 1961.
99. Whitehorn, J. C. Comment: Psychiatric implications of "placebo effect". Amer. J. Psychiat., *114:* 662–664, 1958.
100. Whitehorn, J. C. and Betz, B. J. A comparison of psychotherapeutic relationships between physicians and schizophrenic patients when insulin is combined with psychotherapy and when psychotherapy is used alone. Amer. J. Psychiat., *113:* 901–910, 1957.
101. Whitehorn, J. C. and Betz, B. J. A study of psychotherapeutic relationships between physicians and schizophrenic patients. Amer. J. Psychiat., *111:* 321–331, 1954.
102. Whiteside, T. The suds conflict. New Yorker, pp. 42–65, Dec. 19, 1964.
103. Wilder, J. Modern psychophysiology and the law of initial value. Amer. J. Psychother., *12:* 199–221, 1958.
104. Wittenborn, J. R. *The Clinical Psychopharmacology of Anxiety,* Charles C Thomas, Springfield, Ill., 1966.
105. Wittenborn, J. R. Prediction of the individual's response to antidepressant medication. In Efron, D. H., Cole, J. O., Levine, J. and Wittenborn, J. R., eds. *Psychopharmacology: A Review of Progress, 1957–1967,* pp. 749–756. PHS Publication No. 1836, U. S. Government Printing Office, Washington, D. C., 1968.
106. Zilboorg, G. and Henry, G. W. *A History of Medical Psychology.* W. W. Norton, New York, 1941.