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A Protocol for the Evaluation of New Psychoactive Drugs in Man

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SUMMARY

A protocol is presented that has proven effective in the determination, in man, of the psychotomimetic potency and qualitative nature of action of a new drug. It involves a minimum of animal screening, but relies heavily upon the use of experienced human subjects. This procedure has been successful in the discovery of over 200 novel CNS-active agents.

Key words: Drug evaluation - Psychotropic - Human - Psychotomimetic - Psychoactive

INTRODUCTION

There have been innumerable experimental designs and protocols composed in anticipation of the synthesis and evaluation of new drugs. The choice in any given case is dictated by many factors. Will it be administered in an acute or in a chronic manner? Are there potential side-effects that should dictate caution in its use? Will it be given to animals or to humans?

With this last question (when human studies are intended) a host of new considerations arise that include matters of ethics, legality, and medical and scientific acceptability. If the drug is intended as a treatment for a disease, a balance must be found between the threat posed by the illness and the potentially harmful side-effects of its medication. But when a drug has been designed solely for research purposes, where there is no immediate therapeutic application to be seen, the attitude of the medical and scientific community is often less than liberal. Some hold that with no reward potential at hand, no risk is justified. Others acknowledge that some future social benefit that might be derived from research with human subjects could justify limited research, but feel that public funding is inappropriate. In either case, research in man without an immediate medical rationalization is extremely uncommon.

In the area of psychoactive drug action, medical justification is certainly tenuous. Numerous physicians and psychologists have seen value in connection with psychotherapy, in the treatment of alcoholics, or in softening the death panic associated with terminal disease. Others insist that there is no merit yet demonstrated in these areas. Most researchers feel that the social mischief and hazard that might accompany psychoactive drug research would certainly outweigh the «unlikely» possibility that useful insight into the mechanisms of mental illness might be obtained.

On the other hand, we have held with a minority who firmly believes that there is an extraordinary potential for both social and medical virtue in this area of research. We have been conducting evaluations of many new compounds as possibly psychoactive drugs, and over the course of some twenty years of research a practical protocol has evolved which we have reason to believe might be of interest to others in this field. With many reports written and submitted for publication, we receive editorial or reviewer's comments asking for additional information on the details of the clinical studies, including procedures for the determination of active levels and such evidence as might be provided that would confirm the claim of CNS action. This paper has been designed to serve as a reference source for these procedures. It seems appropriate, however, at this particular place in the paper, to comment on the reasons -both historical and psychological- for the negative im-

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ages associated with the word, «psychedelic,» and the current well-established prejudices against the very concept of a so-called psychoactive drug.

The United States is too young a country to have established an ancient and honored tradition of psychoactive plant use, especially in connection with spiritual and ceremonial practices, as is the case with many other older cultures, including that of the American Indian. It is therefore not surprising that when Dr. Albert Hoffman's discovery, LSD, was first introduced into this country and inspired curiosity and fascination about the effects and implications of consciousness-altering chemicals, whether derived from plants or entirely synthetic, there was no body of American knowledge, either mythic or scientific, to guide the inevitable explorations by young imaginative people. The result was an explosion of investigation, research and publications attesting to the extraordinary potential for psychological and emotional healing that presumably lay in the responsible and educated use of these substances in psychotherapy.

Equally inevitable was the discovery of these areas of interest on the part of the younger generation of Americans, not all of whom were oriented toward either intellectual or spiritual discovery, and many of whom made the chronic use of psychedelic drugs, as they came to be known, a way of life. During the divisive and morally agonizing Vietnam war, that increasingly large segment of the population which made known its anger and condemnation of the conflict included many young people who made a flagrant display of psychedelic drug use as a symbol of their protest against the social and political authorities. To the normal and traditional rebellion against parental authority was added a form of rebellion new to the United States -- rebellion against the established structure and social order. The authorities reacted as they often do when their integrity is questioned, whether in this country or in any other; they wrote new laws and new punishments for what they saw as a new form of anti-social activity, and the communications media began to emphasize that aspect of the use of psychoactive chemicals which supplied the most interesting and controversial news stories: the abuse and the results of abuse. The voices of doctors, psychologists an philosophers went unheeded, and new departments of government were created and staffed in the interests of repressing and punishing any and all use of these materials. Federal funding was unobtainable for this new area of investigation, and most physicians, anxious to avoid compromising both their scientific funding and their careers, decided to avoid the area as too controversial, as did most interested chemists and other scientific professionals.

Psychoactive drugs went underground. Today, there are few if any stories in the newspapers or on the television concerning the use of LSD or mescaline, but serious investigation makes it absolutely clear that the use of these and other psychoactive drugs has remained at the same level it was on twenty years earlier. It appears, however, that by whatever means, the safer and more responsible use of these substances has become the norm, and the average college or university population can be divided, as was the case 20 years earlier, into those who use alcoholic drinks to change their psychological state, and those who prefer the use of psychoactive materials, marijuana being the most widely used.

The research into the uses of any of these psychoactive chemicals for emotional, mental and spiritual growth and healing, their potential value in psychotherapy, and other such investigations, have been at an official standstill during this time; only a very few investigators, remaining free of dependency on state or government funding, have continued to work and discover and evaluate.

DRUG PREPARATION

The philosophy behind the conceptualization and design of a drug that might have an effect of consciousness alteration lies beyond the scope of this report. From a practical point of view, a target structure is decided upon, largely following considerations of analogy to known CNS-active agents. With a target structure in mind, several rational syntheses are designed with the hope that at least two will be successful, in case difficulties arise. This two-pronged approach has so far served to resolve ambiguities of structure. A final verification of structure employs such spectroscopic and analytical criteria as are deemed sufficient to an organic chemist. The criteria of purity are felt to have been met with the completion of structural proof and the spectroscopically established absence of isomers or inconsistent spectral contributions. An additional component of this preparation stage is the complete recording of the synthetic procedures in a manner that would permit independent duplication.

ANIMAL STUDIES

Prior to clinical experimentation in man, animal studies are performed initially to establish toxicity. The LD-50 in the mouse is often employed. In our very earliest studies we would routinely determine this

number with each new potentially psychoactive drug. Two generalities became obvious. All of the LD-50s seemed to group in the area of either 50 mg/kg or 150 mg/kg. And secondly, neither the number itself, nor the «family» wherein it was to be found, gave any useful correlation with the potency or the character of action to be shown by the drug in man. Many voices are now being raised claiming that there is little if any predictive value as to the safety of a compound in man to be gotten from the establishment of its lethal level in lower animals. It has now been nearly two decades since we have killed mice experimentally, and we cannot foresee any need to do so again.

A second form of preliminary experimentation that we feel is equally limited in value is the effort to determine the psychoactive potential of a compound by animals studies. Behavioral models such as nest building among mice, open field behavior with rats, conditioned response disruption (there are many such assays) have all proven to be of limited value in the prediction of psychedelic activity. There is some promise in the recently studied two-drug discrimination procedure, but this is not yet widely applied to the psychedelic drugs. Assays employing physiological responses (such as the rabbit rectal hyperthermia test) appear to have quantitative merit but are restricted to a narrow class of compounds. Unfortunately, numerous compounds have been «established» in the scientific literature as being psychedelic in their action solely on the basis of such animal assays, without any human evaluation having been performed.

A third form of animal study does indeed have merit. This is the cardiovascular monitoring and eventual pathological examination of an experimental animal that has been given an increasingly large dosage of a test compound. Prior to the first broad clinical study of 3-methoxy-4,5-methylenedioxyamphetamine (MMDA), a cardiac dog was run with increasingly large boluses of drug, intravenously, up to a final lethal level. From this data it was clear that there was both a modest blood pressure and pulse rate increase, that the acute cause of death was cardiovascular collapse, and that there were trivial organic disruptions apparent upon post-mortem examination. This information played no role in the structuring of the clinical studies that followed, and experiments such as this one have not been repeated with any other compound.

Whereas animal studies may be useful in determining acute toxicity or cardiovascular side effects, they are of little or no utility in defining subjective effects of CNS active drugs.

Obviously, those drugs which promise to have clinical utility must, and should, go through the established procedures of IND and clinical trials prior to large-scale studies in humans.

QUANTITATIVE SCALE OF POTENCY

Some comment is needed concerning the scale used for the ranking of the intensity of a drug's effects, as perceived by the human researcher. Ideally, such measurements should be objetive — the ranking of a subject by an observer. However, with the peculiar nature of the action of these drugs — effects seen only within the subject's sensorium — it is only the subject himself who can observe and report the degree and nature of the intoxication. Hence, the subject *is* the observer and objectivity in the classic sense is impossible.

The method that we have evolved over the years is one of assigning symbols which refer exclusively to the perceived strength or intensity of the experience, and to no other aspect of its nature. The procedure could be equally well applied to other classes of psychoactive drugs, such as sedative-hypnotics or antidepressants. There is the assignment of five levels of effect:

(—) or Minus. There is no effect noted, of any nature, that can be ascribed to the drug in question. This condition has also been called «baseline,» representing the status of psychological and physical homeostasis called «normal» by the particular individual. «I am of exactly the same state of mind and body that I was before I entered into this experiment.»

(+/-) or Plus-minus. There is a move away from baseline, but there is not neccessarily a conviction that it is drug-related. This condition has also been called the «alert» (if this is the prelude to furthur development) or being «aware» (if this is the extent of development). Each subject has his own individual signal — one experiences decongestion of the sinuses, another notes a runny nose; one researcher reports a paraesthesia, another perceives an absence of a chronic tinnitus. Often it is the reminder to the subject (by whatever internal signal) that he has indeed taken a compound; strange as it may seem to anyone not involved in this form of research, it often happens that an experienced researcher can be distracted by something of interest, such as an important phone call, and can indeed forget a few moments that he is participating in an experiment. His own form of the so-called alert serves to remind him. This category is replete with false positives; it is common for such a report to

be summarized with a final (—), as the subject concludes that whatever he interpreted as signs of activity must have been, in fact, products of his imagination.

(+)or Plus One. There is a real effect, and the duration but not the nature of the content can be discerned. The «alert» has progressed into something unmistakable. There may be nausea or even active vomiting, or lightheadedness, or compulsive yawning, or restlessness, or a wish to remain motionless. But there is a real effect. There are rarely false positives here. This is a level that will give the first real indication of the duration of action. As a rule, the more common physical complaints are dissipated within the first hour, and the subject is left with the first suggestion as to the nature and quality of the effect of the drug on the central nervous system (CNS), and is able to note the duration of the effect and its ebbing, *e.g.,* «It will be long-lasting, but I can't say yet just what kind of experience it will be.»

(+ +)Plus-Two. There is an unmistakable effect, and both the duration and the nature of the effect can be stated. It is at this level that the first attempts at classification can be made, *e.g.,* «There is considerable visual enhancement, and much tactile sensitivity, despite a light anaesthesia.» At a plus-two, one might still be able to answer a telephone sensibly, but would most probably choose not to attempt to do so. One could drive a car with much care, but would wisely choose to do so only in a life-and-death emergency. Cognitive faculties are largely intact, and much of the drug's effects could be supressed if the need should arise. When this level of drug activity has been confirmed, a second experimental subject is usually brought into the protocol scheme.

(+ + +) Plus-Three. this is the level of maximum intensity of drug effect. The full potential of the drug has been realized. Its character can be spelled out (assuming that amnesia is not one of its properties) and the chronological patterns to be expected are defined. With experienced subjects, there can be a surprising subtlety attempted in splitting categories — «I was pushing a plus two and a half, but felt that it hadn't quite hit its full activity!» It is the area between + + and + + + that is used in the definition of the «active level», and it is the dosage that leads to this level of activity that is considered the «active dose».

One additional symbol is occasionally needed, this for the «peak experience» in the terminology of Abe Maslow. This is a serene and magical state which is largely independent of what drug is used if a drug at all, and moreover, cannot be repeated at will with a repetition of the experiment. It is the extraordinary place, that one-of-a-kind, mystical or religious experience which will never be forgotten. It has, within this coding system, been given the name + + + +, or *Plus-Four,* but this is not to imply in any way that it is more than, or comparable to, the + + +. It is simply in a class by itself, and has no suggestion of quantitative value.

PRELIMINARY SCREENING

The determination of an appropriate dosage for clinical trials must call upon a preliminary screening process in man, to establish an effective dosage. The single, most difficult number to find in this area of research is an initial trial level at which one may have the confidence that there will be no effects. There is no completely safe procedure. Every line of logical reasoning leads to a dosage level likely to be inactive in man, and the prudent researcher begins his exploration at the lowest of these. Then one says, «Yes, but what if?» One can argue *after* the fact that the ethyl group increased the potency over the methyl group because of lipophilicity, or decreased the potency because of ineffective enzymatic demethylation. Our decisions have been a mixture of intuition and probability. There are very few drugs that, upon structural change by a single carbon atom (homologation), change their pharmacological potency by an order of magnitude. There are very few compounds that are orally active at levels much below 50 micrograms. And, as to unexpected quality of action, there are very few CNS-active compounds, dangerous to the subject at effective dosages, which do not display some preliminary warnings at a threshold level.

So, the usual starting point with a new drug is some 10 to 50 times less, by weight, than the expected active level of its closest analog. And, if in doubt, we go down by a x10 again. Some new compounds that are closely related to previously assayed drugs have been started at levels of tens of milligrams, as they are close structural analogs of compounds that have proven to be without activity. Yet other compounds, those of some entirely new class in unfamiliar territory, may actually be started at levels below a microgram.

Once this initial dosage has been shown to be without effect, a regular regimen of increasing dosage on alternate days and in alternate people, if possible, is instituted. The usual increment is something less than x2. This allows some 4 or so levels of assay to be explored within each order of magnitude.

Once the study of a compound has been initiated, there are several additional considerations that must be

kept in mind during the exploration of sub-active levels. If a drug is assayed too frequently, a tolerance to it may develop even if there is no perceived action, so that increasing doses may appear to be inactive. Further, when different drugs are interposed in the schedule, cross tolerance may obscure activity. To minimize this potential loss of sensitivity, no drug is repeated on sequential days and, if convenient, drugs of separate classes are interspersed. In addition, any researcher who is the primary screener should periodically allocate a week to being completely drug free. This is especially important if a number of different drugs of similar structural properties are being screened within the same period.

PRECLINICAL ASSAY

The results of the above screening are used to establish the dosage range for eventual clinical trial. A dosage that lies between + + and + + + is taken with a second subject, to explore the potential for interactive aspects of the drug's activity. As the complete psychological profiles of the eventual research group are well known, an informed judgement may be made as to an appropriate schedule for the clinical study. And with an accurate estimate of the expected chronology, a reasonable program for an initial group study can be determined. Thus, with two preclinical studies completed, the program for expansion to a group of some twelve persons can be designed.

CLINICAL EVALUATION

The initial total clinical evaluation of a new psychedelic drug usually involves twelve subjects. There are some meetings of this group at which only eight or nine are present, and there have been occasions when up to 14 were involved, but the usual number is twelve.

These people are volunteers, chosen from an inventory of scientific researchers who have brought with them many needed credentials. As individuals, they are experienced in the effects of a wide number of psychotropic substances and thus they «know the territory.» This experience has, time and time again, proven to be of inestimable value, in that they may make direct comparisons to other, familiar altered states, and equate or critically compare some particular property of a drug's effect. The eventual description of the qualitative nature of their sessions with a new drug will be more useful due to this experience.

The question of informed consent must be approached quite differently in the contex of this kind of research group and this type of research. The subjects are completely aware of the risks and the returns to be expected from the experiment, and have volunteered freely to involve themselves in it. The concepts of legal redress or accusation of malpractice are without meaning within this voluntary group. It is understood by all members that any form of damage, either physical or psychological, suffered by any member, as a result of experimentation with a new drug, would be responded to by all other members of the group in any way required, and for as long as it would take for the injured person to regain health: financial aid, emotional support and any other needed kind of assistance would be forthcoming without reservations. It should be noted, however, that exactly the same kind of support and care would be given by any member of the group to any other member in need under circumstances unrelated to drug experimentation. In other words, this is a group of people who have become, and expect to remain, close and devoted friends.

It should also be noted here that, over the course of these studies, no physical or mental damage has occurred to any member of the research group. There have been occasional instances of mental or emotional distress from which the subjects fully recovered, following dissipation of the drug's effects.

The question of blind studies, or especially double-blind studies, is pointless and verges upon the unethical. The ultimate rationalization for «blindness» in an experiment is to protect against possible subjective bias on the part of the subject. Objectivity may be desirable when one is evaluating the clearing of acne or the avoidance of pregnancy. But here, the subject is to be possibly promoted into an altered state of consciousness, and to fail to advise him of this possibility and the nature of this state would be completely improper and unethical. Since he *has* been advised as to the identity of the drug and the general kind of action which can be expected at the particular levels of dosage which have been found to induce activity, as well as the time and place of the experiment, the term «double conscious» has been used instead of «double-blind.»

All subjects are some twelve hours post-absorptive, and have been some three days free of any psychotropic drug usage. Any health concerns, or recent medication for same, will serve to exclude a person. The age range has been from 35 to over 70, and participants are of both sexes. The environment provided for a research session is always the private home of one or another of the subjects; there is sufficient space to allow each subject the freedom to relate to or dissociate from others in the group, to actively participate in the en-

joyment of music, talking, looking at art books, or to introspectively withdraw. Each of these private homes has garden space for the enjoyment of those who wish to spend time among plants and in the fresh air.

Only two procedural demands are enforced. In this group, it is understood that the words, «Hand in the air,» preceding any statement, is a euphemism for reality-based problems or concerns, and must be immediately respected. To say, «Hand in the air,» (always accompanied by an actual raising of the speaker's hand) and then to say, «I smell smoke,» means that there is a genuine worry, and not some form of fantasy or game-playing, associated with the words. This rule is drilled into the minds of all members of the group, and the rule is re-stated at the beginning of each research-group session.

The second is the concept of veto. If anyone in the group feels discomfort or anxiety about a particular proposal concerning the direction in which the study might go, then the power of a veto is complete, and must be respected by all. For instance, if one person proposes the playing of music on the radio or phonograph at a certain time in the experiment, and is joined by others in the group who would like to hear music, it is understood that the vote must be unanimous; one person feeling discomfort about music insures that none will be played. The problems that might be expected to arise from this kind of situation are often easily resolved; in most family homes which are large enough to accommodate a group of 12 people for such an experiment, there is usually an extra room in which music can be played without disturbing the quiet of other rooms.

In a case where a disagreement over certain aspects of the experiment is seen to arise, the attention of the group is eventually drawn to the implications of the behavior which resulted in discomfort or anger or irritation on the part of one or more subjects; the reasons for the difficulty are explored, either at that time or in a later group, just as they would be in a psychotherapeutic encounter session or any other form of group therapy. It has long been understood by members of this research group that exploration of the psychological and emotional effects of a psychoactive drug are, inevitably, synonymous with exploration of their individual psychological and emotional dynamics.

There is on occasion a need for an adjustment of dosage, usually due to a subject's failure to detect activity at the dosage level which had been assumed sufficient for him. If there is any question, before the experimental session begins, most subjects will opt for a more modest dosage and any needed correction can be made at the one to two-hour point. These changes are limited beforehand, and are dictated totally by the subject's experiences in the past. Such changes are made at a point that is determined by the expected chronology of the experience; at one hour for short-lived materials, at 1-1/2 to 2 hours for drugs of intermediate duration, and at two to four hours for the extremely long-lasting psychedelics. Occasionally the drug (usually in solution in water, as the hydrochloride salt and taken orally) is sipped over the course of an hour or so, to circumvent nausea.

The experimental environment is made comfortable and safe. Fruit juices, fruit, and usually soup and bread are brought by members of the group, and provisions are made for staying and sleeping overnight. No objective observer is present, but emergency medical assistance is available upon short notice, having been arranged for in advance of the session.

QUANTITATIVE CONSENSUS

The appropriate values of the plus-scale mentioned earlier are assigned by each subject, and this serves as the basis of the assignment of quantitative potency ascribed to the drug. Many of the subjects have become familiar with the effects of mescaline (at 400 mg of the sulfate salt) and a comparison to this experience serves as a measure of relative potency. The division of the active dosage of mescaline by the effective dose of the drug in question establishes a quotient of potency that has been called the «mescaline unit» of potency. This is the number that is sought and used by the behavioral pharmacologists. It does not imply a nature of action, simply a potency of action.

QUALITATIVE CONSENSUS

This is, of course, the raison d'etre for all of this research. It is difficult to try to distill a generalized portrait of psychopharmacological action from a typical experiment. Each person will record and evaluate those aspects of the experience that had particular meaning for him. It should be noted here that each subject in the research group is asked to write a report or, at least, a summary of the experiment, and to submit a copy of it (assuming that the original will stay in their private notebooks) within as short a time as possible to the leader of the experimental session. These reports form the basis for the subsequently written and published articles delineating the effects of the new drugs.

Within the area of the psychoactive drugs, certain subjective experiences are more common than not -- the

eleboration of sensory input, visual distortion, the experience of eyes-closed imagery and easily elicited fantasies, the slowing of time, ease of talking and interacting without defensiveness. These are almost always observed. There are other aspects of the drug experiences that are more rare: a constructive insight into a personal problem; an authentic reliving of some event or events in one's personal past; being able to come to grips with an especially threatening or uncomforable archetype; the achievement of an unexpected exalted state or religious experience. These are personal things which give value to the qualitative report, and which might, in time, give properties to this or that specific psychoactive drug. It is in this contex that properties are revealed which lead to the discovery of therapeutically useful drugs.

This is an overview of the process that has been used by us for the evaluation of new materials which might prove to be psychoactive. It is readily admitted that it is unusual in structure, but there is no way to determine the subjective effects of a psychoactive drug, other than by human experimentation. It is estimated that some 200 psychoactive drugs have been discovered and characterized by this method. Some representative examples of different psychotropic classifications are given below, with literature citations.

Antidepressant

The drug Dimoxamine [1-(2,5-dimethoxy-4-methylphenyl)-2-aminobutane, BL-3912A] was brought into clinical trials by Bristol Laboratories, New York, as an anti-depressant and memory adjuvant (1). This compound has gone through Phase II of the FDA IND evaluation procedure.

Sensory amplification: A deceptively simple tryptamine DIPT (N,N-diisopropyltryptamine) has been reported to amplify and distort the auditory sensory input signals (2) in preference to the more frequently seen visual distortions. This modality is closer to the usual symptomology of endogenous schizophrenia, and may well serve as a discriminating tool for differential research.

Therapeutic adjuvant

The stimulant and therapeutic facilitator 1-(3,4-methylenedioxyphenyl)-2-methylamino propane (MDMA, Adam, XTC) was initially described (3) and subsequently exploited (4) as a psychotherapeutic tool. Its legal and clinical definition is as yet uncertain (5).

Psychedelic agent

The compound 2,5-dimethoxy-4-methylamphetamine (DOM, STP) (6) found its way into popular usage in the late 1960's and was widely abused as a street intoxicant. Its action has been confirmed in several clinical tests (7) and it has been widely accepted by the scientific community as a prototype of a hallucinogenic drug. Studies into its metabolism have provided valuable insight into the mechanism of action of these agents (8). Furthermore, as a pharmacological model, it has proven to be a valuable tool in understanding the role of serotonin in brain biochemistry (9).

Psychotomimetic agent

The induction of a psychosis-imitating state has been recorded by the action of 3,5-dimethoxy-4-methylthiophenethylamine (10). This analog and its homologous extensions are being evaluated as models of the schizophrenic syndrome (11).

Free-association enhancer

The ethyl homolog of the psychedelic agent DOM is 2,5-dimethoxy-4-ethylamphetamine (DOET) which proved to be relatively free of sensory distortions and thinking disorganization at dosage levels that allowed alteration of normal cognition and enhanced free association. These properties were confirmed in independent double blind studies (12).

Somatic sensitizer

In addition to an extensive visual syndrome, the phenethylamine 2-CB (4-bromo-2,5-dimethoxyphenethylamine) (13) produces an intense awareness of physical responses to stimuli: olfactory, auditory, gustatory and sexual.

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