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PSYCHOPHARMACOLOGY AND BEHAVIOR

by

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PSYCHOPHARMACOLOGY AND BEHAVIOR

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History relates, that in the 14th century during the siege of Rapperswil the confederates broke through a passage under the city wall and into the wine cellar and there, instead of continuing the attack, got drunk and were overwhelmed by the city defenders. This small episode from Swiss war history is an example of the deep-seated behavioral changes which a psychotropic drug can induce. As an historical event it is hardly a scientific experiment and, perhaps, does not justify the conclusion that alcohol converts belligerently-inclined individuals into peaceful drunken companions.

Nevertheless, this even contains all the factors underlying in principle the effect of psychotropic materials on human behavior, namely:

1. The chemical structure and dosage of the drug,
2. The tissue of the central nervous system, upon which the drug works,
3. The personality of the warriors, who forgot their war campaign when confronted by a wine cellar,
4. The situation, i.e. of finding a magnificent opportunity to drink, instead of encountering heavily armed defenders when they penetrated a besieged city, and

5. The influences of the group.

While the historian merely reports how it happened and cites the event perhaps as an example of the discipline of the Confederate soldiers at that time, the behavior scientist views this historic change in behavior of our bellicose ancestors as a complex interaction of the five above-mentioned factors. From this event he can only derive hypothesis, e.g. investigate under what conditions alcohol dampens or promotes aggressiveness and then test these hypothesis under experimental conditions. He must vary these conditions in such a way, that valid statements can be made about individual factors and their interactions, which are experimentally repeatable and permit predictions. But, in order to do this, he needs to be able to measure aggressiveness, personality and constants for situative conditions, or generally stated: yardsticks, i.e. suitable quantitative methods are needed to investigate behavioral changes due to psychodrugs.

These simple findings will immediately elicit the protest of those psychiatrists and psychotherapists, who are of the opinion that man's mental life cannot ^{be} measured, that in any event, animal behavior might be rationally expressed in terms of numbers, but that this would have to be erroneous in the case of human beings.

What hides behind this protest? The critical observer, who is familiar with the anthropological bases of psychotherapy, as well as with the experimental methodology of behavioral science, recognizes immediately that the protest

levelled against reduction of man to a mechanistic organism-environment model, i.e. it is directed against a mechanistically understood behaviorism. This displaces the question of whether human behavior can be measured, from the level of methodological discussion to that of viewpoints about the philosophy of life. A modern science of human behavior is by no means identical with the mechanistic determinism of the behaviorists, as MATSON [10] has recently shown. The complexity of the nature of human behavior is not questioned by it, but the only dispute is that it forms an absolute special position of human beings, which excludes the objectivizing and measuring process. Nevertheless, it has been shown that a very large amount of methodological effort is needed to comprehend human behavior quantitatively, and it assumes that a factual knowledge is insufficient for our long-range psychiatric development. Therefore, even today, there is no schism in psychopharmacology between the pharmacological and biochemical effects of psychotropic materials on the animal, which can be determined with great precision, and the results of clinical trials, which are based mainly on overall evaluations. IRVIN [7] maintains this chasm is a result of anthropomorphism of the clinicians, who shy away from a consequent behavioral science way of considering human beings, and does not lie in the matter itself, i.e. in the fundamental differences between psychopharmacological effects on animal and human behavior.

Since psychopharmacology is not an end in itself, but whose ultimate goal is to create better therapeutic possibilities for

psychiatric patients, the clinician must perceive that our patients themselves have a great interest in the development of suitable objectivizing and measuring processes, for only by so doing can the better therapy be differentiated validly from the poorer. He must learn at the outset from experimental psychology, how to investigate complex human behavior by quantitative methods. Practical acquaintance with these methods would show him, that the behavioral science aspect of man is not a philosophy of life, but rather a methodological problem, and in no way precludes other aspects.

Is we now consider the five principal factors involved in a psychopharmacological influence on human behavior, from a methodological standpoint, we see at once, that they are characterized by varving degrees of unequivocacy, or conversely, by different stages of complexity.

In this case, the unequivocacy of detection is inversely proportional to the stage of complexity of the phenomenon. The chemical formula of an active material possesses the highest degree of unequivocacy. Even the question of the receptor in the central nervous system is at a higher stage of complexity, i.e. it is less clearly understood. This, not primarily because of the localization of the point of attack, but because of the mode of action. For example, catecholamine deposits are already model concepts, which can only be inferred experimentally. Complicated experimental devices are necessary to differentiate the model concept of the reserve depot from the mobile depot.

Personality factors, situative and interhuman factors,

... are important for the psychotropic effect of a material on man, can only be investigated on the behavior level, which has a still higher degree of complexity. At this level we can, in turn, differentiate two different degrees of unequivocacy of the mode of detection, namely the measurable behavior variables and the behavior description. The latter includes the judgment of the observer, who characterizes human behavior on the basis of speech. As COHEN has shown [1], very little research has been done on this evaluation picture. Here we find ourselves methodologically at a stage of highest complexity and least unequivocacy for making possible statements. Since the psychiatric clinic thus far still has far too few systematic experiences with measurable behavior variables, we must generally be content for the present with behavior description as a means of evaluating psychotropic effect on patients.

Table 1. Principal factors underlying the effect of psychotropic materials on human behavior.

1. Chemical structure and dose
2. Tissue of the central nervous system
3. Personality structure
4. Situation
5. Interhuman influences (e.g. group dynamics)

Behavior description belongs to the clinical routine and, therefore, appears unproblematical for the clinician. The behavior scientist, who is forced to make critical comparisons in the field of psychopharmacology, e.g. report an action profile

For a certain active material discovers, however, a highly contorted linguistic problem concealed behind the harmless description of human behavior in the clinic. It may be formulated as a question, as follows: are the current psychopathological concepts of the clinic used in the same way by different observers to characterize human behavior, or what is the degree of agreement in clinical observation parlance, among different observers? Traditional psychopathology has never investigated this question systematically, because it assumed that psychopathological concepts could be made clear to everyone, through use of definitions and concise descriptions, so that their use would pose no problems.

Table II. Degree of unequivocacy

1. Chemical formula
2. Neuropsychological model (e.g. catecholamine depots)
3. Measurable behavior variables:
 - a) Expression Mimicry, voice
 - b) Subjective changes Questionnaires, polarity lists, characteristic word lists
 - c) Psychic performances Concentration, fine motor sphere psychic stress reactions
4. Behavior description Common observation parlance

But if we examine the terminology of clinical routine that is used to characterize behavior, it becomes readily apparent that it is very heterogeneous. For example, it contains words of colloquial speech, whose abundant significance corresponds

to a vague limitation in use, i.e. "confused," "quiet," "pitiful," and "excited," as well as colloquial words, whose meaning is narrower, due to psychiatric usage, e.g. "memory disturbance," "flight of ideas," "compulsion" and finally, psychiatric terms, whose precise significance has been lost through penetration into ordinary speech, e.g. "depressive," "ambivalent," etc. According to KAMILLAH and LORENZEN [8], these characterizations of behavior belong linguistically to predicates, i.e. sound sequences or signs learned by example and counter-example, i.e. they must be introduced by example.

We tested the degree of common observer parlance on a group of 12 assistants and found an agreement coefficient of only 46% for the frank description of behavior. It has become conventional in psychopharmacology during recent years to employ lists of symptoms to evaluate psychic effect and to prepare action profiles. This limits the symptom area available for characterizing behavior. We conducted a similar experiment with these same assistants, using a list of symptoms containing 99 symptoms, and found that the commonness of observer parlance increased only 10%, by limiting the symptom area. In order to set up critical comparisons between psychodrugs at this complexity stage, it is obviously insufficient merely to report symptom definitions, but the evaluator would have to have been subjected to systematic training, which is the only way to create a basis for differentiated comparisons of psychopharmacological effects on patients.

Therefore, in the following discussion we shall turn to measurable behavior variables and examine to what extent the effects of psychodrugs on behavior of the healthy human being can be determined exactly. This research trend was established by KRAEPELIN [9] and has provided a plethora of results under the term pharmacopsychology, which have been fundamentally important for the question of psychopharmacological influence of human behavior. We shall confine ourselves here to three questions:

1. Can typical psychodrugs be differentiated in measurable behavior variables on healthy test persons?
2. In what respect do personality characteristics affect psychopharmacological effects?
3. What is the significance of interhuman influences on the action of psychodrugs?

In using measurable behavior variables to define psychotropic effects, we must confine ourselves to a certain number that still permit repeated measurements during the course of the test, and at the same time furnish the greatest possible amount of information about various behavior areas. We have grouped these variables for our pharmacopsychological studies, according to three methodologically defined behavior areas:

- a) Mimic expression and expression of the speaking voice when objectively detectable signals of condition can be recorded on film and tape. We have developed this method for the calculation of the constants of symmetry and agitation parameters of the mimicry process, and which provide quantitative comparisons

(HEIMANN [3]). The vocal expression can be copied as amplitude and average frequency and compared. But our previous experience has shown that the interindividual scatterings in these areas are quite large, with the result that we still can not presently establish slight differences in condition.

b) Subjective changes in behavior are detected by means of a questionnaire containing 21 questions, with a list of characteristic words and a list of polarities (HEIMANN et al. [5]), to which we shall return.

Table III. Summary of the effect of typical psychodrugs on different behavior regions. Significant changes compared with the placebo ($2\alpha = 5\%$)

	Condition	Psychomotor sphere	Concentration	Psychic stress (stimulus reaction apparatus)
Neuroleptic 10 mg HF-1854	++	++	N.S.	++
Thymoleptic 100 mg Tofranil	++	N.S.	+	N.S.
Antiepileptic with psychotropic action 200 mg Tegretol	+	+	N.S.	N.S.
Psychotic 10 mg Muscimol	+	+	+	N.S.

c) In the area of psychic performance behavior, we used one test series to investigate concentration, various aspects of the psychomotor sphere and the stress reaction and recovery produced by excessive stimulus in a stimulus reaction apparatus.

These relatively widely scattered behavioral variables yield

Table IV. Subjective effects of typical psychodrugs (characteristic word lists). Significant changes in the categories compared with the placebo ($2 \alpha = 5\%$)

	Contact extra- version	Relax- ation	Directed activity	Mood extra- version	Undirected activity
Neuroleptic 10 mg NG-1854	N.S.	N.S.	N.S.	↓	↓
Thymoleptic 100 mg Tofranil	N.S.	N.S.	↓	↓	↓
Antiepileptic with psychotropic action 200 mg Tegretol	N.S.	↑	N.S.	N.S.	↑
Psychotic 10 mg Muscimol	N.S.	↓	↓	↓	↓

quantitative information about changes in healthy test persons after administration of psychodrugs. It is necessary in this case, however, to consider certain fundamentals of the test program and the random sampling, which we have discussed in detail elsewhere, and which we can not go into here, for reasons of time (HEIMANN [4]).

1. Table III gives a diagrammatic summary of the effect of typical psychodrugs, compared with the placebo, on different behavior areas, as measured by our methodology. Even in very low doses, the neuroleptic differs clearly from the thymoleptic Tofranil^R by a reduction of performance in all psychomotor tests, as well as by a marked reduction in performance under acute psychic stress conditions. In fact, Tofranil also adversely affects condition, but not psychomotor performance or psychic stress reaction, although it definitely does affect performance

in the concentration test. The antiepileptic Tegretol^R, which is known to have a psychotropic effect and which has a chemical ring structure resembling Tofranil improves condition and performance in some psychomotor tests, while the psychotic Muscimol depreciates all behavior areas except the psychic stress reaction.

Thus, different types of psychodrugs can be differentiated in the behavior variables in healthy individuals. At this juncture, it would lead us too far afield to compare results of individual tests and indicate how more delicate nuances between psychodrugs could be demonstrated within different behavioral areas. In order to indicate, at least, the possibility of differentiating among them, I shall confine myself to results of characteristic word and polarity lists in the area of condition.

Test person No. 44 has characteristic words in the characteristic word list and must report which of these words are consistent with his mood at any particular moment and which are not. Table IV contains a summary of the effects of typical psychodrugs established in connection with the characteristic word list, compared with the placebo, in the various mood categories. Here also, the products used differ decidedly. Tegretol, in 200 mg dosages, causes relaxation and increased directed activity, while the other preparations, in graded manner, have a negative effect on two to four categories.

The polarity list consists of 30 opposite pairs of adjectives, between which the test person is supposed to classify his subjective condition. In an earlier work we reported results of a preliminary factor analysis, by which we could detect six

mood dimensions of the momentary condition (HEIMANN et al., [3]). Meanwhile, we have factored the results of 150 students and extracted only four mood factors, as the most useful factor solution.

Table V. Factors (principal components. Varimaxrotation) of a polarity list for detecting subjective mood.

Factor designation and variables	Factor load	Fraction of the extracted total variance
1. Self-evaluation		
sure - uncertain	0.71	
free - restricted	0.70	
flexible - rigid	0.65	
good - bad	0.59	
clear - diffuse	0.55	
light - heavy	0.54	
active - passive	0.53	
agreeable - disagreeable	0.52	
courageous - cowardly	0.50	34%
2. Intimacy - readiness for contact		
familiar - unknown	0.74	
merry - timid	0.61	
high - low	0.60	
hot - cold	0.56	
full - empty	0.56	
extraverted - introverted	0.54	
pretty - ugly	0.53	
near - distant	0.51	
large - small	0.50	30%
3. Readiness for action		
healthy - ill	0.80	
alive - dead	0.57	
young - old	0.55	
alert - tired	0.50	20%

Table VI. Subjective effects of some typical psychodrugs (polarity list). Significant changes in the four factors, compared with the placebo ($2\alpha = 5\%$)

	Self-evaluation	Intimacy readiness for contact	Readiness for action	Excitement tension
Neuroleptic 10 mg NP-1854	+++	++	++	N.S.
Thymoleptic 100 mg Tofranil	++	+	+	N.S.
Antiepileptic with psychotropic action 200 mg Tegretol	N.S.	N.S.	N.S.	++
Psychotic 10 mg Muscimol	+	+	+	N.S.

These are entered in Table V, along with the corresponding variables and factor loads, according to their fraction of total variance extracted. The factors "readiness for action" and "excitement-tension," correspond to the earlier factors 1 and 2.

Table VI is a diagrammatic representation of the effects of typical psychodrugs in the four factors of the polarity list. Here the neuroleptic shows the greatest reductions in the first three factors, followed by the thymoleptic, the psychotic and only after Tegretol do we find an opposite picture, i.e. no changes compared with the placebo in the first three factors and a marked increase in the fourth factor, "excitement-tension."

The following Figure shows results of effects of an iminostilbene in the polarity list; this compound differs only from Tofranil by a double bond between C₁₀ and D₁₁. Pharmacologically,

It is very close to Tofranil. Except for the "excitement-tension" factor, it exhibits dosage-dependent decreases in condition in all factors, compared with the placebo.

The result corresponds up to the four highest loaded polarities in the self-evaluation" factor, to that after Tofranil, thus, this factor is more strongly affected by the iminostilbene.

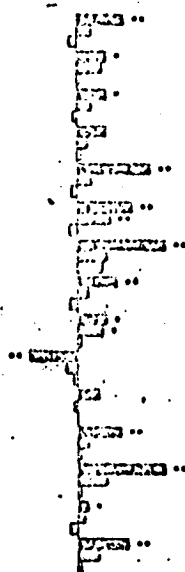
2. The influence of personality on psychotropic effect was demonstrated by DI MASCIO [2] in impressive experiments on healthy test persons: after one-week administration of 150 mg imipramin daily, the students exhibited no significant decreases in anxiety and depression scores, compared with the placebo. But if the random sample is subdivided according to the height of anxiety scores, into one group of test persons with strong and one group with weak anxiety, the group with the high anxiety score exhibits a significantly decreased anxiety, compared with the placebo. Subdivision of the same random test sample according to depression scores ("depression" here in the sense of a measurable personality characteristic) into a weakly depressive and a strongly depressive subgroup, also yields a decreased depression score for the strongly depressive subgroup, compared with the placebo.

DI MASCIO conducted similar experiments with the minor tranquilizers chlorodiazepoxide and oxazepam. When all test persons were pooled, there were no significant decreases in anxiety after one-week application of the active material, compared with the placebo. On the other hand, if the test persons are subdivided according to the degree of anxiety in the MMPI,

1. Self-evaluation

sure
free
flexible
good
clear
light
active
agreeable
courageous

variable
organized
alive
strong
nerry
large



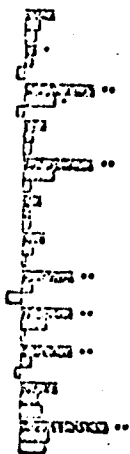
uncertain
restricted
rigid
bad
diffuse
heavy
passive
disagreeable
cowardly

constant
disorganized
dead
weak
timid
small

2. Intimacy-readiness for contact

familiar
nerry
high
hot
full
pretty
near
large

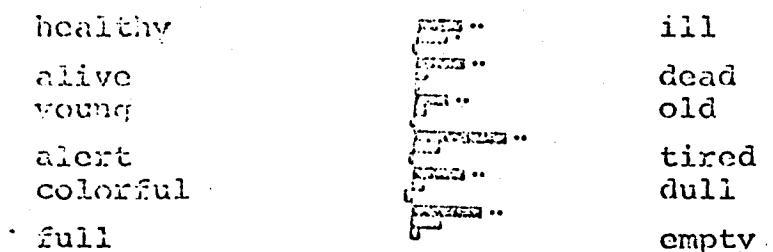
colorful
gay
active



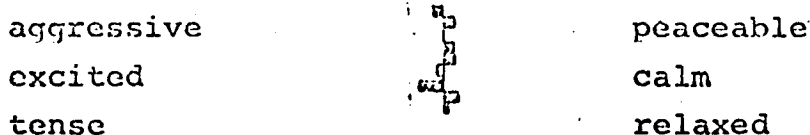
unknown
timid
low
cold
empty
ugly
distant
small

dull
sad
passive

3. Readiness for action



4. Excitement - Tension



.. = 2 p < .05
 ** = 2 p < .01

□ = 100 mg GP 31406
 □ = 50 mg GP 31406
 □ = Placebo

Fig. 1. Subjective effect profile of an iminostilbene resembling Tofranil, in the polarity list (average difference scores (3h - 0h)).

into weak, moderate and acute anxiety subgroups, there is a definite differentiation with significant decreases in the acute anxiety test persons.

These differential effects of psychotropic materials correspond, on a test basis, to detectable personality characteristics. They were confirmed repeatedly by JANKE [6], LIENERT and others.

3. The influence of interhuman relationships on the effect of psychodrugs, particularly through the dynamics of the group situation, has not yet been adequately investigated. An im-

extensive experiment by REED and WITT [11], however, illustrates the great importance of these conditions: two test persons are in a darkened room and are required to conduct rational physiological experiments. One of them, test person A, receives 100 mcg LSD per os and the other, test person B, the placebo under single-blind conditions: both test persons exhibit psychotic placebo reaction is explained to the same test persons, before a second experiment. The experiment is repeated, but test person B, who previously received the placebo, now receives 100 mcg LSD, and the other one, test person A, receives the placebo. Now, neither have any abnormal reactions except some fatigue. The experiment shows, that with suitable motivation in a very specific interhuman situation, the psychic effects of 100 mcg LSD can be induced, as well as completely suppressed.

Thus, we have returned to the starting point of my remarks. If the euphorizing and relaxing effect of alcohol had not been decisively intensified in the group, by the influence of interhuman relationships, our ancestors in the Rapperswiler cellar would probably never reached a premature, and as it turned out, an unjustified drunken triumph, from which they did not awaken.

SUMMARY

The principal factors in the psychotropic effect are discussed with regard to their degree of unequivocacy. Methodological problems of measurable behavior and the description of behavior, especially the terminology problem of agreement in

scientific observer parlance, are presented at the complexity of behavior. It is shown, through an example of a systematic pharmacopsychological investigation in three methodologically defined areas of behavior, that psychotropic effects of various types of psychodrugs on measurable behavior variables in healthy individuals are different. Finally, two examples from the literature are used to demonstrate how measurable personality traits can differentiate psychotropic effect, and how interhuman relationships can suppress the LSD-effect, as well as provoke the placebo effect.

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