Drugs occupy a unique place among the various factors which bring about changes in behavior. Relief from intractable pain, operative pain, psychotic and neurotic symptoms, seasickness, headaches, fatigue, boredom, the induction of moods, and the facilitation of learning and sleep are but a few of the alterations which psychopharmacological agents attempt to bring about.

The implications of these various drug effects on the physiology, biochemistry, and overt behavior of the organism have drawn research workers from many diverse disciplines to the field of psychopharmacology. The research literature, in the general area of drugs and personality, reflects interests in (1) behavior theory and personality measurement, (2) the nature of drug action, and (3) the interaction between these two, i.e., the influence of personality factors on reaction to drugs and the effects of drugs on personality.

The general approach of this chapter will involve reviewing and assessing the interaction of drug effects and personality factors. The main intention will be to search for the more promising channels along which work in this area might be directed. The study of psychopharmacology and personality change is very much in its infancy and suffers from a lack of sound, testable theory and adequate methodology to apply to its problems. The theory and recommendations which will be presented here will hopefully contribute toward clarification of some of the basic issues in the field.

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Personality Measurement

In a discussion of the effects of drugs on personality—or indeed a discussion of whether or not there is, or can be, any experimental evidence for such effects—the present vague status of the concept of “personality” has to be dealt with. Obviously, only a concept which is relevant to experimental investigation can be accepted for our purposes. Such a concept of personality must permit change and its detection. As everyone would agree, the concept of personality, as representing the unique pattern of behavior of the individual, is no more than a scientific model. If it has ceased being a useful model, we ought to discard it. If it is still useful in the study of behavior, it ought to be retained.

Traditionally, measurement in personality has been introduced at two different levels, depending upon the model of personality adhered to by the investigators. A review of the various scientific models proposed for personality (Zubin, 1954) indicates the following models: (1) differential, (2) clinical, (3) personalistic, and (4) neurophysiological. In the differential model, an analysis of behavior into traits is made first and then techniques are chosen for assessing these traits. The trait theorists have approached measurement by assembling independent but additive factors of personality which they sought to identify and then measure. Their primary statistical tool is factor analysis. In the clinical model, normal personality is regarded as the central portion of behavior which in the extremes are psychopathological. The basic approach here is the identification of types of behavior over many dimensions and the attempt then to isolate the measures which characterize these types. These holistically oriented investigators begin with a totality and try to analyze it through measurement. The personalistic approach is geared to the single individual, considering each person as a separate universe. The neurophysiological approach is more like the differential, except that it deals with behavior reflecting brain function rather than with behavior reflecting organized traits. For the purpose of this chapter, measurement in the field of personality can be thought of as the attempt, first to isolate, but then to synthesize the dimensions on which the behavioral uniqueness of the individual rests.

No matter what organizational principles may be postulated (needs, traits, etc.), personality is inferred from behavior. It might be interesting to classify observable behavior into its parts in order to recognize that sector for which a concept of personality is useful. Behavior includes parts which are overdetermined by biology and hence highly predictable, e.g., reflex action, imprinting, and other natively endowed behaviors. It also is composed of parts
that are overdetermined culturally, e.g., language, food habits, dress, etc. While these two types of overdetermined behavior are highly consistent and characteristic, they do not differentiate among individuals in the same social-cultural and biological subgroup, and hence are not useful in predicting individual systematic behavior. There is a third class of behaviors, which may be regarded as accidental or erratic and unsystematic, which are not useful in prediction. The rest of behavior may be sampled for its usefulness as measures of personality.

It seems that personality is here to stay no matter how much objectively minded psychologists may disdain it. Our problem is to find a suitable model or structure for it, which can be examined scientifically and from which testable hypotheses can be drawn. An evaluation of the present status of the concept of personality in drug research will be gained from the section of this chapter which reviews the methods now in use in attempts to measure the influence of personality on drug response and the changes in personality brought about by drugs.

Nature of Drug Action

Pharmacology is the study of the interaction of exogenous chemical agents (drugs) with the endogenous chemical substances of a living organism. Within the general body of pharmacology, the study of chemical interactions which involve the central nervous system is designated as psychopharmacology if those chemical interactions lead to changes in behavior, or, neuropharmacology if they lead to merely local neural changes.

Since the nervous system is itself composed of chemical substances, and is characterized by ongoing chemical processes, one can readily see why a knowledge of neurochemistry is so essential for the understanding of psychopharmacology. Unfortunately, the science of neurochemistry is also in its infancy, and the knowledge that is available requires a high degree of specialization for its understanding. Consequently, many behavioral scientists are reduced to the status of watching a “black-box” from the outside to note the effects of the exogenous factors that are added to it. Hopefully, this is only a temporary state in the preparation of research workers in this field.

In considering the variety of techniques which may be useful in gauging the effect of drugs on the behaviors which reflect personality, it is necessary to bear in mind that the drugs bring about their physiological effects through alterations in the biochemical milieu of the nervous system. Since we are not concerned with peripheral or segmental aspects of the central nervous system but with its higher centers—those which presumably are concerned with
personality—we must look for techniques which measure behaviors altered by alterations in brain function.

REVIEW OF THE LITERATURE

The question of whether drugs are capable of producing changes of an enduring nature in the personality is still very much an open one. A definitive answer to the question will require less ambiguous evidence than is so far available. Most of what is known in this area is derived from studies in which drugs are administered on an acute basis (single dose) and the methodology which would be appropriate for assessing changes of any depth has usually been lacking. Methods of measurement developed in the field of personality have, however, made a contribution to our understanding of the mechanisms of drug action. Before reviewing some of these general findings it will be worth while to indicate several restrictive characteristics of the research in this area.

Studies with normals are characterized by an avoidance, for the most part, of the more potent tranquilizers, despite the fact that this class of drugs has had the greatest impact in the clinical area. This restriction is based partly on practical considerations. These drugs are more potent, can have more disturbing side effects, and their general effects are not as well understood as those of the older stimulants and sedatives. This is especially troublesome to the non-clinical investigator who may be using drugs to study other phenomena and prefers to confine himself to those drugs on which a good deal of information is already available. On the other hand, chronic studies, i.e., drugs administered over extended periods of time, have usually been carried out by clinical investigators. Here it would seem that the opportunity for exploring the more profound effects on personality would be greater. Unfortunately, methods which would be appropriate for the investigation of such changes are usually not included in these studies because of the following: (1) the investigator's assumption that profound changes will not occur; (2) the lack of adequate methodology for dealing with the problem; and (3) the lack of training in experimental methodology of clinical investigators.

Results from clinical investigations of the tranquilizers and the work with the psychotomimetics, would lead one to think that basic changes are certainly possible, and that there is a great need for the application of more appropriate methods. The problem is somewhat like that encountered in the investigations of the effects of psychotherapy. The field of personality suffers, in general, from a lack of adequate methodology for studying basic change. Inventories are influenced by factors which have nothing to do with the aims of these studies, e.g., social desirability. The record of projective tech-
Techniques in formal research is still not very laudable despite some of the newer promising approaches to quantification (Katz, 1960), and the relating of performance measures to personality factors is still in a very early stage of development.

These techniques have managed to contribute to our understanding of drug effects and the influence of personality factors on drug response, despite their limitations. Inventories, i.e., self-reports, rating scales, projectives, and performance tests have provided some dependable information in this field and it will be of value to review the more consistent of these findings.

**Influence of Personality on Drug Action**

One relatively consistent finding is that atypicality of drug response and increased reactivity to drugs are related to "personality maladjustment." This stems from the work of von Felsinger, Lasagna, and Beecher (1955, 1956) in which maladjustment as measured with the Rorschach was related to atypical or unusual patterns of response to different drugs, from Kornetsky and Humphries' (1957) finding that extent of deviance as measured by several MMPI scales was positively related to the amount of subjective effect derived from a given drug, and that the factor of "neuroticism" on the Maudsley Personality Inventory is related to the likelihood of a toxic reaction to methylpentynol (Bartholomew and Marly, 1959). With regard to the problem of predicting response to drugs from personality type, van Ree (1960) was able to demonstrate a relationship between introversion-extroversion as measured by the Maudsley Medical Questionnaire, to type of reaction to LSD, though the data analysis is somewhat sketchy in this research. Introversion was more likely to lead to a "schizophreniform" (withdrawal) reaction under LSD; extroverts tended to react to LSD with a "maniform" (manic) reaction. Klerman and DiMascio (1959) are using MMPI patterns along with several other indices to separate out two contrasting somatotypes, and have been successful to some extent in predicting differential reactions to drugs.

Individual "atypicality" of response to drugs is apparently almost as common as typicality. Von Felsinger, Lasagna, and Beecher (1955) found approximately 50 per cent of subjects on such drugs as morphine, amphetamine, and phenoobarbital produced atypical responses. The relating of personality factors to individual differences in drug response would seem to be, then, a natural direction for research in this area to take. For the most part, the techniques for classifying subjects into personality types have not been highly refined and the unresolved conflict between the holistic and the trait approaches tends to inhibit this kind of research. General traits such as neuroticism, deviance, introversion-extroversion look promising as predictors, but other
more specific traits have not been experimented with to any great extent. The
work of the Michigan group (Kelly et al., 1958), which employed a large
number of specific personality variables from the MMPI, CPI, EPFS, and Cat-
tell’s 16-PFT, was very discouraging in this respect. Despite some limited find-
ings, careful analysis failed to relate any of the measures to drug effects.

When one is attempting to link up a single trait with drug response he
has, however, to contend with the fact that his subjects, though having one
personality trait in common, are also likely to differ in other traits and thus
make it impossible to relate the trait in question to the drug. This, in addi-
tion to the impreciseness of our measures of traits makes this particular pre-
dictive approach highly tenuous. On the other hand, the holistic approach
introduces another set of methodological problems. A personality type implies
a pattern of characteristics. It becomes difficult to find subjects who match
all of the required characteristics and difficult to set up objective criteria for
determining whether they do. The holistic approach is usually forced to set-
tle for less precision in the typing of people than it would like, which then
makes it difficult adequately to test the predictive hypotheses. The more
general traits such as introversion-extroversion and neuroticism seem to repre-
sent a compromise here and have in fact worked reasonably well as noted.
The Kleiman-DiMascio work and the patterning approach to the MMPI used
by Heartzen and Hill (1959) and by Belleville (1956) with several types of
psychophaths demonstrates, though, some real promise for the patterning ap-
proach.

Effects of Drugs on Personality

If work in the predictor area is still very much in an exploratory stage,
results from research on the effects of drugs on personality are probably even
less definitive. If we accept the assumptions that personality structure is
highly stable and that drugs produce only temporary effects, one should not
then expect drugs to produce any profound effects on personality. Most in-
vestigators in this area have learned to operate with these assumptions and
consequently, attention has been focused on the measurement of those aspects
of personality which also have a somewhat temporary quality. These are
the aspects of “mood” or “affect.” It should be noted also that the field is
influenced by the pharmacological and clinical nomenclature of drugs which
tend to emphasize the effect on mood as against other possible effects. The
majority of psychotropic drugs are classified, for example, as sedatives, stimu-
lants, tranquilizers, and antidepressants. Where the major interest is in the
concept of mood, these drugs have become highly useful tools in its study.
Nowlis and the group at Rochester (with the study of mood as a prime concern) have contributed to the methodology in this field by constructing an inventory to assess the various mood factors (Nowlis and Nowlis, 1956). The Clyde Mood Scale (Clyde, 1961) as another instrument of this type was developed specifically for the measurement of drug effects and has been used in a wide variety of studies. These inventories, because they offer added refinement to the measurement of subjective effects, tend to supplement older symptom questionnaires in studying drugs and, in many cases, replace them. In the long run, their promise would seem to lie in their ability to provide data on differential mood patterns in reactions to various drugs, which should also help in refining the nomenclature (Lindemann and von Felsinger, 1961). At present, there are little data of this type available.

Other promising approaches to the measurement of affect under drugs come from the field of verbal behavior. Gottschalk and Gleser have developed and partially validated measures of anxiety and hostility with the verbal sampling method (Gottschalk and Hambridge, 1955) and have demonstrated its sensitivity to the effects of perphenazine in reducing the hostility of patients (Gottschalk et al., 1960). It has the advantage of avoiding some of the methodological difficulties of inventories and may provide some sort of bridge toward more objective methods in this area. Other work on verbal behavior is particularly relevant to problems in this area and will be gone into in greater detail later in the chapter.

As far as the concept of mood is concerned, we will probably always want to ask the patient how he feels after the administration of a drug, but given the difficulties with inventories, i.e., halo effects, response sets, etc., we would prefer to have other more objective indices of his affect state.

Mood as Nowlis (1956) and Kubie (1960) point out, however, is not always so temporary. We sometimes use the concept to denote a fairly stable characteristic of temperament. Kubie conceives of this more enduring mood concept as a basic emotional attitude, e.g., pessimism or optimism. Do drugs have any effect on this aspect of personality? From what has been learned through acute (single) dosage studies, the likelihood, as previously noted, is small. To determine whether changes of this type will occur under chronic administration, one would have to apply methodology from the personality area which is aimed at assessing durable change in the basic structure. This has not been done and the reasons as previously noted may, for the most part, be tied to our lack of adequate methods.

Basic emotional attitudes, perceptions of and attitudes toward self and others, and mechanisms for dealing with anxiety are some of the fundamental characteristics of the concept of personality structure, and the available meth-
methods for measuring these phenomena have not turned out to be wholly reliable or satisfactory. This, of course, only becomes a problem if we think that drugs are presently capable of promoting such changes or that new drugs will appear which will force these issues. Clinical experience with chronic administration of tranquilizers has certainly raised these questions, and the psychotomimetics have produced profound effects in people, which we must continue to admit are not fully understood. These questions as noted, for all intents and purposes, remain open.

The Testing of Theory

With regard to either of the central problems, the personality factors which influence drug response or the effects of drugs on personality, it is evident that we are presently forced to work with a great many unknowns. It may be that the technical problems of objective measurement in this field are less of an obstacle where the research is guided by an explicit and testable theory.

In this respect, Eysenck's work (1957) represents one of the few attempts to follow a program of research on drugs and personality which is aimed at systematic testing of hypotheses within an explicit theoretical framework. His theories of drug action, which are based on those of McDougall and Hull, have to do with the differential effects of stimulants and depressants on cortical excitation, and have resulted in a series of discrete hypotheses and experiments. There is broad and selective application of experimental psychological methods and the results have been very helpful in providing information on the effects of standard drugs on a wide variety of behaviors. Some of the predictions and results are summarized in Table 1.

It is worth noting that the testing of his predictions failed as often as it succeeded in giving significant support to the predictions. It is difficult to attribute this lack of consistency in confirmation to any specific aspects of Eysenck's theory, but he seems to be operating with several questionable assumptions. For example, he oversimplifies the action of d-amphetamine and sodium amytal when he designates one a "standard stimulant" and the other a "standard depressant." As demonstrated in previous work with these drugs, they are not as consistent in their effects as he proposes (see previous discussion). His tendency to work with very few subjects in most of these experiments only helps to exaggerate this problem. There is little sound information on the effects of these drugs on cortical excitation, and his assumptions in this area are again of a highly speculative nature and represent a somewhat oversimplified picture of neurophysiological processes. Nonetheless, the data add to our general knowledge about the effects of contrasting drugs on psychological functions and the systematic nature of the research program contributes to the needed theoretical stimulation in this field.
Table 1. Experimental Tests of Predictions Based on Eysenck’s Theory

<table>
<thead>
<tr>
<th>Prediction</th>
<th>Result</th>
<th>Prediction</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Long visual after-effects (rotating spiral)</td>
<td>+(-31)</td>
<td>1. Short visual after-effects (rotating spiral)</td>
<td>−(36)</td>
</tr>
<tr>
<td>2. Slow perspective reversals</td>
<td>−(35)</td>
<td>2. Fast perspective reversals</td>
<td>−(35)</td>
</tr>
<tr>
<td>3. Lower threshold for suppresion of primary visual stimulus</td>
<td>+(27)</td>
<td>3. Higher threshold for suppresion of primary visual stimulus</td>
<td>+(27)</td>
</tr>
<tr>
<td>4. Decreased static ataxia</td>
<td>−(29)</td>
<td>4. Increased static ataxia</td>
<td>+(29)</td>
</tr>
<tr>
<td>5. Continuous work facilitated</td>
<td>+(28)</td>
<td>5. Continuous work impeded</td>
<td>+(28)</td>
</tr>
<tr>
<td>7. Less kinaesthetic after-effects</td>
<td>−(33)</td>
<td>7. Greater kinaesthetic after-effects</td>
<td>−(33)</td>
</tr>
<tr>
<td>8. Higher auditory flutter-fusion threshold</td>
<td>−(34)</td>
<td>8. Lower auditory flutter-fusion threshold</td>
<td>−(34)</td>
</tr>
</tbody>
</table>

* Eysenck has, upon our request, made the following comments concerning this table and the evaluation of his work presented here. We were unable to implement these suggestions, due to time considerations, but include them so that the interested reader may be made aware of Eysenck’s views and pursue the problem further on his own, if he wishes.

“Table 1 deals only with experiments I have done myself, and is incomplete even as regards these; for a tally of successful and unsuccessful predictions I think it would be necessary to include the many studies made by other people in my department and elsewhere as well. Upon quick inspection of a random 100 articles from my list, I found that the number of successful predictions is well above the 80 per cent level. It is natural that the proportion in my own experiments would be smaller because in the natural way of things I would give the more obvious and certainresearches to students and do the more unlikely and novel ones myself.

“Failure in confirmation of a prediction is often an indication, not of any fault in the theory, but rather of a defect in the connecting link between general experimental psychology and my prediction. I have discussed in Experiments in Personality, H. J. Eysenck, London: Routledge & Kegan Paul, 1960, one such case in detail, i.e., that of the bowing of the serial learning curve. The argument used there applies to other apparent failures as well.

“I don’t think it is true to say that I over-simplify the action of certain drugs; at least I have made a systematic attempt to provide a methodology for testing the assumption I make (in Experiments in Personality). We have found the drugs to have consistent effects in experiments relevant to my hypothesis, clearly related to the excitation-inhibition balance. Inconsistencies outside that framework are not relevant to my hypothesis.

“I agree with what is said about our lack of knowledge regarding the effects of drugs on cortical excitation, but I am making no assumptions on the physiological level; the processes I am talking about are explicitly defined in behavioural terms.”

* Confirmation of prediction.
− No significant confirmation.
* No predictions made from theory, simply a finding.
Numbers indicate references.
Summary

On the basis of previous findings then, the question of the durability of the effects of drugs on personality still appears to be an open one. Drugs administered acutely, as far as we can tell, produce only short term changes. There is a need for more chronic dosage studies and a need for the inclusion in such studies of methods which are appropriate to measuring the long term effects on personality. Personality measures so far have been more helpful on the predictive side than they have in the assessment of drug effects. This applies particularly to research in which general rather than specific traits have been related to drug response. More refined techniques are now available for measuring the effects on subjective mood, and objective measures of affect are becoming available. These techniques will assist in the specification of mood patterns for various classes of drugs and contribute to improvements in the precision of nomenclature in this area. The available data, then, do not provide definitive answers concerning personality change, but from this brief review of findings and methodological problems, it would seem that research which is guided by explicit theory can contribute a more systematic base for the gathering of this information.

A MODEL FOR STUDYING DRUG EFFECTS ON PERSONALITY

The Variables

The study of personality, concerned as it is with such phenomena as motivations, feeling, organizing principles of experience and behavior, suffers greatly from a lack of adequate criteria with which to measure its characteristics. The history of personality measurement has involved a continuing search for those external behaviors which are most relevant to the understanding of the intervening internal phenomena. In seeking appropriate techniques of investigation in this field, the following elements require attention: (1) the behavior to be measured; (2) the environmental situation in which the behavior takes place; (3) the individual under observation, and (4) the chemical agent.

In a previous study (Burdoeck, Sutton, and Zubin, 1958) a classification of the types of measurable behavior that can be observed under controlled conditions and which presumably reflect brain function as discussed earlier has been provided. By utilizing the classical categories of physiological, sensory, perceptual, psychomotor, and conceptual responses as the basic types of re-
sponses of which human beings are capable, it is shown that each of these types of responses can be found under each of the classes of stimulation, ranging from the idling state, in which no stimulus is applied, through energy stimuli and signal stimuli as shown in Table 2. (For the definitions of these terms see Burdock, Sutton, and Zubin, 1958).

The idling state is merely the initial state of activation present when the stimulus is applied—and can vary the entire gamut from drowsiness to extreme alertness. Energy stimuli refer to those stimuli whose physical energy is in some way related to the intensity of the response, while in signal stimuli no such relationship exists, the stimulus merely serving to trigger the response.

This table, however, deals only with two aspects of experimentation—the stimulus and the response. In order to deal with the total spectrum of possibilities, not only the stimulus but all the parameters of the various facets which determine a response would have to be included. The variety of facets on which a response may depend are shown in the following equation based on Graham (1951): \[ R = f(S, R_c, I, O, H, \ldots, X_i) \], where \( R \) represents the response as a function of \( S \), the stimulus characteristics; \( R_c \), the receptor organ(s) on which the stimulus impinges; \( I \), the possible instructions for carrying out the task to be performed; \( O \), the possible states of the organism at the time the stimulus is applied; \( H \), the varieties of histories which may characterize the organism with reference to the task under consideration; and \( X_i \), possible facets which have, so far, gone unrecognized but which are needed to explain the residual but systematic variation.

Each of the facets consists of many possible parameters—e.g., the stimulus facet consists of intensity, spatial extent, temporal duration, wavelength of energy, etc. Each experiment represents a selection from the Cartesian product of the multiplicity of possible parameters in each facet (Zubin, 1957a). If these parameters are sufficient to predict the response in a sample of individuals, we can end the equation with \( H \). However, if a systematic residual variance appears which is not attributable to variations in the parameters of the facets, it may be necessary to introduce an additional facet of parameters, the \( X \)'s, to take up the slack.

It may eventually be discovered that these \( X \) parameters correspond to personality traits such as impulsiveness, anxiety proneness, etc. If we eventually find endogenous factors such as components of body fluids, or exogenous factors such as past traumas which are the underpinnings of such personality traits, we would attribute them to the state of the organism (\( O \)) or to history (\( H \)), where they would rightfully belong.

It should be noted that only the first three facets—\( S \), the stimulus properties; \( R_c \), the receptor organ; and \( I \), the instructional variables—are subject to direct manipulation by the experimenter. The state of the organism, \( O \), is
Table 2. Examples of Measures Used at Each Behavior Level for Each Class of Stimulus Under the Load of Drugs

<table>
<thead>
<tr>
<th>Level of Observed Behavior</th>
<th>Energy Variables</th>
<th>Signal Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Idling State</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appropriate</td>
<td>Inappropriate</td>
</tr>
<tr>
<td></td>
<td>Otis, Viersky, &amp; Lebovin, 1958</td>
<td>Tone estimation—Ammon, Silverstein, &amp; Klar, 1959</td>
</tr>
<tr>
<td></td>
<td>Idling *</td>
<td>Sleep Test II</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Static arbor test—Benedos, 1960</td>
<td>Personality inventories—Kelly, Miller, Marquis, Gerard, &amp; Ueh, 1958</td>
</tr>
<tr>
<td></td>
<td>Reaction time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Link movements to skeleton—Bengelmann, Paré, &amp; Sandler, 1958</td>
<td>Kelly, Miller, Marquis, Gerard, &amp; Ueh, 1958</td>
</tr>
<tr>
<td></td>
<td>Pursuit rotor—Evans, Case, &amp; Troxel, 1957</td>
<td>Marquis, Kelly, Miller, Gerard, &amp; Kapcinski, 1958</td>
</tr>
<tr>
<td></td>
<td>Kelly, Miller, Marquis, Gerard, &amp; Ueh, 1958</td>
<td>Frank &amp; Troxel, 1958</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Manual RT—Wall, Belleville, &amp; Wikler, 1957</td>
</tr>
<tr>
<td>Perceptual</td>
<td>Orientation to direction of white noise</td>
<td>Physical stimulus to pressure on eye</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Physiological</td>
<td>Temperature—Manoian &amp; Pappalovich—Eysenck &amp; Easterbrook, 1963</td>
<td>Heart rate during pressure on ECG during phase-driving</td>
</tr>
</tbody>
</table>
only partly under the control of the experimenter. Such factors as age, sex, and psychopathology cannot be manipulated, but subjects can be selected according to these parameters. The same holds true of H, the previous history of the organism with reference to the task at hand.

One of the valuable assets of the facet equation stems from the fact that we can titrate changes brought about through the drugs by means of alterations in values of some of the parameters in the three manipulatable facets—S, R, and I. Suppose a drug raises the threshold for perception of light; the increase in the intensity of light necessary to attain threshold value is in a sense a measure of the effect of the drug in terms of illumination units. Thus, the effect of the drug can be titrated by increases in intensity, or temporal duration, or area of stimulation, etc. This titration may lead to an understanding of how and where the drug brings about its effects. By triangulating the drug effect against changes in intensity across modalities, or with temporal duration or spatial extent, deeper understanding of the biochemical nature of the drug and how and where it interacts with the neurochemistry of the organism may eventuate. When the response of the organism to various stimuli is examined while the organism is under the influence of a drug, some consideration of the new idling state produced by the drug must be undertaken. To distinguish such states from the unrestricted free idling state, the drug can be designated as a load and the new idling state under the influence of the drug can be referred to as being under a load. Thus, a load is a constraint imposed on the organism prior to measurement of the behavior being investigated.

If the drug is considered to be a stimulus and is the only stimulus used, no special problem is encountered, since a measure of a particular ongoing activity, such as blood pressure in the idling state, can be readily obtained and the change produced by the drug noted. A direct approach to the discovery of changes in behavior attributable to drug effects utilizes the idling state itself as the vehicle for detecting the change, and no new stimuli except the drug need to be introduced.

The introduction of a chemical agent may alter the idling state and also bring about changes in ongoing behavior. If these behaviors are to be measured, in the spirit of this direct approach, they must be of a variety that does not need a controlled external stimulus for elicitation. Physiological activities fall into this category as do highly practiced behaviors such as conversation, writing, reading, walking, and swimming.

Physiological measures like blood pressure, heart rate, and similar vegetative functions have long been used as measures of drug effect, because severe changes in these functions are a threat to survival, and also because they yield good quantitative indices. In searching for conceptual changes induced by
drugs, speech or verbal behavior can serve a similar purpose in tapping the conceptual level as do blood pressure and heart rate in tapping the physiological level. For this reason, studies of verbal behavior before, during, and after drug administration can yield meaningful data.

A Measure of the Conceptual Response

The utilization of verbal behavior as a measure of drug effects already has an extensive literature, although most of it deals with uncontrolled clinical observation. The parameters of verbal behavior which have been measured under drug effects are (1) fluency, (2) intelligibility, (3) grammatical structure, and (4) conditionability.

These, however, do not exhaust the possible parameters that could be employed. Frieda Goldman-Eisler (1956) has proposed additional variables concerning relative rates of speech and respiration, and the predictability of words in a given context. She has related changes in speech rate, breathing, and muscle tension to interview content. Certain relationships seem to have been found between the objective measures and stages of "catharsis or abreaction through talking." These relationships might be studied with respect to certain personality factors as well as with respect to the course of the psychotherapeutic process.

The parameters described above can be utilized in the evaluation of drug effects. An example of the application of some of these methods to the investigation of chlorpromazine is afforded by the work of Salzinger and his coworkers (Salzinger, Pisoni, Feldman, and Bacon, 1961), in the Biometrics Research Laboratory.

It was possible to demonstrate a lawful reduction in rate of speech with increase in dosage in 25 mg steps in one normal subject. A comparison of the control conditions and the largest dosage condition (125 mg) in three other normal individuals corroborated this finding. On the other hand, a schizophrenic subject who had been reinforced for self-referred affect statements rather than speech in general (as had the normals mentioned above) did not show a decrease in speech rate but rather in affect statements. This suggested the hypothesis that chlorpromazine influences behavior only through its effect on the reinforcement which controls the behavior. A further effect of the drugs consisted of interference with the extent to which context controls the emission of words. Thus, the "intelligibility" of speech under the influence of chlorpromazine was lowered as measured by the Cloze Technique.†

As far as the general conclusions of the study are concerned, it is reasonable

†The Cloze Technique was introduced by Taylor (1953).
to say that it demonstrates that greater stimulus control over behavior produces more lawful results in response to drugs.

The extent of control over the behavior is revealed by the fact that the normal subject who was reinforced for speech received the maximum number of reinforcements over all dosages despite changes in speech rate. There were relatively few degrees of freedom left for him to vary in and, therefore, little chance that variables, other than those applied systematically, would have any effect.

Further evidence for the point that more stimulus control allows the drug effect to reveal itself more lawfully has been found in weight judgment experiments. The time required for judging heaviness of weights varied more lawfully under conditions where a heavy weight had been introduced before each standard weight than when this anchor was not introduced.

A Measure of the Physiological Response

In the previous examples we dealt with the effect of chlorpromazine on an ongoing conceptual function—speech. Here the effect of increasing dosage is to interfere with the ongoing conceptual activity and presumably, if the dosage became large enough, greater and greater conceptual distortion would occur until finally the physiological component would overwhelm the individual and put him to sleep. Let us now examine the influence of the drug on an ongoing physiological function—pupil dilation and contraction. Ordinarily, the pupil diameter waxes and wanes to changes in light intensity (a sensory-physiological response), but it also responds to conceptual stimulation accompanying fear, anxiety, etc. To the latter it dilates, but only light can cause it to contract. The contraction has been related to parasympathetic innervation while the dilation has been related to sympathetic activity. When a low dosage (50 mgs) of chlorpromazine is injected in a normal individual, as Hacerem and Sutton (1962) have done in the Biometrics Research Laboratory, the diameter of the dark adapted pupil remains unchanged as compared to the predrug state. However, repeated stimulation with brief light stimuli (1 millisecond in duration) prevents the pupil from recovering to its initial size during the interpulse periods of darkness. The undrugged pupil, on the other hand, can readily accomplish this recovery during the several seconds of the interpulse period. Otherwise, the pupillary response to the light pulse shows no differential between the drug and control states. Thus, even the small 50 mgs dosage of chlorpromazine, which requires fine biochemical tests for its detection, shows its effect on an ongoing physiological response.

A single, relatively high dosage of chlorpromazine used in the normal individual (125 mgs) causes profound sleepiness, slight ptosis, and other reportable
side effects. From the point of view of pupillary measurement, the diameter of the pupil after thirty minutes in darkness is more contracted, or smaller, than in the predrug or idling state. However, the response to light stimulation seems to be the same as for the lower dosage. This would be consistent with a reduced sympathetic tonus which would tend to reduce the dilation of the pupil. Incidentally, the findings for acute schizophrenics, not under drugs, was that they are characterized by a smaller dark adapted pupil diameter than normals. In other words, schizophrenics seem to show a reduced sympathetic tonus.

The Integration of Response Levels

The Mendelejeff-like table giving the relationship between responses and their stimuli represents the results of a theoretical analysis of experimentally elicited human behavior. In actual experience these heuristic elements do not occur in isolation any more than the chemical elements occur in the pure state in nature, although certain underlying dimensions tend to separate the five levels.

Before considering the interdependence of the response levels in a total behavioral event, it may be well to clarify some basic assumptions regarding the two extreme ends of the spectrum—physiological and conceptual responses. The physiological response is elicited by any stimulus which excites the central peripheral or autonomic nervous system. Physiological responsiveness underlies all levels of responses, but there is no reason to assume an identity between the physiological aspects and the total response. By conceptual responses, we mean responses based on previous experience—on the stored memories of the organism. This conceptual response must, to be sure, have neurophysiological concomitants, but its primary essence is its dependence upon prior experience. As one goes from physiological to sensory, perceptual, psychomotor, and conceptual responses, the importance of prior experience and reinforcement increases. Regardless of whether the stimulus is an external object or event, or an internal spontaneously occurring event, the conceptual response is highly dependent upon memory storage which, in turn, may depend on intricate neural or protein organization.

To understand the interdependence of response levels first let us consider the threshold response. Determination of absolute thresholds is usually regarded as belonging to the category of sensory response. The determination of the presence or absence of light or sound stimulation is a psychophysical process which has a long history and in practiced hands is said to yield results which reflect the sensitivity of the organism to such a high degree that variations in threshold determination have been attributed to fluctuations in the
stimulus, rather than fluctuations in the response (Hecht, 1934). More recently, however, Swets (1961) has pointed out that the absolute nature of the threshold is very much in doubt, and the very existence of thresholds has been questioned.

The redesigning of the classical threshold experiment to include "catch" trials during which the experimenter actually does not present a stimulus, provides a new perspective on threshold determination. Apparently, the number of times a subject gives an inappropriate response (i.e., reports presence of stimulus when there is none, and vice versa) depends on the proportion of trials during which the stimulus really is or is not presented. For example, if the stimulus is presented in 90 per cent of the trials, the expectancy created by the induced set is such that during the catch trials (when the stimulus is not presented) the subject will report it as present (false alarm) 62 per cent of the time; but, when it is present, he will report it absent (misses) only 3 per cent of the time. On the other hand, in a series of trials in which the stimulus is presented in only 10 per cent of the trials, the comparable figures are 4 per cent false alarms and 72 per cent misses. The introduction of rewards for correct responses (saying yes when the stimulus is on and no when the stimulus is off) and of punishments for incorrect responses is another method for manipulating the results (Galanter, 1962).

Apparently the expectancies experienced by the subject and his system of values regarding monetary or other rewards and punishments, loom large in determining sensory responses. These are definitely conceptual components (based on memory storage), and hence sensory responses can no longer be regarded as independent of the other systems of response.

Now let us examine one situation where the conceptual and physiological responses have to coexist in order to bring about a given pattern of behavior, and where it seems possible to prevent this pattern from occurring if one or the other component meets interference. The reaction of a subject to a frightening object involves the entire spectrum of responses from the conceptual to the physiological. Thus, following the usual analysis (Arnold, 1960) the sighting (sensation and/or perception) of a fear-inducing object leads to an immediate appraisal of its dangerous character (conceptual—based upon prior experience) and is accompanied by visceral (physiological) excitation and leads to flight (psychomotor). The initiating sensory or perceptual response and the final psychomotor response 2 seem to have been taken for granted by

2 Some disagreement regarding the psychomotor aspects of emotional behavior is raised by Bull (1945, p. 51) in which the perception of an emotion producing stimulus gives rise immediately (through some organismic linkage such as neural predisposition) to a motor attitude which then leads to the emotional state and to action (see Arnold, 1960, Vol. I, p. 150). This has not been verified experimentally.
most theoreticians, but the relative importance and temporal sequence of
the conceptual and physiological components have given rise to one of the
classic controversies in psychology (James and Lange, 1922; Cannon, 1927,
1929, and 1931; Duffy, 1934, 1948; Arnold, 1960). Attempts have been made
to demonstrate the relative importance of these two components experiment-
ally. Experiments by Maranon (1924) confirmed later by Cantril and Hunt
(1932) and Landis and Hunt (1932) demonstrated that the physiological
response induced by an injection of adrenalin does not by itself yield a genu-
ine experience of fear in which all the components are activated. Though the
sympathetic discharge (physiological) common to strong emotional states was
present (palpitation, tremor, face flushing, etc.) a full-blown emotional state
did not develop (no psychomotor response), because conceptually there was
no basis for it. The subjects knew the source of their physiological reactivity
and did not have to "fear" it (conceptual) or run away (psychomotor).

A subject, however, can sometimes experience a genuine emotion after the
injection of adrenalin if he spontaneously generates a conceptual response
suitable to the occasion. Thus, one of the subjects reported "I seemed op-
pressed with a vague fear of something—feeling much the same as when I'd
lain awake all night, frightened that Bill might die" (Cantril and Hunt, 1932,
p. 303). In her case, a genuine full-blown fear seemed to have taken place.

An example of how the elimination or reduction in the physiological com-
ponent will interfere with an expected response is the experiment of Schachter
and Wheeler (1962). They induced the conceptual component (evoking of
stored memories) by a comic film which elicited laughter and euphoria in
most people. They blocked the physiological response in one group by ad-
ministering 25 mgs of chlorpromazine and contrasted the behavior of this
group with another which had been given 1/2 cc of epinephrine solution
(1:1000 solution of Suprarenin) and with a third group given a placebo.

The group which received adrenalin showed the highest degree of overt
amusement or euphoria, the placebo group was second, and the chlorpromazine
group showed the least amount of euphoria. Apparently, the sympathetic
pattern elicited by adrenalin seems to be able to enhance the expressions of
emotional states while the blocking agent (chlorpromazine) reduces it con-
siderably. Thus, emotional expression can be brought under the control of
chemical agents.

The contrast between the physiological and conceptual component has oc-
curred in several other experiments, though the experimenters were not al-
ways aware that their work was focused on this problem. It has been known
for a long time that such techniques as psychosurgery reduce the conceptual
aspects of pain (anticipation, fear, anxiety), while the sensory threshold for
pain remains unchanged (Mettler, 1949). More recently, Beecher has con-
cluded (1960) that both placebo and active drug treatments are more effective in bringing about relief when conceptual components (stress and anxiety) are present, and are not as effective in relieving the simple sensory pain responses. Similarly, Wikler and his colleagues have shown (Hill, Kornetsky, Flannery, and Wikler, 1952) that morphine is more effective in reducing the tendency to overestimate pain induced by electric shock when considerable anticipation (through induction of anxiety or fear) of the pain is promoted by the experimenter. When no anticipation of pain is introduced, morphine does not interfere with the accurate subjective estimate of pain as gauged objectively by the intensity of an electrical current. Here again, the conceptual component is the one which morphine seems to influence most, leaving the sensory aspects untouched.

The role of the conceptual or cognitive component is further stressed by Beecher and his coworkers (1959). He found that 10 mgs of morphine increased subjective responses of friendliness in one test environment (in which the needs of the subjects were supported) and decreased it in another environment in which their needs were frustrated.

We can subsume the facts of social facilitation in drug studies under the conceptual component, since a subject's awareness of his colleagues and their mood is probably based more on conceptual than on physiological factors (Hyde, 1958; Schacter and Singer, 1962a). Whether the presence of others alters directly the biochemical balance within the organism and thus brings about a different interaction between the chemical agent and the endogenous chemicals within the organism, or whether the presence of others serves indirectly to distract the individual from paying as much attention to his inner-goings-on, or to orient the expression of his feelings regardless of his physiological responses, remains a question for further examination.

Some animal experiments also throw light on the relative importance of the conceptual and physiological components. An example of the importance of the conceptual or stored memory component is afforded by Harlow's (1962) experiments with the mothering behavior of monkeys who are themselves raised on surrogate mothers. Though these mothers experienced the entire physiological cycle of gestation, they do not have the conceptual or stored memories of their own mother's behavior nor of play experience with their siblings. Without this conceptual component, they fail to care for their offspring. On the other hand in Birch's (1956) rats, the mothers who possess the conceptual component fail to mother their offspring if the chain in the physiological component is broken by interfering with the self-licking sequence mechanically. This was accomplished by placing a collar about their necks to prevent them from licking the fluids emanating from their vaginal areas during the gestation period. In their next pregnancy, when no such
interference occurred with the physiological cycle, normal mothering behavior ensued.

Following the same pattern of analysis, Seymour Fisher (1962) has manipulated the conceptual component directly by varying the instructional variable or set in drug studies. He has shown that dextroamphetamine, compared with placebo, has its greatest effect in elevating mood and facilitating psychomotor performance when subjects expect to be aroused by the drug. When the same drug is given to subjects who think they are being given a depressant, there are no differences in effect between drug and placebo. Here again arousal of the conceptual component acts to make certain the appearance of the mood or the emotional state, and the arousal of a contrary conceptual component tends to reduce it.

Perhaps the waning of sexual arousal with age can be placed in this framework. While the conceptual component provided by visual, auditory, tactual, and olfactory stimulation may still operate, the absence of physiological reinforcement through depletion of endocrine supplies may eventually extinguish even the conceptual arousal. One wonders whether the rise in threshold for anxiety and other psychopathological feelings in psychosis after ECT, lobotomy, and some drugs may not reflect the same type of process—i.e., reduction in the involvement of the sympathetic nervous system, with subsequent extinction of the conceptual component of anxiety, depression, etc. If we assume that the emotion of anxiety permeates the conceptual behavior of the patient, and that this conceptual anxiety produces reverberations in the physiological responses of the patient and sets up a vicious circle of mutual reinforcement between the conceptual and physiological component, it becomes possible to understand how interference with the physiological component may bring about a reduction in anxiety. If the conceptual response of anxiety continues, but the physiological component is reduced by therapy, the conceptual anxiety will eventually be extinguished for lack of physiological reinforcement. This, then, represents a direct attack on the physiological component in order to eliminate the conceptual component.

An example of a direct interference with the physiological component preventing a full-fledged emotion from arising may be inferred from the work of Steinberg et al. They

... found that an amphetamine-barbiturate mixture markedly increased the exploratory behavior in a Y-maze of rats which had not been in the maze before, but that the drug mixture had no such effect on rats which had had repeated previous experience of the Y-maze. It is possible that these differential effects could largely be accounted for in terms of fear reduction by means of the drug mixture; "inexperienced" rats were afraid of the new environment and, therefore, responsive to fear-reducing medication; "experienced" rats had presumably already
overcome their fear of the environment, and so the drug mixture had no effect. Amphetamine/barbiturate mixtures are often used in psychiatry in the treatment of anxiety states.  

From the point of view of the paradigm that we have presented for the interaction between the conceptual and physiological components, we may regard the failure of the "inexperienced" rats to show fear as the effect of an interference with the sympathetic arousal. The drug mixture prevented this arousal, and hence only the conceptual component (perception of the environment as strange and "potentially dangerous") was operative. Since the conceptual component alone is insufficient to evoke a full-fledged emotion of fear, the competing drive of curiosity took over, leading to the uninhibited exploratory behavior which is normally expected in a rat in a non-fearful new environment.

If we utilize the same paradigm it becomes possible to explain the extinction of the conditioned emotional response in rats (Howard Hunt et al., 1952, 1956), by postulating that chlorpromazine prevents the sympathetic arousal when the conditioned tone is heard. The conceptual experience which the tone induces is insufficient to arouse a full-fledged experience of fear, and therefore the rat blithely keeps on pressing the bar as if it heard nothing. Similarly, the patient under chlorpromazine can experience episodes which ordinarily would arouse his anxiety but which fail to do so because the chlorpromazine prevents sympathetic arousal. It would, of course, be extremely enlightening if it could be demonstrated experimentally that chlorpromazine actually interferes with sympathetic arousal by direct recording of electric potentials.

By the same token, one may view psychotherapy as a direct attack on the conceptual component in emotional disorder. Once the conceptual component is reduced, it will in turn gradually bring about the extinction of the sympathetic component because of the reduction in the interaction between the two. Behavior therapy perhaps is explicable on this basis. For example, the reduction of tics may be accomplished by separating the psychomotor response from its conceptual (anxiety) substrate. By repeatedly practicing the tic without the anxiety accompaniment, the link between the two can be eventually extinguished (Dunlap, 1932). Similarly, hysterical blindness can be eliminated by conditioning to light and thus breaking the link between the sensory-perceptual component and the conceptual fear or anxiety (Brady and Lind, 1961).

To summarize, both the conceptual component of a given pattern of behavior or emotion as well as the physiological are necessary for the existence

*Personal communication.
of the pattern. Thus, our analysis of behavior into the five components of physiological, sensory, perceptual, psychomotor, and conceptual responses seems useful, since it permits experimentation with each of these components so that the nature of the total response can be better understood.

Earlier in this chapter, it was indicated that four basic elements must be considered in a discussion of research in the field of drugs and personality. The first two, the behavior to be measured and the environmental situation in which the behavior takes place, have received the most attention so far. The last two, the individual under observation and the chemical agent, must now be considered more fully.

**The Individual Under Observation**

The individual under observation is sometimes naively regarded as representative of all other individuals who might be selected at random. This is a tenuous assumption. First, the subject usually is a person who has volunteered for the experiment, and there is considerable evidence that volunteers may not represent the general population (Esecover, Malitz, and Wilkens, 1961; Pollin and Perlin, 1958). Secondly, there is a tremendous difference among individuals in response to drugs.

One important source of variation in response to drugs is the subject's own body chemistry. While drugs may bring about certain expected changes in most people, it should be remembered that the enzyme systems of individual subjects are quite distinct and may respond quite deviantly to certain ingested chemicals. For example, while most individuals will respond within given limits of tolerance to insulin, a diabetic may not show the same response. In this chapter, we are not considering deviant body chemistry. But even normal body chemistry shows considerable variation, as Roger Williams has shown (1960). Just how these deviations affect behavior still remains to be determined.

In considering the individual under observation, one might liken the relationship between personality and drugs to the relationship that exists between personality and disease. It has been pointed out elsewhere (Zubin, 1958) that the most tenable hypothesis today regarding mental disorder and personality is the hypothesis of independence, i.e., that there is no relationship between premorbid personality and the occurrence of psychopathology. Once the disease occurs, however, the personality of the patient may determine the direction the disease will take. Similarly, the effect of the drug may correlate with the kind of personality the subject possesses.

Because of the difficulties presented by present day typological approaches, it might be useful to eliminate them entirely and substitute more empirically
The Induction of Change
determined subgroups utilizing some new statistical developments along the lines indicated by Mahalonobis' distance function (Rao, 1952). Since the Mahalonobis distance function is applicable only when the subgroups or types that exist in the population are already known, we cannot make use of this method. Instead, the test profiles of each possible pair of individuals in a given group can be compared and the standardized distances between these profiles computed over each of the tests in the profile. These distances may then be decomposed into discrepancies in shape and in level. On the basis of these two kinds of discrepancies, the whole population can be fractionated into homogeneous subgroups or types (Zubin, Fleiss, and Burdock, 1962).

The Chemical Agent

The drug itself presents a series of problems with regard to measuring its effects on behavior. One of the stumbling blocks to research in this area is the lack of a universally accepted general system of drug classification. Tentative classifications have been based on either the chemical structure of the drug, the site of the drug action (acting on heart, thyroid, etc.), or its mode of action (antidepressant, sedative, etc.).

Isolated knowledge of the chemical structure of a drug has been of little relevance for the psychopharmacologist, at least, until now. He has been more concerned with the site and mode of action, but, especially the latter. Unfortunately, research on the mode of action has, so far, revealed considerable variability among subjects, and such classifications are decidedly tentative and occasionally misleading.

One of the most serious drug problems is that of dosage. What may be a "load" for one person may be no load at all for another. The characteristic differences between individuals with regard to minimally effective dosage and maximally effective dosage may be likened to the effects of a snowfall on the landscape. If the snow is heavy enough (maximum dosage) it will cover the whole landscape uniformly and hide any individual differences in its parts. If the snow is not sufficiently heavy, though it falls on all parts alike, the forms it assumes are, to paraphrase Thoreau, "as various as those of the twigs and the leaves which receive it." In submaximal dosages, the personality of the subject may be a more important predictor of the behavioral change than the drug itself (Kornetsky and Humphries, 1957).

Perhaps the effects observed in the middle range of dosage, between little or no drug and maximum dosage, is the resultant of the two contending forces which we have described earlier—the conceptual and physiological. In the lower dosages, the conceptual factor, induced either by the instructional variable, or by spontaneously generated expectancy, may be the prepotent fac-
tor. As the dosage increases, the physiological and sensory responses begin to play more and more important roles. Finally, when the maximum dosage takes effect, the role of physiological and sensory responses are fully in command. Perhaps, we will some day find that the point of inflection in the dosage curve indicates some sort of balance between the two factors contending for control of behavior, the conceptual and the physiological components. This conceptual component especially when triggered systematically from within, may be the personality characteristic with which this chapter is concerned. For low dosages, personality is in command regardless of the nature of the drug. For the maximum dosage, the physiological component takes over regardless of personality.

Dosage curves have to be developed for each individual to determine the range of change in behavior characterizing a given individual. These dosage curves may differ from person to person in level of dose necessary to bring about a given change in performance and in the shape of the dosage curve. It is necessary to find a way of grouping people into homogeneous groups with regard to these dosage curves and the distance method suggested previously may prove suitable (Zubin, Fleiss, and Burdock, 1962).

At the present time, because of the lack of knowledge about drugs and because of the lack of knowledge about personality, drug investigations are limited to a specific type of behavior investigated with regard to a specific type of drug, without the scope necessary to transcend individual function and individual drugs. As our knowledge increases, greater scope can be given to these investigations. Apparently dosage curves are superior to single measurements with single dosages.

But dosage is only one of the factors to be taken into consideration in producing a given effect. Leake (1961), suggests the following formula:

\[ I = f\left(\frac{D}{r_A}, P, S\right) \]

Where \( I \) = intensity of the action of a chemical on biological material

\( D \) = dosage expressed in terms of mass of chemical per mass of living material

\( r_A \) = rate of absorption and distribution of the chemical through the living matter

\( r_E \) = rate of detoxification or excretion of the chemical from the living matter

\( P \) = physical chemical properties of the chemical which really determines the activity of the chemical on living material

\( S \) = the specific and peculiar characteristics of the living material concerned, including its organizational status (in terms of macro-
molecules or ecological milieu), its age, its metabolic state, its "allergic" sensitivity, its pathological status, and such integrating factors as enzyme systems and sex.

All of these factors are capable of precise scientific study and the expression $D(t_A/t_B)$, the product of the dosage by the ratio of the rate of absorption and distribution to the rate of detoxification and excretion, gives the concentration of the drug in the living tissues at any time after administration. It is this concentration, with its mass action effect, according to Leake, which is a predominant factor in drug action.

NEW DIRECTIONS AND PROSPECTS IN PSYCHOPHARMACOLOGY

In contrast with the rather continuous progress made in pharmacology under the impetus of the sudden appearance of the tranquillizers and energizers, the progress in psychopathology has been rather meager. The psychopathologist has apparently been caught off guard. While pharmacology and psychopharmacology have made great practical strides forward, the strides in personality measurement, for example, are notably absent.

Why has there been so little progress in the development of the relationship between pharmacology and personality? Pharmacology is undergoing a revolution according to Woolley (1958). Until recently progress in the discovery of new drugs depended on chance only. While this is still true, certain principles have been developing as guide lines for the synthesizing of new compounds that are predicted to have certain properties. One of these principles is the antimetabolite principle which may be briefly stated as follows. There are a certain number of chemical substances which are vitally essential to metabolism. If any of these vital compounds is missing or in short supply, normal processes fail to occur. Sometimes an excess of the vital substance also interferes with normal processes. It has been found that if the chemical structure of one of these metabolites is changed in any one of several defined ways, the molecule which results is not able to substitute for the metabolite in living processes. Instead this new substance has the capacity to evoke in the organism the specific signs of deficiency of the metabolite which it resembles. It is as if it serves as an inadequate key in the lock of the metabolic process. It gets stuck in the lock and prevents the genuine metabolite from entering and opening the door to the progress of the metabolic process. Such antagonists, or antimetabolites, as they are called, can be used to control an excessive amount of the metabolite, e.g., antithyroxine for the control of excess thyroxine.
Another principle is that of biochemical individuality proposed by Roger Williams at the University of Texas (1960). In brief, this principle states that an examination of the biochemistry of each individual would reveal reliable and consistent differences between individuals which could be found useful in the classification of people into relatively homogeneous subgroups. Another emerging principle is that of regional organization of the neurochemistry of the nervous system. In contrast with the earlier studies of brain function in which the brain tissues were macerated and chemical tests applied to the resulting mass, the newer approach rests on the hypothesis that the brain is compartmentalized, and that the particular site of a chemical reaction in the brain is equal in importance to substrate and enzyme activity in determining outcome.

While these new principles seem to keep the field of pharmacology stirring, the field of personality measurement has reached a static plateau cushioned by factor analysis on the one hand and by psychodynamics on the other. In contrast with the revolution in pharmacology, personality is in the doldrums. Results from research on the effects of drugs on personality are, therefore, not very definitive.

It seems that we may have gone as far as we can go with the present methods of investigating personality through psychometric methods (inventories and rating scales) and perhaps also through psychophysical and other experimental methods. Perhaps our stimuli penetrate the web of personality only superficially and not with sufficient reliability. The individuality of the person is lost in a maelstrom of insufficiently reliable indicators produced by tickling his epidermis. New methods are required. It might be possible to replace, at least temporarily, psychophysics, on the basis of which much of our testing is done, and clinical methods, through which most of our classification is done, by psychochemistry. If we could begin to cluster people into subgroups in accordance with the changes that occur in their ongoing behavior under various dosages of specific chemical substances, we might strike at a deeper layer of personality. These new subgroups, obtained through the clustering on the basis of similarities in shape and level of dosage curves for a variety of selected chemical agents, on a variety of ongoing naturally occurring activities like conversing, writing, walking, or engaging in other highly practiced activities, might serve as new starting points for the investigation of like-structured homogeneous subgroups.

With the similarity of response to drugs in these basic activities established, we could begin looking for other variables which a given like-minded group of individuals may possess in common and thus provide a new typology to replace the present unsatisfactory personality variables by means of which we
attempt to classify people or predict change. The kinds of stimuli which we utilize now in our experimental approaches to assessing personality are evanescent. Intermittent light for flicker fusion, tachistoscopic exposures for concept elicitation, inkblots for mental content, etc., merely touch the surface of behavior. They can hardly evoke as much response as a drug which influences the total nervous system. Perhaps after we have discovered the natural lines of cleavage in human populations through psychochemical methods we can return to a study of the psychophysical and psychometric functions that now hold the field.

CONCLUSIONS

Our survey of the relation between psychopharmacology and personality change has forced us to realize that neither of these two fields is sufficiently defined to enable us to make definitive conclusions regarding their interaction at the present time. Both fields are themselves at a low level of articulation and any attempt at studying their interaction is very hazardous.

We have not yet reached an integrative state in psychopharmacology, nor in personality or in their interaction. Perhaps we never will. As the Abbé Galien said without discouragement (as quoted by Thompson, 1961) "Science is plutôt destiné à étudier qu'à connaître, à chercher qu'à trouver la vérité" (p. 14).

On the positive side, however, we have drawn up a model based on some of the assumptions and definitions arising from the observations that the literature and our own work have provided which may have heuristic value. Let us regard the behavioral change accompanying any drug dosage as an interaction between the ongoing brain activity present when the drug enters and the effect of the drug. We can relate the former, the ongoing brain activity, to the conceptual or cognitive component, i.e., memory storage, which, if it is systematically characteristic of the individual, may be designated as personality. The immediate drug effect on the brain may be equated to the physiological sensory and perceptual aspects of behavior. As the dosage rises from 0 to a maximum the role of the conceptual component declines and the role of the other components rises. That is why it is so important in drug research to specify the state of the organism, its environment, and the ongoing conceptual trend as well as the dosage. When these factors are specified, it becomes possible to integrate observed results that now seem contradictory under one model. This includes such events as the contradictory effects under various instructional and situational variables, placebo effects, and drug effects which will elicit hostility in one situation, friendliness in another, elation in still another, and apathy in still another.
The model of the interaction between the conceptual and other components permits a systematic investigation of testable hypotheses which may accomplish for our generation what psychophysics accomplished for the gay 90's. But we must not dally too long. Let us hurry up and develop psychochemistry while the drugs still work!
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<td>- (29)</td>
<td>7. greater kinaesthetic</td>
<td>- (33)</td>
</tr>
<tr>
<td>5. continuous work</td>
<td>+ (21)</td>
<td>8. lower auditory flutter-</td>
<td>- (34)</td>
</tr>
<tr>
<td>6. Less visual signal</td>
<td>- (33)</td>
<td>fusion threshold</td>
<td></td>
</tr>
<tr>
<td>after-effects</td>
<td></td>
<td>9. slow pupil contractions*</td>
<td>+ (22)</td>
</tr>
<tr>
<td>7. Less kinaesthetic</td>
<td>- (33)</td>
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<tr>
<td>after-effects</td>
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<tr>
<td>8. Higher auditory flutter-fusion</td>
<td>- (34)</td>
<td></td>
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</tr>
<tr>
<td>fusion threshold</td>
<td></td>
<td></td>
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<tr>
<td>9. Fast pupil contractions*</td>
<td>- (34)</td>
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<td></td>
</tr>
</tbody>
</table>

1. + Confirmation of prediction
- No significant confirmation
* No predictions made from theory, simply a finding
Numbers indicate references