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Chapter 45

Operant Conditioning Techniques in the Measurement of Psychopharmacologic Response*

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Determining the effects of chemical agents on the behavior of psychotic patients is among the most complicated experimental problems facing modern behavioral science. This great complexity is due to the myriad of variables which can act to modify drug effects. Description of these variables is facilitated by grouping them into five categories: (1) general variables controlling drug effects on higher organisms, (2) general variables controlling behavioral responses, (3) specific nature of the disease complex called psychosis, (4) nature of the hospital environment in which psychotic patients live, (5) nature of the behavioral measurement devices used to record effects.

PROBLEMS IN MEASUREMENT OF PSYCHOPHARMACOLOGIC RESPONSE

Among the *general variables controlling drug effects* on higher organisms, interspecies differences and inter-individual differences in drug response are well known. A rabbit, for example, can live on belladonna leaves, but a human will die from just a few. The development of drug tolerance and hypersensitivity in repeated administrations is equally well known. Drug interactions, both facilitative and suppressive, are also common problems to the pharmacologist. In addition, dose-response functions are seldom monotonic, having maxima or minima which must be empirically determined. These general problems make experimental pharmacology burdensome.

Some of the *general variables controlling behavioral responses* further complicate psychopharmacologic research. Behavior appears to be more sensitive to the effects of external stimuli and other influences the more recently it has been acquired and the less practiced and overlearned it is. Furthermore the sensitivity of behavioral response to external stimulation decreases as motivation increases. Therefore, overlearned, highly

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motivated behavior is less sensitive to the action of drugs than recently acquired, not highly motivated behavior. In addition, behavioral responses show wide inter-individual variability, making generalization from subject to subject difficult without controlling a host of other variables. Probably the response most disturbing in drug research is the "placebo" effect, profound behavioral changes which occur as a function of need, implicit instructions, or prior conditioning. In psychopharmacologic research, it is extremely difficult to control this effect. Additional difficulty is produced by drug-behavior interaction[8] and intra-individual differences in effects due to a drug acting differently upon two responses with different histories in the same organism at the same moment.

The specific *nature of the psychoses* introduces even more difficulty into psychopharmacologic research. There is evidence that certain drugs which have no effect on normal individuals have a marked therapeutic effect on some mentally ill patients. In other words, to determine the effect of a drug upon a disease, one must include the disease in his experimental preparation. In addition, there appears to be more than one specific disease entity included in some of the general classifications of psychoses. There are also marked individual differences among psychotic patients with respect to their responses to chemical agents. Even more disturbing is the fact that a given patient with a specific type of psychosis is apt to respond to drugs differentially, depending upon the phase or episode of his illness at the moment.[6]

The *nature of the hospital environment* in which the mental patient resides presents still more problems to the researcher. It is extremely difficult to control medication for research purposes in admissions units. Even when this is accomplished, it is almost impossible to prevent administration of other forms of "therapy" (*e.g.*, psychotherapy, group therapy, play therapy, home visits). It is equally difficult to insure that patients actually take all of the prescribed medication. Personnel in understaffed and overcrowded mental hospitals cannot exercise the care, experimental control, and additional labor in making observations which are necessary for highly controlled research.

The nature of the specific *behavioral measurement technique* used to record responses is of paramount importance. Until recently, most behavioral measurement devices have not eliminated the effects of a great deal of observer bias. Moreover, they have not permitted continuous and direct measurement of behavioral responses.

Although the mere listing of some of the problems facing psychopharmacologic research seems to suggest that we are overly optimistic in undertaking such research, these problems are not necessarily insurmountable. The action of some of the variables described above can be eliminated and the action of others greatly reduced by perfecting and refining our methods for the measurement of the behavioral responses. The purpose of our research is to provide psychiatry with reliable and valid laboratory devices in order to simplify measurement of psychopharmacologic responses in patients with mental disorders.

ADVANTAGES OF FREE-OPERANT MEASUREMENT OF PSYCHOPHARMACOLOGIC RESPONSE IN PATIENTS

The most reliable and sensitive method for the experimental analysis

and measurement of behavior yet developed in the experimental psychology laboratories is the method of free-operant conditioning.[2, 9,10] The plan of our research is to adapt this method for the laboratory measurement of psychopharmacologic responses in mental patients. The details of these adaptations have been described elsewhere[6] and are summarized in Chapter 8. It is important to mention, however, how free-operant measurement eliminates many of the psychopharmacologic research problems listed above.

Fully automatic environmental control, which includes the recording of the behavioral response and the programing and presentation of the discriminative and reinforcing stimuli, completely eliminates observer bias and the need for double-blind drug studies. This high environmental control produces behavioral data so reliable and so stable that conclusions can be drawn with respect to single organisms. This permits us to use a patient as his own control in drug research designs. We can thus eliminate inter-individual and inter-disease differences in psychopharmacologic response. It is important to note here that group research designs (in which drug responses are compared from one group of patients to another) include a large portion of the variables listed above as error or within-group variance. This inclusion makes it extremely difficult to determine any but extremely gross psychopharmacologic responses. The use of a patient as his own control also eliminates the need for presentation of placebos for control of placebo response, since lower dosages of the same drug or dosages of a different drug which do not produce the observed response can be used for this purpose.

The *continuous measurement* provided by the free-operant method enables the psychopharmacologic researcher to obtain a single, continuous record of the complete response to a single dosage of a drug in a single patient, going from a pre-drug baseline extending through the drug effect up to complete return to the pre-medication baseline. Such a procedure permits the rapid determination of the duration and pattern of responses to single administrations without confounding the data with the effects of other variables. This procedure greatly facilitates determining the effects of drug tolerance, hypersensitivity, and interactions.

Direct measurement of the adjustive behavior, or rate of free-operant responding, of a psychotic patient while he is behaving psychotically rules out inter-species, inter-individual, and inter-disease differences in drug response. Direct measurement also eliminates validation problems involved in measuring other forms of behavior (*i.e.,* rating scales) and in using physiological responses to predict behavioral response.

Simultaneous measurement of the effects of a drug on symptomatic and nonsymptomatic adjustive behavior provides the most powerful measurement system for the determination of therapeutic psychopharmacologic response. This procedure eliminates inter-behavioral response differences because the drug response record has within it a separate measure of the severity of the behavioral disturbance from moment to moment within the experimental session. This permits the direct comparison of the effect of a single dose on both the socially desirable and undesirable responses of the patient.

In general, chronic psychotic patients (rather than acutely ill patients) are to be preferred for drug screening, unless of course the drug is specifically planned for use with acute psychotics. The chronic psy-

chotic is much less apt to have a "spontaneous" recovery which could be misinterpreted as a drug-induced recovery. In addition, the back ward environment of the chronic psychotic is closer to the research ideal of a stable and controlled environment than is the admissions unit, with its phrenetic changing of medication and therapy. If the researcher conducts his own physiological controls (daily blood pressure, pulse, temperature, and body weight determinations, and a clinical examination along with weekly laboratory urine and blood tests) he adequately rules out physiological illness. It is important to control for physiological illness because the free-operant method is sensitive to its effects.

Free-operant behavioral measurement does not eliminate the problems of drug tolerance, hypersensitivity, and interactions. Drug-behavioral interaction and non-monotonic dose-response functions also remain. However, the experimental analysis of these problems is greatly simplified by the use of the free-operant method.

FOUR EXAMPLES OF FREE-OPERANT PSYCHOPHARMACOLOGIC MEASUREMENT

These examples have been selected to show how different types of psychopharmacologic response of interest to the psychiatrist can be measured by using the free-operant method. The behavioral response in all cases is the same: pulling a plunger in an experimental enclosure for candy and cigarettes on a 1-minute variable-interval schedule of reinforcement;[6] however, by making slight changes in the experimental environment, it is possible to determine the effects of drugs on very different sorts of behavior. For example, by changing the nature of the reinforcing stimulus, drug effects on behaviors as different as charity, television viewing, and homosexual interest can be determined. By changing the schedule of reinforcement, the effects of drugs on counting and time-telling behavior can be determined. By changing the discriminative stimuli and/or the possible number of responses, the effects on discrimination and differentiation can be determined (see Chapter 8). By adding other individuals and demanding integrated performance, the effects on cooperation, competition, and differential leadership can be determined. Modifications of this sort have previously been described.[4]

The *immediate effects of a single dosage* of 20 mg. benactyzine‡ on directly and simultaneously recorded manual plunger-pulling reinforced with candy on a 1-minute variable-interval schedule and vocal hallucinogenic responding of an hallucinatory chronic psychotic adult are shown in Figure 1. Two continuous experimental sessions of over 5 hours duration are shown. The cumulative response records are made by a pen moving a short distance up the recording paper for each response while the paper moves continuously. The pen takes 500 responses to cross the paper, at which point it resets and is ready for another excursion. In this way the rate of response is indicated as the slope of the record, steep lines indicating extremely rapid responding and horizontal lines indicating no responding at all.

‡ The benactyzine and methastyridone (MK-202) were provided by Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania. The iproniazid was provided by Hoffman-LaRoche, Inc., Nutley, New Jersey.

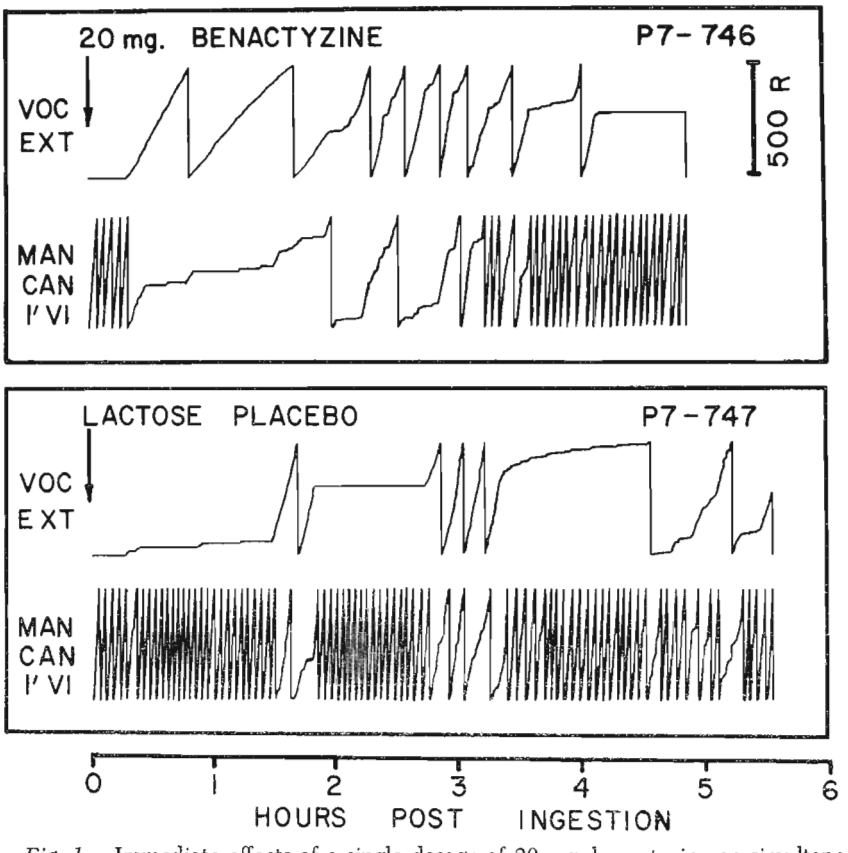

Fig. 1. Immediate effects of a single dosage of 20 mg. benactyzine on simultaneously recorded vocal hallucinogenic responding (VOC) and operantly reinforced manual plunger pulling (MAN) of an hallucinatory chronic psychotic adult. Lactose placebo session included as a control.

The bottom pair of records were taken immediately after the ingestion of lactose tablets which were identical in form and number to the benactyzine tablets which were given the day before. These lactose placebo records show the baseline resting psychotic state of Patient Number 7. During this control session (#747) the patient made 38,000 manual responses (6,570 per hour). There were three periods within the 5-hour experimental session (lasting for 20, 37, and 23 minutes respectively) during which the patient pulled the plungers at a reduced and less adjustive rate. During this time the patient engaged in hallucinatory behavior, talking and shouting to nonexistent individuals. This hallucinatory vocal responding was recorded by a hidden microphone which activated the pen in the upper record (VOC).[5, 7] These vocal responses were never reinforced and hence were extinguished (EXT). Note that the three psychotic outbursts are marked by an increased rate of vocal responding.

These control records indicate the extreme difficulty in conducting drug research on patients with intermittently occurring psychotic episodes of this sort. For example, if continuous and simultaneous measure-

ment had not been used and the researcher happened to sample the patient's behavior during the control session while the patient was engaging in a "spontaneous" psychotic episode, no difference between the effect of the drug and the control would have been recorded.

The upper two records were taken immediately after the ingestion of 20 mg. benactyzine. Eighteen minutes after ingestion vocal hallucinatory responding was catalyzed. This heightened hallucinatory behavior was maintained for more than 3.5 hours. The manual or adjustive, nonsymptomatic responding began to be reduced in rate 18 minutes after ingestion. At 22 minutes after ingestion the high rate of response was fully suppressed. The maximum reduction in manual responding occurred 1.0 to 1.5 hours after ingestion.

From these two experimental sessions on a single patient, we were able to conclude that rather than being a psychotherapeutic drug,[1] benactyzine was actually hallucinogenic. Furthermore, we were able to say that a 20 mg. dosage produced a response with a latency of 18 minutes, a maximum effect occurring from 1.0 to 1.5 hours post-ingestion, with a duration of 3.5 to 4.0 hours. These records were collected on July 31 and August 1, 1957. Subsequent clinical field trials have supported the conclusion that benactyzine is truly a hallucinogenic compound with little antipsychotic value.

It is important to note that an ideal anti-hallucinatory compound should decrease the rate of vocal hallucinatory output during a psychotic episode and at the same time increase the rate of nonsymptomatic responding during that same episode. However, we have found only drugs that will increase both rates (d-amphetamine), drugs that will decrease both rates (chlorpromazine), drugs that catalyze and increase the duration and intensity of these psychotic episodes (benactyzine), and drugs that have no apparent effect. Even if a drug entirely eliminated the hallucinatory vocal responses, it would not be truly anti-hallucinatory unless it restored the nonsymptomatic manual responses to their normal rate during the episode. Merely eliminating the vocal responding is no more therapeutic than clapping a hand over the patient's mouth, or stuffing the ears of those around him with cotton. If the hallucinator's nonsymptomatic response rate remains low during these episodes, he still is psychotic. In less technical terms, he might still be listening to his voices, but simply not talking back to them.

The technique of direct, continuous, and simultaneous recording of symptomatic and nonsymptomatic responding is the most sensitive index we have yet developed for screening psychotherapeutic compounds. Maximal research efficiency is obtained when the compound being screened can be injected intramuscularly during a continuous experimental session and has immediate effects similar to its chronic effects. If the effects last no more than several hours, experimental sessions long enough to include both pre- and post-medication control responses can be run. Such pre- and post-medication control eliminates day-to-day variability and greatly simplifies experimental analysis in drug screening.

Figure 2 shows *the immediate effects of 9 single doses* (0.5 to 6.0 gm.) of methastyridone (MK-202) on free-operant response rate (solid line), pulse rate (heavy dashed line), and diastolic and systolic blood pressure (light dashed lines) of a chronic psychotic adult. This drug

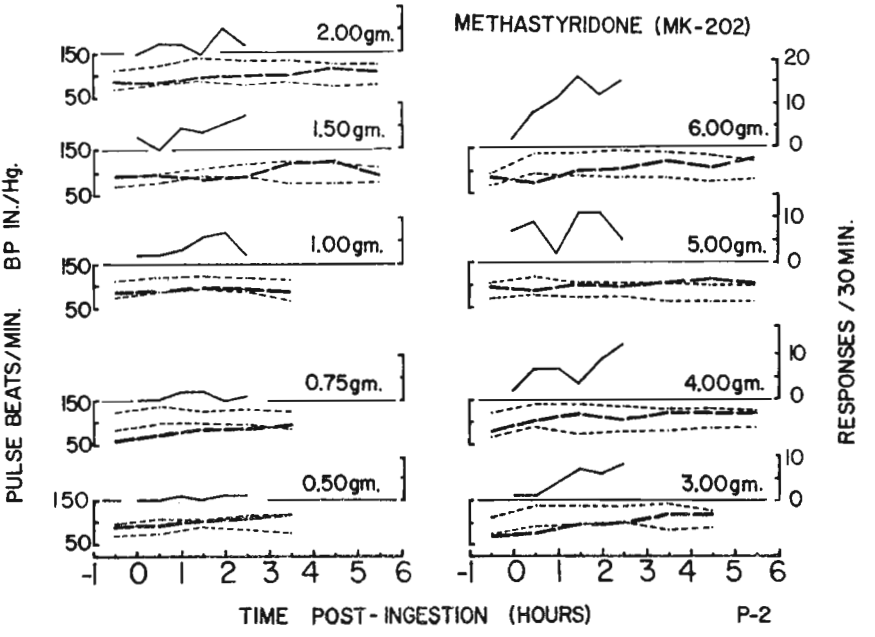

Fig. 2. Immediate effects of single doses (0.5 to 6.0 gm.) of methastyridone (MK-202) given once a week on operant responding (solid line), pulse rate (heavy dashed line), and blood pressure (light dashed lines) of a chronic psychotic adult.

was psychotherapeutic to the extent that it increased this patient's extremely low (severely psychotic) rate of response. However, the amount of increase in rate fell far short of anything that could be considered of great clinical importance. Even at the extremely high dosage of 6 gm. the rate of response was less than 40 responses per hour. A "normal" rate of response is above 800 per hour. In this figure, rather than showing the cumulative response records which comprise the raw data (as in Fig. 1), the rate of response for 30-minute periods is plotted. This was done to summarize the experimental results more efficiently.

Note that with this series of experimental determinations, there is no need to run placebo controls. The graduated dose-response effects seen in Figure 2 serve as an active placebo. Note also the advantage gained by including circulatory measurements as physiological controls. Ideally, the experimental rooms should be equipped with telemeter transducers so that physiological indicators could be continually monitored. If a behavioral response did not occur, physiological responses would assure us that we had an active compound and that it was properly ingested. Ideally, as mentioned above, compounds should be selected which can be injected intramuscularly to insure ingestion and absorption of the agent.

In Figure 3 the *cumulative effects of the weekly single doses* of methastyridone are plotted. It is important to note that the behavioral and physiological effects were greater on some days that the drug was not given than they were on the days of administration. This is an example of drug-behavior interaction and is the reason this drug was given only once a week, allowing seven days for recovery of the be-

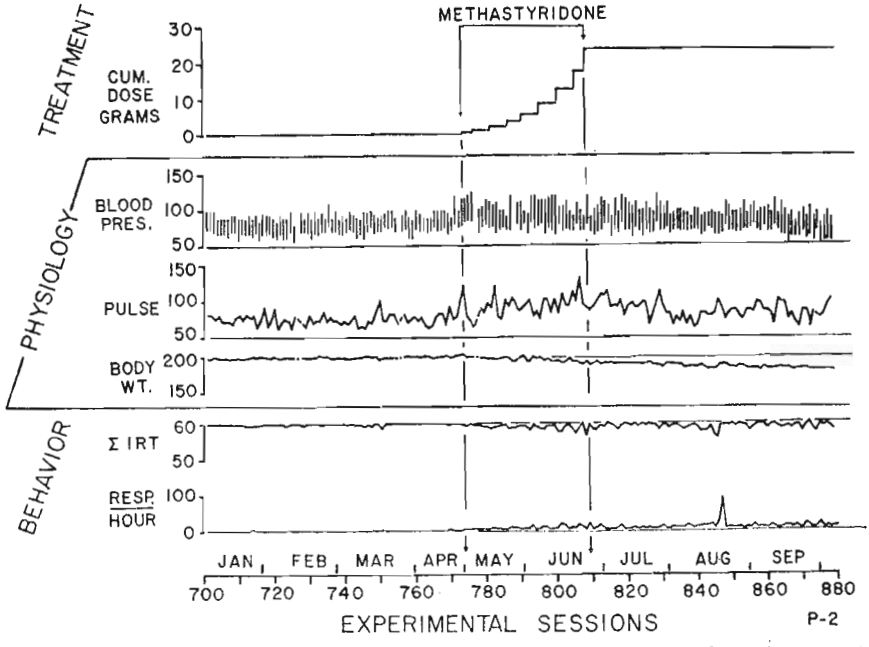

Fig. 3. Cumulative effects of weekly single doses of methastyridone (MK-202) on operant responses and physiological indicators in a chronic psychotic adult. (The immediate effects of this medication series are shown in Fig. 2). Note that the effects are greater on some of the days that drug was not given.

havior. Our research design, rather than being obscured by drug-behavior interaction, isolates and elucidates the nature of this interaction. Note the value of the three-month long pre- and post-drug series controls. Note also that this entire graph starts on the 700th experimental session, with 700 prior experimental sessions providing a baseline of over 7 years to use in evaluating the drug effect, determining its clinical significance, and ruling out the possibility of "spontaneous" recovery.

Although methastyridone was one of the most exciting compounds to come out of the animal behavioral screening laboratories because it was found to have strong stimulating effects upon behavior without the major behavioral and physiological side effects of d-amphetamine,[11] it was not markedly effective with psychotic patients. Patient Number 2, whose psychopharmacologic responses are shown in Figures 2 and 3, showed the greatest rate increase, or therapeutic response, of the 7 patients given this drug in the same dosages. By measuring the effects of methastyridone on normal volunteers, we can determine whether the great differences between the animal behavioral results and our results with mental patients are actually due to species differences or to the presence of psychosis.

The *effects of chronic medication* can be easily determined without controlled group design by the use of long pre-medication baselines. Figure 4 contains the experimental history of a chronic psychotic responding on a variable-interval schedule for various reinforcers: female nude pictures (FN), feeding a hungry kitten (FK), extinction (EXT) nickels (5¢), and small pieces of candy (CAN). This history covers a

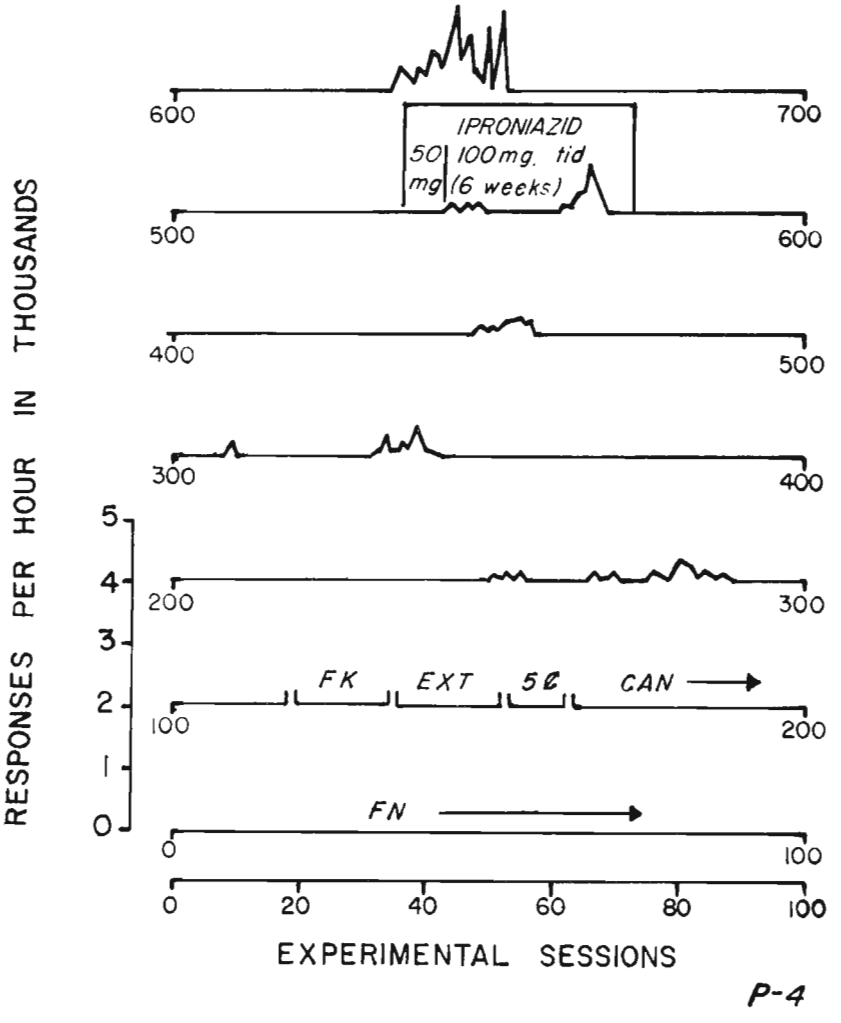

Fig. 4. Increases in operant response rate (recovery) of an inactive chronic psychotic adult during maintenance medication with iproniazid compared with "spontaneous" recoveries during continuous experimental history of 4.5 years (600 experimental sessions).

period of almost 6 years of daily experimentation and reveals severely depressed operant behavior with several "spontaneous" recovery phases of extremely low magnitude. The different reinforcers were used during the first 200 sessions in attempts to determine the most appropriate reinforcer for this patient. None seemed truly appropriate for this individual, but since candy is the most appropriate reinforcer for chronic psychotics in general, it was used in the subsequent sessions.

Fifty mg. t.i.d. of iproniazid was administered for 4 weeks, beginning at the 535th experimental session, with no therapeutic effect. On the 545th session the dosage was increased to 100 mg. t.i.d. and a slight rate increase occurred for a few days. Three weeks after the rate had declined, there was another temporary period of increased rate of re-

sponse. After 6 weeks of 100 mg. t.i.d., liver damage began to develop and the medication was terminated. From the 640th through 660th session another "spontaneous" rate increase occurred in which the rate went even higher (to 1,500 responses per hour).

From the comparison of the effect of this chronic iproniazid medication with the long pre-medication baseline, we must conclude that iproniazid, given in the heaviest maintenance doses medically feasible, produced only two "recovery cycles" in this chronic patient which were no greater than spontaneously occurring ones. This patient and this medication series were included in a drug study in which 20 patients were given iproniazid and 20 patients were given placebos. Psychiatrists and ward personnel (triple-blind, to be sure) independently evaluated the recovery of these patients. The patient whose "recovery" is shown in Figure 4 was 1 of the 4 (out of the 20 receiving medication) who were reported as "markedly improved" by the clinical evaluations. The psychiatric evaluations, however, had no prior baseline for reference and comparison. The two iproniazid "recovery" cycles in Figure 4 are significant only because of their timing with respect to the change in dosage of the drug. The "recoveries" have little therapeutic significance, for they were not maintained during or after the drug administration and were of no greater magnitude than the several spontaneous improvement periods in the patient's experimental history.

As our experimental baselines grow, each medication series serves as an active placebo control for the others. This eliminates wasting valuable experimental time on placebo controls and cross-over research designs. More than one medication series on the same baseline permits the direct comparison of the therapeutic effects of one compound with the effects of any other in the experimental history.

Daily blood pressure, pulse rate, temperature, and body weight determinations are available and could have been plotted with the operant response data in Figure 4. A marked increase in body weight occurred during the iproniazid medication. There is reason to believe that this was one of the indicators upon which the psychiatric and ward personnel based their report of "markedly improved."

Recently we have added Forrest Rapid Urine Color Tests for phenothiazine excretion as a check on the accuracy of the chronic medications administered by hospital personnel.[3] The addition of laboratory data of this sort further refines our research design and rules out more of the variables which plague the psychopharmacologic researcher.

However, measurement of the effects of chronic medication is inordinately time consuming. The risk of the action of other variables becomes great as the duration of the experiment is extended. Ward changes, home visits, seasonal effects, psychotic phases[6] and the constant risk of physiological illness threaten to obscure the drug effect in such long-term investigations. Furthermore, it takes many weeks or months after the termination of a chronic medication series with psychotherapeutic drugs for the behavior to recover and for the patient to be ready to receive another compound without compounding drug effects. Thus, it is much more efficient and economical to screen for immediate effects of single doses of drugs whose immediate effects are similar to their chronic effects.

SUMMARY

Although a few of the problems inherent in the measurement of psychopharmacologic response cannot be solved by the development of valid and reliable laboratory behavioral measurement techniques, many can be solved by these methods. An ideal screening procedure would involve (1) determining the toxicity and behavioral action of a new compound in the animal laboratories, (2) selecting compounds with similar immediate and chronic effects on the behavior of small animals, (3) determining the duration of action and the dose required to produce immediate effects from single administrations to a few selected patients with appropriate target symptoms, (4) determining the dose and daily medication frequency necessary for chronic maintenance medication from the dosage and duration of the immediate single dosage effects, (5) determining the effects of chronic medication on patients with long experimental baselines which include chronic medication series with several other psychotherapeutic compounds for direct drug comparison. A drug which has successfully passed these screening tests could then be submitted to the arduous, prolonged, and expensive clinical evaluation.

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