ADVANCES IN NEURO-PSYCHOPHARMACOLOGY

Editors

O. VINAŘ, Z. VOTAVA, P. B. BRADLEY

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PREFACE

Modern Neuro-Psychopharmacology is still a young rapidly growing scientific field although it ought to have crossed the age of adolescence. It was not easy for the Program Committee of the 7th CINP Congress to choose topics which are currently of major importance. If the success of the choice could be measured by the number of authors who wished to participate in the symposia, the members of the Program Committee would have had good reason for a feeling of complete satisfaction: the interest in the topics chosen for symposia was even greater than a Congress with 8 concurrent sessions lasting 4 days could fully absorb.

If the Proceedings of the Congress had included all the papers read it would represent books with several thousands pages. Nobody risks such a publication in these days. It was impossible to agree on criteria for selection of only a minor part of all presentations based on some hierarchy of scientific importance of individual papers. On the other hand, the chairmen of Symposia had done a certain selection when proposing the program of the respective Symposium. We decided therefore to go the same way and publish papers read in Symposia: their chairmen were well known scientists in the subspeciality covered by the topic of the symposium and their choice of contributors was made according to their knowledge of the field. There are only few exceptions when a paper read in the Symposium is not published here.

Clinical and pharmacological aspects of lithium therapy is the topic of the first symposium. Even though some doubt about the scientific evidence of the prophylactic action of lithium in recurrent manic-depressive psychoses remains, it is now clear that the very idea of prophylactic medication is a qualitatively new step in psychiatric care. The studies of the mechanism of action of lithium have contributed to the knowledge of the pathophysiology of affective psychoses. In this respect, the topic of the second symposium (amine precursors in the treatment and study of affective disorders) was a logical continuation of the first symposium. It has been shown that a simple and direct relationship between the levels of the amines and the mood as hypothetised some 15 years ago have been replaced by more complicated schemes. The theoretical importance

of these studies is self-evident: even more important is the fact that some first experiences with the experimental treatment proposed according to the new hypotheses were successful.

In terms of the number of people who take psychotropic drugs the third symposium was the most important: it dealt with methods of evaluation of anxiolytics. Although new possibilities for the prediction of the clinical effects on the basis of pharmacological studies in animals exists, it is still the clinical trial which decides whether a new compound has advantages in comparison with the existing ones. Social aspects play an important role in the efficacy of anxiolytics and the design of a clinical trial in out-patients is not an easy undertaking. The majority of the anxiolytics are prescribed by general practitioners in routine practice: their patients differ from those who are seen by psychiatrists. The organization of trials of anxiolytics performed by general practitioners is of great importance, therefore.

The knowledge of the possibilities of chemical substances to change the mental state has also its disadvantages: the abuse of these drugs is one of the serious challenges to the health of the society in some countries. The fourth symposium dealt with some aspects of this problem: "pharmacological and theurapeutic aspects of amphetamine and hallucinogen abuse". We still do not know enough about the real extent of the problem, i.e. about the number of persons who are drug-dependent. On the other hand, the studies of electrophysiological and biochemical changes in subjects who have an amphetamine psychosis can be helpful in promoting the research of the pathophysiology of some functional psychoses, e.g. schizophrenia.

The fifth symposium was devoted to the influence of drugs on social behavior. An analogy in the effects of drugs on animals and men could be demonstrated even in this area. The success of the anti-androgen treatment of sex offenders was shown in this symposium as an example of new possibilities of pharmacological control of deviant human behavior.

The controversy between the pharmacological and psychotherapeutical approaches in psychiatric treatment belong to the past. The sixth symposium (Effects of drugs on interpersonal processes, psychodynamics, drugs and psychotherapy) brought new evidence about the usefulness of the close coordination of the pharmacological and psychotherapeutical efforts. Better understanding of the psycho-

dynamics of patients treated with drugs and of the interpersonal context they live in may contribute much to the success of the treatment. Whether hallucinogenic drugs are really helpful in accelerating the psychotherapeutic process remains to be studied under strictly controlled conditions: several studies performed up to now have produced controversial results.

Current methodological problems of clinical psychopharmacological investigations were dealt in the symposium No 7 (Special questions: placebo, drug combinations, subjects in new drug trials). The possible biochemical basis of some mental disorders and the mechanism of action of drugs was the topic of the eigth symposium, focused on the role of putative central transmitters.

It is clear that a great diversity of topics covered in the symposia is connected with a diversity of methods employed. The psychotropic drug is sometimes the only connecting link between different papers: the emphasis in this book is not in the homogeneity of contents but in the current importance and in the overview of the current activities in the areas where the progress is rapid. The editors do not feel that they can always agree with the methods used and/or their ethical aspects. Nevertheless, also in these instances, we think it useful to make the material presented in the symposia available to all who wish to contribute to the progress of knowledge which is needed to alleviate the suffering of the mentally ill and their social partners.

Oldřich Vinař
Zdeněk Votava
Philip B. Bradley

March 1971

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CRISES AND CONFLICTS IN NEUROPSYCHOPHARMACOLOGY

H. E. LEHMANN

Douglas Hospital and McGill University, Montreal

Our young science of neuropsychopharmacology is rapidly approaching maturity. At the next meeting of this College, modern psychopharmacology will have grown out of its teenage and will be 20 years old. During two decades of dynamic growth and progress the new science has had to face many problems, and in my address today I want to talk about some of its current problems, conflicts and crises.

I know that this runs counter to established tradition which prescribes that the outgoing president reviews mainly the important achievements of the recent and distant past. However, I feel confident that neuropsychopharmacology today is sufficiently strong and secure to tolerate a more searching examination. In fact, I feel that a critical look at our science might be more exciting and more constructive than a simple progress report.

Let me discuss todays' problem areas of neuropsychopharmacology under three headings — the methodological, the moral and the social. In the area of methodology we are being confronted by frustrating scientific dilemmas. In the moral area, troublesome conflicts of conscience have arisen. And in the social field we are facing the compelling social and legal problems of the contemporaneous drug scene, of the worldwide misuse of psychotropic drugs for non-medical purposes.

None of these problems existed — or were even suspected — when some of us started our research in the early phases of psychopharmacology. At that time, in the 1950's, what mattered to us most was discovering the effects of the new drugs which had made such a spectacular appearance, like unexpected realizations of a science-fiction phantasy. Next we wanted to make certain that our first

observations were really valid beyond any doubt. Finally — having gotten the taste of the thing and having become somewhat greedy — we wanted to discover more and more drugs with new and ever more dramatic effects. It was a time of inspiring enthusiasm, of naive optimism and of pragmatic empiricism. It was gold rush time — when pioneers needed little more than a lot of energy and a little luck to make valuable discoveries.

But now times have changed. No longer are energy and luck all that is needed; no longer can we blithely trust in serendipity; no longer can we dream expansively of easy and dramatic "breakthroughs". Neuropsychopharmacology has become a serious science with all its gnawing uncertainties of methods and theories, with all its rapidly rising needs for greater rigor and more sophisticated instrumentation, with all its grinding slowness of progress and lack of glamor in its day-to-day work — in short, with all the properties which characterize any modern research.

Methodological problems

At that early time, when psychopharmacology came into being and had to prove its claims, it was only natural that it fell back on statistics. The new generation of computers had just been born and made it possible to apply statistical procedures of previously undreamt-of complexity. The need to prove its claims, combined with the opportunity to do so easily with the aid of computers, made the statistical model the mainstay of all psychopharmacological research. But since human transactions were involved in these investigations, special procedures, designed to neutralize any potential bias, had to be employed routinely. Thus, double-blind control became the generally accepted methodology.

Statistics and double-blind-based experimental designs were indeed useful and necessary developments, but unfortunately they soon seemed to absorb almost all creative energy of those who were engaged in the new science; and psychopharmacological research threatened to deteriorate into an unceasing repetition of uniform, controlled clinical trials, a form of pharmacoclinical engineering which today is still dominating most of our investigational efforts and has for a long time stifled creative imagination and fresh investigational approaches. But now, in addition to being static and sterile, the very basis of our methodology — of which we could,

rightfully, be so proud 15 years ago — is no longer trusted as a solid foundation.

Several major attacks have been launched against it. Statisticians have pointed out that most clinical trials in psychopharmacology may be invalid because the patient samples are usually of such small size that they do not allow for the application of statistical procedures which would be powerful enough to avoid type II error, i.e. statistical analysis might not reveal any significant differences when such differences in fact exist (OVERALL, HOLLISTER, DULAL, 1967).

The second major attack on present methodology points to the doubtful homogeneity of many, if not most, of patients' experimental and control groups. Homogeneity of the sample is a *sine-qua-non* condition for nearly all our statistical methods. However, in the absence of objective criteria for almost all psychiatric conditions, the only means for constructing homogeneous samples based on measurable data today are our behavior rating scales, personality inventories, and structured interview schedules.

Yet, some clinicians protest that the use of such "instruments" for the "objective" rating of patient's behavior is a procedure of doubtful validity. Perhaps it represents the best we can do at this time to reduce subjectivity of evaluation of behavior, but this is far from being objective, and the data derived from behavior rating scales and similar devices are only as valid as is the clinical judgement of those who score them (LEHMANN, BAN, DONALD, 1965).

Faced with these difficulties, the investigator in psychopharmacology is now confronted with this conflict: either he increases the size of his patient and control groups to satisfy the statisticians, which means that he sacrifices much of the homogeneous quality of his groups — or he insists on the best possible quality of his groups, i.e. on the highest homogeneity which can only be assured by very intensive clinical study going beyond the routine use of rating scales; and this means that he accepts to work with comparatively small samples.

Because we have not yet solved these problems, we find ourselves today in a situation where different researchers often report conflicting results, although they have used identical experimental designs and control measures. This forces us to resort to some kind of "scoreboard" approach, where we apply homemade statistics to the number of published positive and negative outcomes of the same

experiment while we use personal weightings, based on questionable "ad hominem" evaluations of the competence of the various investigators who have reported these conflicting results.

This is certainly a highly unsatisfactory state of affairs. Should we nevertheless continue with our present system of counting heads and symptoms and continue to draw conclusions on the effects of psychotropic drugs exclusively from empirical observations which are derived from extensive clinical trial designs? Or should we conclude soberly that the old approach, which psychopharmacology has so successfully applied for two decades, is no longer likely to reveal worthwhile new substances, i. e. drugs which either produce radically new effects or are significantly more effective — or safer — than any existing drugs? Is it not time now to make the fateful decision to abandon — at least partially — the well-oiled machinery of traditional clinical trials of new drugs?

Possible alternatives would be the use of individual-oriented "intensive" experimental designs, which Chassan (1967) has proposed, instead of the presently used, group-oriented extensive designs, and the application of the medical model rather than the statistical model as the heuristic foundation of neuropsychopharmacology.

After all, we must not forget that whatever reasoning is contained in our present investigational system in psychopharmacology is mainly based on analogy, i.e. the analogy of certain animal models. For example, alterations of avoidance conditioning behavior, induction of catalepsy and prevention of stereotyped chewing following amphetemines in rats, constitute a paradigm for antipsychotic effects of unknown substances in man. Other empirically collected, behavioural contingencies in animals serve as models for antidepressant or antianxiety drug effects in man.

This has always been considered an extremely questionable working hypothesis by some clinicians who found it difficult to accept mere empirical coincidences — of very different behaviors in very different species — as the heuristic basis for the discovery and testing of psychotropic drugs in man. Supporting this doubt, Hekimian, Gershon and Floyd (1970) in a recent paper demonstrated the lack of validity of such assumed coincidences on the basis of four different drugs, all of which fitted well the generally accepted animal model for antidepressants but were clinically ineffective.

On the other hand, examples of the slowly rising importance

of psychopharmacological research along the lines of the medical model can be found in the increasing number of drug studies based on the biogenic amine theory of affective disorders (COPPEN, 1967), (SCHILDKRAUT, 1965) and the transmethylation hypothesis of the schizophrenias (BAN, LEHMANN, 1970). Studies of this type represent the medical model, in that they are founded on theories of action mechanisms rather than on empirical trial and error methods. Thus, they offer the possibility of testing systematically not only the final, global effects of drugs, but also each intermediate, predicted, metabolic step by means of objective — biochemical or neurophysiological — criteria.

There is much to recommend this turning towards the medical model in modern psychopharmacological research — not the least of the benefits being the reconstruction of the almost lost methodological links between psychiatry and the rest of medicine. But we will also have to guard against the danger of throwing away the baby with the bathwater, lest we will be putting now all our energies into this kind of research effort to the exclusion of all potential gains that may still lie hidden in more empirically oriented or also in more speculative, psycho-socially founded areas of investigation which may even aim at "the establishment of a transactional relationship between psychopharmacology and psychoanalytic metapsychology" (ORNSTEIN, WHITMAN, 1965.) Also, we must keep in mind that investigators following the medical model are exposed to their own dilemmas, arising out of conceptual and methodological problems which characterize this particular approach because of the close relationship of psychopharmacology to the ancient epistemological mind-body problem (LEHMANN, to be published).

ETHICAL UNCERTAINTIES

I remember how a colleague asked me 17 years ago whether I did not feel any pangs of conscience whenever I decided to treat a schizophrenic patient with chloropromazine instead of insulin coma. Nowadays, the two or three ethics committees which must first review every research project involving the use of new drugs in patients would relieve me of much of the personal responsibility which in those days every investigator had to carry alone.

Yet few of us then had thought the problem through. True, insulin coma therapy was clearly the best of the three recognized

treatments of schizophrenia around 1950; the two others were electroconvulsive therapy and lobotomy. Every new treatment was a venture into the unknown. Yet it seemed to be obvious to me that hypoglycemic therapy, with which I had extensive clinical experience, was much more dangerous and much less effective than pharmacotherapy with neuroleptics. This clinical impression proved to be right in the end, but at the time I was certainly naive in believing that my personal conviction was all that mattered.

We know now that serious mistakes may result from conclusions and actions based on uncontrolled observations. We have learned that the patients' informed consent is an essential prerequisite for applying any new and experimental treatment. But are we sure of what we mean by "informed consent"? The World Medical Association, in the "Declaration of Helsinki" (1964), stipulates that the physician must explain to the subject of clinical research all the risks involved. Others have added that the patient should also be informed that not all of the risks are known. Some advise, therefore, that a statement be added to the effect that it is always possible that unforeseen things may happen since some drugs produce serious and even fatal results. But, as BEECHER (1962) has rightly pointed out, no one could soundly consent to such a risky proposition, and it has been stated that the principle of informed consent is, of course, accepted by all, but that its feasibility in all situations is doubtful (LASAGNA, Von FELSINGER, 1963). The Food and Drug Regulations in the U.S. require that every investigator obtain a signed consent from all participants in a clinical drug trial, "except where this is not feasible or, in the investigator's professional judgement, is contrary to the best interests of the subjects."

One may easily conceive a real conflict between an investigator's ethical conviction that it would not be in the best interest of his patient to inform him — for instance in the case of a very anxious or hypochondriacal patient — and the investigator's understandable concern that he might be legally held responsible if he acts on this ethical conviction.

Another generally accepted principle is that prospective subjects for any experiment involving drugs must have given their consent freely. At first glance this seems to be a straightforward proposition. However, if the definition of "free" consent is to be interpreted as excluding any direct or indirect pressure exerted on the subjects

by the investigator or the circumstances surrounding the experiment we are faced with a tough problem. A patient's sickness by itself may put him under some pressure to volunteer for a clinical experiment. Such motivation would, I suppose, be acceptable to most. On the other hand, MORRIS (1967) points out that ideally none of the following should be allowed to volunteer: "minors, the very elderly, the very poor, prisoners, patients suffering from fatal, incurable or seriously debilitating diseases, the insane or seriously emotionally disturbed, personnel in the Armed Forces, medical students, laboratory workers and conscientious objectors". If one would accept these restrictions, there would certainly not be enough motivated and eligible subjects left to allow even the most modest clinical research to continue. Even the acceptability of tangible rewards for subjects, e.g. money, has been questioned.

Not everybody realizes that a written form does not *per se* constitute legal consent, although the form is important evidence as a memorandum of the discussion and agreement. The responsibility for clinical research never falls on the subject but always remains with the research worker. This implies, of course, the possibility of financial liability and compensation (Editorial, 1967).

In a recent article in the journal "Science", HAVIGHURST (1970) expresses his surprise and concern over the fact that ethical considerations until now have almost exclusively focused on preventive and consensual aspects and do not seem to enter into the question of what should be done for a research subject when he has been injured during a clinical experiment. He suggests that government and drug industry could provide for insurance through mechanisms yet to be developed. Moreover, he argues that in such an insurance scheme the primary decision maker's (e.g. the research institution's) financial incentive should to some extent also remain involved, to make sure that the risks of the experiment do not exceed the potential social value of the research. He points out that "reliance on ethics alone would neglect the small but critical class of cases at the margin, where ethics may be weak and peer groups inattentive, but where economic instincts may be especially acute." I am inclined to agree with the author's thesis that research institutions and the drug industry ought to share the ethical obligation to provide such insurance coverage for subjects of psychopharmacological experiments and clinical trials.