

ISGIDAR

INTERNATIONAL
STUDY
GROUP
INVESTIGATING
DRUGS
AS
REINFORCERS

NEWS LETTER

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TABLE OF CONTENTS	APPENDICES
RESUME OF ACTIVITIES..... 1	A. Annotated Bibliography of Experimental Drug Self-Administration
POLICY STATEMENT ON ISGIDAR AND ITS OBJECTIVES..... 2	B. Questionnaire on Methodologies Used in Primates - Circulated Only to Members of the Working Committee of ISGIDAR
MEETINGS..... 9	
CURRENT WORKING COMMITTEE MEMBERSHIP....10	
OTHER MEMBERS OF ISGIDAR.....11	

RESUME OF ACTIVITIES

ISGIDAR is, at present, a loosely organized ad hoc group of pharmacologists and psychologists. Its "members" are interested in the systematic investigation of (a) those properties of drugs which predispose them to act as reinforcers of drug-seeking behavior and/or (b) those aspects of behavior which are involved in the process of seeking out and repeatedly using drugs for purposes other than therapy. At present, or better, so far, the group has consisted mainly of persons who are keenly interested in the use of infra-human primates for the study of drug-seeking behavior and/or the examination of the extent to which drug self-administration by monkeys can be used as a part of a strategy for predicting human abuse potential.

The present situation suggests that a "clique" of persons working with drug self-administration in monkeys has self-appointed themselves to initiate what might reasonably be expected to grow into some kind of formal group involving a much larger population of individuals with somewhat broader research interests. There may be more than a little truth in this suggestion. At any rate, the original group was assembled in Washington, D.C. on February 22nd at the invitation of the NRC-NAS Committee on Problems of Drug Dependence, largely through the efforts of Dr. Nathan B. Eddy. He had been prompted in this action by a suggestion made at the satellite session on drug self-administration held during the May 1972 meeting of CPDD in Ann Arbor. Simply stated, the suggestion was that a cooperative effort to standardize test methodologies might lead to better strategies for predicting human abuse liability.

There were twenty participants, representing 18 different laboratories, at the one-day meeting. In addition, there were six observers representing the NRC-NAS CPDD committee, the FDA, the NIH and the BNDD.

A report of this meeting was prepared by James Woods (University of Michigan) and Duncan McCarthy (Parke-Davis). This report was given to the CPDD at their meeting in Chapel Hill, North Carolina in May 1973. This meeting was also reviewed by Duncan McCarthy at a satellite session especially devoted to discussion problems relevant to ISGIDAR. The official report to the committee will be published as part of the committee minutes for those who might be specifically interested in it. Excerpts are included below for the benefit of recipients of this "News Letter" who might not have access to the CPDD minutes.

At the Washington meeting, observers representing university research centers, industrial research laboratories and government agencies agreed that it would likely be possible to develop useful and fairly reliable means of predicting those aspects of human abuse liability of drugs and chemical substances which relate to their pharmacologic properties. It was recognized that those pharmacologic properties of a drug determining drug-seeking behavior are only a small part of a complex set of determinants leading to self-administration, misuse and abuse. Such factors as the economic, ethologic, moral, sociologic and legalistic may be as, if not more, important than the pharmacologic in defining some substances as drugs of abuse. Unfortunately, these important aspects influencing human behavior do not lend themselves well to systematic study in man and are virtually without equivalents for controlled study in laboratory animals. Recognizing this limitation, the group attempted to: (1) explore the possibilities of developing coordinated and correlated procedures so that comparability of findings may be assessed among laboratories, (2) consider details of the procedural variation which might affect results, (3) explore the possibility of developing sufficient standardization that any laboratory choosing to cooperate could have the benefit of results of the work being carried out in other cooperating laboratories. Assuming a realistic appraisal of the above objectives, the group might then proceed to evaluating the present status of the procedures in terms of laboratory testing.

The difficulties in meeting these objectives was recognized. However, any useful contribution that would help avoid continuation of the present situation whereby it is necessary for each laboratory in itself, of itself, by itself to study representative examples from each class of dependence-producing or reducing drugs upon which information might be sought would be a progressive step.

All participants agreed that any cooperative effort leading to some sort of test standardization must avoid placing any limitations on inquiry into the behavioral and other aspects of drug-seeking behavior or place restrictions on innovative or imaginative developments in this type of research.

The CPDD, Dr. Eddy, and several representatives of the industrial research laboratories and government agencies expressed a keen interest in the possibility that the techniques of self-administration might be useful in helping to predict the relative human abuse liability of drugs and chemical substances not generally available for human use.

The participants in this conference quickly arrived at the position of defining major objectives in terms of what was possible and what was not. They recognized, with general agreement, the following:

- (1) The propensity of a drug to act as a reinforcer of drug seeking behavior is unlikely to be a sufficient criterion to define fully the abuse potential of a drug.
- (2) It seems likely that well-controlled studies carried out in monkeys (and probably other laboratory species) can be expected to yield far better quantitative data on the reinforcing properties of drugs than has been or perhaps can be collected from man. Hence we lack means to make the necessary correlations for arguments by analogy.
- (3) Any means which would improve the accuracy, the reproducibility, the reliability of animal tests, or reduce the cost of research resources and time devoted to this end, would be contributory to our comprehension of drug dependence and drug-seeking behavior.
- (4) Standardization of test procedures offers certain advantages not only to those interested in predicting pharmacologic properties promoting drug-seeking behavior, but also to those interested in studying the behavioral and neuropharmacological aspects of drug self-administration.

Standardization of procedures, or more accurately, procedural strategies, have obvious advantages such as:

- (a) Transposition of data among laboratories by utilizing common reference bases.
 - (b) General acceptance of data generated among laboratories using identical test methodologies.
 - (c) General emphasis on the part of cooperating investigators to encourage reduction in the introduction of unnecessary minor variations in test procedures which contribute very little to increasing our understanding of anything at all.
 - (d) Possible acceptance by regulatory agencies of data obtained from defined test procedures.
- (5) Standardization of test procedures is not without certain limitations which should be recognized. For example:
- (a) Research prerogatives may be stifled if any single test or battery were given some kind of official sanction.
 - (b) There is an unfortunate inertia associated with changing standardized procedures after evidence clearly shows them to be superseded by better tests. Thus investigators are often caught up in a situation where they are expected to perform experiments in less than the

optimum fashion because of the value of historical controls. Parenthetically, it may be anticipated that procedures will change to take advantage of new information and techniques in the area of drug self-administration in animals so that new "standards" will be arrived at as problems are more completely described.

- (c) Some investigators have barely sufficient financial support to continue pursuing their own research objectives. While they would like to adapt the technical aspects of their research to be compatible with acceptable standard methods (if or when these are agreed upon and if or when these are in concert with their own research objectives), they may not be able to afford to do so.
 - (d) There will be expenses incurred in evaluating the extent to which variation in the technique(s) can be altered without compromising the obtained results.
- (6) It seems likely that the benefits to be realized by close inter-laboratory cooperation, regardless of the degree of standardization can only hope to further scientific progress at a more rapid rate than continued fragmentation of effort especially as it relates to the immediate practical need in defining potentially abusable substances before they reach the point where they may develop into abuse problems.

The group spent considerable time considering procedural details. The extent to which formal experiments have investigated manipulanda, infusion parameters, stimulus-light configurations, caging facilities, lighting conditions, watering and feeding regimens, etc. is limited. There was a general agreement that these minor technical differences and sources of variation may have remarkably less influence on the results obtained and the conclusions drawn than one might have expected. Some even suggested that the influence of minor procedural differences may very well have less influence on self-administration performance than the individual differences among particular test animals. Some of the participants agreed to assemble data on the influence of certain variables on self-administration and report these when the group reconvened at the time of the Chapel Hill meeting.

A good deal of time was spent discussing technical details which would improve the quality of the test animal and hence influence test results.

Testing strategies were discussed, with agreement that primary self-administration studies in drug naive animals and/or drug substitution techniques offered the greatest advantage as primary evaluating techniques. Choice procedures and progressive-ratio techniques, while obviously reliable and powerful, have not yet been studied in sufficient detail to consider them at the present stage of planning.

It should be emphasized that while the group focused its attention on self-administration technique it recognized the unequivocal importance of other aspects of the pharmacology of substances being evaluated.

Dr. Eddy encouraged the group to enter into a comparison of technique and result on a basis similar to that used to evaluate compounds for morphine-like physical dependence in the Rhesus monkey at Michigan. To this end he proposed that one or two compounds be evaluated on a blind basis by the cooperating laboratories. This idea received considerable support with 13 laboratories indicating interest and 9 laboratories indicating they would definitely accept "unknowns". This step in evaluation was uniformly felt to be most important in assessing results in terms of the differences in techniques used by different laboratories.

The numbers and types of compounds were not agreed upon nor was it agreed that the protocol for distributing the drugs should have any objective other than that of establishing the degree of inter-laboratory or, perhaps, intra-laboratory reliability with respect to substitution-type experiments.

No representative from any laboratory suggested more than four compounds, and everyone felt that two compounds might be sufficient. Assuming a reasonable amount of reliability and agreement will be arrived at, the next and more interesting step would be an independent assessment of drugs for which little or no information on self-administration is available. The group clearly needs to designate a person(s) who will coordinate the distribution of drugs and to act as a collector of the results within proscribed time limits.

It was agreed that this problem and others related to the protocol for disposition of drugs would be discussed in Chapel Hill at the time of the CPDD meeting there.

The conferees then directed their attention to means whereby the group could collectively act to improve testing procedures and evaluations. They overwhelmingly favored adoption of some means whereby information could be more rapidly disseminated. However, there was little general agreement on how this should be done. Some favored a clearing house which could act as a recipient of test results and make them available at the earliest possible time to other investigators--perhaps something like the Survey of Anti-malarial Drugs, subsidized during World War II by the Office of Scientific Research and Development and which was ultimately published under the Editorship of F. Y. Wiselogle. Others objected to the clearing house concept on the grounds that it seldom worked very well because of personal and corporate proprietary attitudes. The group unanimously favored semi-annual convocations of the interested parties for open forum discussion of the type being held at this conference.

The group recognized the importance of comments made by the conference observers representing NIH, FDA, BNDD and the NRC-NAS. These observers expressed considerable interest in the conference objectives, offered suggestions, and proposed means whereby their respective agencies might be of assistance. They recognized the problems facing individuals and groups attempting to predict the pharmacologic factors contributing to the abuse of a given drug. Their continuing interest in the objectives of the group is of utmost importance.

The participants of the meeting, either at the meeting or subsequently, have arrived at a number of specific recommendations for consideration by the CPDD.

1. That the Committee continue to support satellite sessions on the progress of the group interested in drug self-administration evaluation in animals, and, to the necessary extent, support financially other workshops of those actively participating in the venture.
2. That the Committee publish the outcome of these workshops and satellite sessions as addenda to the Annual Report of the Committee.
3. That the Committee financially sponsor, directly or through solicitation, a bi-monthly newsletter to include an annotated bibliography of papers concerned with self-administration, notes on experiments submitted directly to the newsletter, results from cooperative testing and other pertinent subject matter. The compilation of a newsletter might be accomplished by an interested graduate student, the student being supported financially for his efforts. Mailing and duplication costs would have to be incorporated as well.
4. The group should petition the CPDD or some appropriate granting agency for financial support of research covering examination of unknowns.

Essentially, the same group of interested participants in the Washington Conference, with some notable additions, assembled at the Chapel Hill meeting of the CPDD on Monday evening of May 21. It was a lively, well-attended meeting. Duncan McCarthy presented the synopsis of the Washington meeting, pretty much as outlined above and also reported on the response of the Committee to the overview presented to them on the previous day. There was a suggestion from the audience that the group could move forward toward some of their objectives most rapidly by assembling and comparing self-administration data on compounds that have already been studied.

Joe Brady (Johns Hopkins) presented data on a behavioral procedure using a progressive-ratio technique, and a choice procedure to study initiation of drug-reinforced responding. His suggestion was that early members of response chains reflect the reinforcing properties of drugs, and his results with baboons suggest that comparisons among compounds with respect to the terminal ratio they will support reflects well their abuse liability. Bob Schuster (University of Chicago) talked about a variety of techniques and training procedures that can be used in both choice and substitution techniques and emphasized the objectivity of these tests in relation to observational techniques. Harold Wakeley (IIT) reported on effects of environmental change in the laboratory such as light-dark conditions and the presence of extraneous stimulation as influences on drug-reinforced responding.

Steve Goldberg (Harvard) and Bill Gill (Smith, Kline and French) reported on self-administration techniques in squirrel monkeys. Goldberg talked about dose magnitude and schedule-controlled responding in first- and second-order schedules of reinforcement with stimulants, barbiturates, and morphine. Gill talked about preliminary findings using substitution techniques with stimulants and behavioral problems associated with high saline-control rates of responding. He also showed some data that suggested that apomorphine will serve as a reinforcer in squirrel monkeys with histories of stimulant reinforcement and in drug-naive monkeys. Woods presented some results of substitution techniques that showed fenfluramine not to serve as a reinforcer, and he presented a rationale for dose ranging with drugs that appear not to serve as reinforcers. The meeting was arranged and chaired by Jerry Malis (Wyeth).

Dr. Everett May was asked if he would serve to send out the appropriate test materials to the participating laboratories when final arrangements for distribution were made. He agreed to act for the CPDD in this capacity.

In spite of the original plan to have a round table type working session on means to develop inter-laboratory cooperative efforts, the satellite session included more in the way of formal presentation of individual laboratory accomplishments than had been planned. For this reason, a working luncheon (generously sponsored by Wyeth Laboratories) was held on Tuesday. At this meeting, plans were made to implement the assembling of data already collected--both published and not yet published--from investigators and laboratories willing to cooperate. C. R. Schuster volunteered to act as a recipient of information and with the help of his associates assemble the data so that appropriate deductions could be made from it. It was agreed that the first step in this process would be the preparation of an appropriate questionnaire that could be rather rapidly completed by each of the participating laboratories. This questionnaire was to be mailed out as soon as it could be prepared. Woods and McCarthy volunteered to assemble, publish and distribute a news letter. This communication would contain items of interest to members of ISGIDAR and perhaps to others who are also interested in drug seeking behavior. It was (and still is) their intent that this news letter will get published as often as necessary to meet the needs and objectives of ISGIDAR. Brief communications, letters, notices of meetings, grants, contracts and other news items relevant to the subject were invited from interested persons.

C. R. Schuster was chosen by the group to act as its chairman through 1974. D. A. McCarthy and J. Woods agreed to act in a cooperative way as Secretary-treasurers of the group, and to handle such other business as should arise and to assist the Chairman in any way possible. They would use the news letter as a vehicle for communication with other members of the group. In addition, the news letter will be sent out to other persons actively engaged in research involving drug self-administration as soon as such persons indicate an interest in receiving it.

The first issue of the ISGIDAR News Letter, appended questionnaire, and the partial annotated bibliography represents a part of the work carried on since the Chapel Hill meeting.

POLICY STATEMENT ON ISGIDAR AND ITS OBJECTIVES

- 1) ISGIDAR (International Study Group Investigating Drugs as Reinforcers) is, as its name implies, a group of scientists who are attempting to use the technique drug-self-administration to generate presumptive laboratory data about those properties of drugs which would predispose them to human abuse. More especially it is international in scope and it is dedicated to a cooperative effort to achieve its objectives.

- 2) ISGIDAR "membership" at present is limited to: (a) scientists who are actively using infra-human primates in their study of drug self-administration and who are willing and anxious to work with other laboratories to the end of devising means to improve, sharpen and employ their techniques within a cooperative framework; and, (b) representatives of national and international agencies responsible for research on or control of drugs of abuse.
- 3) The Working Committee of ISGIDAR will be limited to one representative from each laboratory. This restriction should keep the group small enough to allow for effective communication at working conferences.
- 4) ISGIDAR is to serve to facilitate the consideration of special problems relating to drug seeking behavior through the dissemination of information by providing forums and meetings.
- 5) ISGIDAR is to provide a means whereby interested parties can cooperate on the testing, evaluating and defining of drugs in infra-human primates for the purpose of predicting human abuse potential.
- 6) ISGIDAR, as an organization, will attempt to accept germain information and facilitate its rapid dissemination not only to its "membership" but also to other scientists who are interested for one reason or another in either the pharmacologic or the ethologic aspects of drug seeking and self-administration. This list would include persons who are interested in the experimental aspects of human drug abuse as well as those interested in the laboratory aspects of the phenomenon.
- 7) ISGIDAR will work toward unifying or standardizing procedures which hopefully will become part of an overall strategy for predicting "drug abuse" potential before new drugs or chemicals appeared in the market place where such definitions are made by those who traffic in and/or use such agents. The "standardized" procedures adopted into the testing strategy and the strategy itself are not intended to become static affairs. ISGIDAR will continually examine its recommended procedures (if and when these evolve) with the recognition that changes must and will be introduced as experience teaches better ways to operate.
- 8) ISGIDAR will attempt to provide legitimate new drug developers, government agencies and international drug control groups such information as may be useful to them in decision making as it relates to the development, testing, distribution, and control of new drugs and chemical substances.
- 9) The watchword of ISGIDAR is cooperation. Its members are well aware of the magnitude of the problem. They are pledged to avoid the expense, redundancy and pitfalls that result from the nervous, proprietary and competitive attitudes which all too frequently cloud research in the medical and biological sciences.
- 10) Membership to ISGIDAR is open to all qualified scientists whose research and interests clearly indicates their commitments to its objectives and who are willing to become active cooperating participants.

Finally, a cautionary note! The policy statement reflects what the writers (McCarthy and Woods) have compiled or a consensus from the two group meetings and their own ideas. It is our desire to reflect the policy and objectives of the group as well as possible at the present time. If the individual members feel this statement does not reflect their attitudes, "let us come together with discussion."

MEETINGS

A tentative meeting of the Working Committee will be held in Chicago during the week of November 12 provided the data on the questionnaires has been received and processed by Drs. Schuster and Johanson by that time. Confirmation of the specific day or days will appear in the next issue of the News Letter.

A general meeting of ISGIDAR will be held in Mexico City at a satellite session to the CPDD annual scientific meeting to be held there on March 10 through 12, 1974. The Working Committee may elect to hold a workshop meeting on the day preceding the Mexico City meetings.

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