



# NEURO- PSYCHOPHARMACOLOGY

PROCEEDINGS OF  
THE FIRST INTERNATIONAL CONGRESS  
OF NEURO-PHARMACOLOGY

*(Rome, September 1958)*

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## PREFACE

This volume contains the proceedings of the First International Congress of Neuro-Psychopharmacology and will be the first of a series. The meeting, which was held in Rome in September 1958 and which was attended by more than 500 delegates, representing 26 different countries, was organised by the International Collegium for Neuro-Psychopharmacology.

The idea for founding the Collegium originated during an earlier meeting in Milan in the Spring of 1957, under the title "Psychotropic Drugs". During this meeting, a small group of interested people representing various disciplines (pharmacology, psychiatry, psychology etc.) held informal discussions and decided that regular opportunities should be provided for the workers in these various fields of research and clinical investigation to meet and to discuss their common problems.

The Second International Congress of Psychiatry, held in Zurich in September 1957, was the scene of the formal inauguration of the Collegium for Neuro-Psychopharmacology. Much of the preparatory work had already been done by the time this meeting was held and the newly elected Executive Committee was given the task of organising the first international Congress of the Collegium. Plans were immediately put in hand for this meeting to be held the following year and Professor Trabucchi's offer to be host was readily accepted. Our thanks are due to the local organising committee which met under his Chairmanship, for all the local arrangements in Rome.

The meeting proved to be such a success that it was decided to publish the proceedings and, on the last day, the Executive Committee appointed three of its members to undertake this task, although at this time the delegates were already beginning to disperse and no publisher had been approached. That this book has in fact been produced is largely due to the friendly co-operation of the publishers who agreed to publish it although very little was known about its contents at that time. We wish to thank them for their patience and forbearance. We are grateful to the authors of papers presented at the meeting who provided manuscripts so quickly and for voluntarily reducing the size in many cases when it was found that we had too much material for one book. We are particularly indebted to those authors of communications who agreed to publish an abstract of their papers, since this enabled us to include all the communications submitted. We regret that some contributions are missing, either because the authors declined to provide a manuscript or because they were received too late for inclusion in the book. It was felt that the value of such a publication would diminish as the time interval between its appearance and the date of the meeting it represented was increased. With this in mind, we were obliged to set a rigid deadline for the acceptance of papers.

It is hoped that this book will serve a twofold purpose. The first part, comprising the Symposia and Plenary Sessions provide the reader with reviews of various aspects of experimental and clinical investigation, together with discussion by various experts in the related fields. The second part contains 133 short papers presenting

the results of recent investigations which have not been reported elsewhere. These papers cover a wide range of topics and provide an introduction to current research in the fields of Neuro- and Psycho-Pharmacology. Whilst it should be pointed out that it is only by chance that this section of the book is the larger, the Editors feel that this is as it should be, since it is only by stimulating more research that we are likely to advance our knowledge of the brain.

July 1959

P. B. BRADLEY

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## OPENING ADDRESS

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Ladies and gentlemen, it is obvious that this address, on the occasion of the first meeting of our Collegium, should approach some of the basic problems of psychopharmacology, a field of medicine integrating the theoretical and therapeutical points of view. Psychopharmacology is as old as medicine itself, inasmuch as plants inducing peculiar changes in emotional and psychic behaviour have been in use for centuries and are still used, either for personal pleasure or for ritual ceremonies. Important precursory and even anticipatory studies have been made in the past. I shall limit my reminiscences, however, to some studies of our century by mentioning the chemical treatment of psychoses by the "Dauerschlaf" with barbiturates (KLAESI AND CLOETTA), shock therapy with insulin (SAKEL) or cardiazol (MEDUNA) on the one hand, and on the other the contributions to an experimental basis for psychopharmacology by the vanguard of progress in neuroanatomy, neurophysiology, psychology, psychiatry and psychoanalysis. However, psychopharmacology of today, as a science exploring the influence of chemical substances upon psychic and emotional behaviour, takes a new trend. The following events have favoured the increasing interest in psychopharmacology:

1. The new and fruitful ideas about cerebral activity and the application of new methods in normal and abnormal conditions.
2. The great augmentation in psychic morbidity in the form of neuroses and psychoses.
3. The present humanitarian concern in social welfare and mental health.
4. The main factors which favoured this movement are two unpremeditated lucky events which provoked an overall, but primarily American, animating drive in psychopharmacology.

In 1943, Dr. HOFMANN, working on the synthesis of lysergic acid diethylamide (LSD), inadvertently ingested a minute quantity of the substance. The effects produced caused him to repeat the experiment deliberately, by taking 0.25 mg by mouth, and this produced the same bodily and psychic changes but in a much stronger degree, since later experiments proved that 0.5–1.0  $\mu\text{g/kg}$  was the average effective oral dose in man. STOLL carried out the first thorough psychiatric study and this was confirmed and supplemented by numerous other workers. The peculiar effects of LSD on psychic behaviour evoked considerable interest amongst both experimental workers and clinicians. This discovery, which was primarily of theoretical interest, was followed in 1952 by that of LABORIT *et al.* of chlorpromazine. They were concerned mainly with the problem of hibernation, their purpose being to avoid the undesirable and noxious alterations caused by automatic reflexes in long surgical interventions. The

new synthetic anti-histaminic compound met this requirement by potentiating the effect of barbiturates. Yet, the main importance of this discovery was that this compound acted upon the emotional and psychic behaviour in psychiatric patients. DELAY AND DENIKER described in the same year the therapeutic effects of chlorpromazine in psychosis: obvious indifference, retardation of the responses to external stimuli, decrease in initiative and preoccupation, emotional and affective neutrality, and these effects occurred without significant alteration of the vigilant consciousness or the intellectual faculties. These two events were the outcome of excellent observation of unexpected, but well-perceived properties of these two compounds. The closely following development of reserpine, with a similar action to chlorpromazine, was based upon an empirical and thorough course of pharmacological and therapeutic studies. These discoveries initiated a great impetus for any kind of scientific approach to brain research as well as for revolutionary consequences in the treatment of psychotic patients. The incentive was not limited to theoretical and practical medical sciences but caused an even greater stimulus to the imagination of chemists, leading to the production of new compounds with a speed that neither pharmacological, biochemical nor clinical investigations could equitably follow.

Are our expectations for these drugs exaggerated? Before I answer this question, let me briefly consult the basic knowledge provided by those divisions of research dealing with psychic and emotional functions. With regard to the "psyche" and its manifold qualitative functions, as a natural scientist, I shall only consider the facts so far revealed by the methods of natural science. I have nothing to deny or confirm with regard to metaphysical views and speculations on this subject. The ever present discussion of the problem of whether the psyche is bound to the functions of the brain, comparable to the physical and chemical cell activities of other organs, has always been full of controversy and discrepancies. Natural science has to face the contemporaneous philosophical viewpoints, as well as religious convictions. The situation in 1921 was well characterised by the publication of EUGEN BLEULER's book *Natural History of the Soul*. He said that some people may call him a fool for admitting that the "psyche" is bound to cerebral functions, but since he was in the company of outstanding men like EXNER and LOEB, who were assumed not to be fools, he hoped the best for himself.

There are numerous objective facts that brain function and mind are in intimate connection and interdependence. They are genetical, physical, chemical and psychical in nature, specific and unspecific in character.

Brain evolution in structure and size parallels the development of mental faculties in animal and human evolution. Changes brought about by physical trauma are obvious and neurosurgical interventions have taught us much about the location of cerebral function. The high susceptibility of the brain to oxygen deficiency is well known. With chemical substances, we are able to diminish different aspects of brain function, such as sensitivity to pain, production of sleep or unconsciousness by barbiturates and with psychotropic drugs we can influence various functions qualitatively. Last, but not least, psychic trauma can produce emotional shock.

The difficulty in paralleling mental and physical functions seems to lie in the ambiguous concept we have for psychic manifestations in contrast to the "apparent comprehension" with which we approach the physical and chemical processes of other organs. But brain activity, including psychic and emotional behaviour may be stimulated, inhibited or modulated in exactly the same way as that of other organs. In addition, we accept physical defects by trauma, tumours or surgical intervention

as causes of "organic psychoses". Thus, our general patho-physiological concept of functional disorders in any organ suggests that unknown physical and chemical disturbances of neuronal activity may be the causes of "functional psychoses".

In considering the fundamental contributions from different divisions of psychopharmacology, we find that the brain is far from being a homogeneous organ. Our knowledge of the differentiated morphological structure and organisation of the neurones, *i.e.* perikarya, fibre patterns and synaptic systems has been advanced by new methods, such as histo-chemistry and electron- and X-ray microscopy. The relatively great size of the brain, together with the enormous number and variety in shape of the neurones and of their connective patterns, are all suggestive signs of the complexity of brain activity. The finding by SHOLL that one afferent axon in the cerebral cortex may influence 5,000 other neurones and that each of the latter may embrace the action field of another 4,000 neurones, illustrates the enormous complexity of neuronal interaction.

Our knowledge of brain function has been admirably advanced in the last few decades by neurophysiology, neuropharmacology, and psychology. Modern electrophysiological techniques enable us to study nervous activity objectively. Using micro-electrodes implanted in any part of the brain for electrical stimulation as well as for measuring bioelectric changes, the investigator can follow simultaneously in unrestrained and unanaesthetised animals the changes in behaviour and bioelectric potentials induced by physiological and pharmacological modifications in the experimental conditions. With such microtechniques, it is even possible to study single neuronal units and to differentiate the specific activity of the cell body from that of the dendrites and their different synaptic systems. Electroencephalography enables us to perform similar studies to a certain extent in man as well. The main aim of these electrophysiological investigations is to detect a relationship between nervous function and anatomical structure. This is the fundamental problem in the localisation of the numerous functions of the brain. The technical difficulties of such procedures are obviously very great and therefore the analysis of the results obtained requires the greatest caution. However, they provide evidence for the following facts:

1. The patterns of psychic and emotional behaviour do not depend exclusively upon the activity of the cerebral cortex (PAVLOV) but also on subcortical areas such as the thalamus, hypothalamus, reticular activating and limbic systems and rhinencephalon.

2. These parts of the cerebrum represent areas or "centres", where co-ordinating processes are focussed, thus acting as the associative apparatus for afferent and efferent impulses in horizontal and vertical directions.

3. The result of these functionally correlated associative areas is the integration of activity and that is the basic task of the brain. Therefore the heart of the problem of psychic and emotional behaviour lies in the integration of simultaneously acting cerebral functions. The "psyche" or Ego, in inconceivable complexity acts in any situation as a unit which stipulates almost complete synchronism of the cerebral processes localised in various parts of the brain. This synchronism is insured by the extremely rapid speed of nervous propagation. Thus, modification of the propagation of nervous impulses by physical or chemical means could be a cause of functional disorder.

4. The most interesting properties of cerebral neurones are not those directly

related to their excitability, *i.e.* stimulation and inhibition, but the modulating influences of nervous impulses by facilitation, summation, recruitment, potentiation and interference with stimulation and inhibition.

Psychophysiology and psychopathology have also made important contributions to our knowledge of mental activity. They demonstrate the complexity of the problem since, in no other field of research, has terminology so much individual or personal meaning. Hence, mutual misunderstanding frequently occurs. Psychology relies on observations of the subject's own Ego or on that of other individuals under normal and abnormal conditions. The purpose of psychopharmacology is the study of changes in behaviour provoked by chemical means. It seems pertinent to distinguish the classical experimental psychology, initiated and well developed by WUNDT, from the newer, analytical method introduced by FREUD. Experimental psychology isolates and examines elementary psychic reactions. It is far from giving coherent comprehension to integrative cerebral activity by neglecting the plasticity and variety of the individual psychic life. The weakness of experimental psychology lies in the fact that the results observed are not brought into relation with the individual acting as a functional psychic unit, a view needed for therapeutic psychology as well as for psychopharmacology.

C. G. JUNG describes what I mean when he says that for a scholar interested in human psychology, it would be advisable to say good-bye to his books and to travel instead, to experience with a warm heart and human feeling all the horror of the prisons, asylums and hospitals, saloons, brothels and gambling places, the drawing rooms of high society, political meetings, churches, revivalist meetings and other sects, to experience love and hatred and passions of all kinds. He would come back with a richer knowledge than could be found in the thickest volume and be a true physician to his patients and a connoisseur of the human soul.

We must therefore not fail to consider the importance of unavoidable environmental influences in experimental and therapeutic studies of psychic and emotional behaviour. There is the experimental finding that psychotropic drugs may be much less active in single investigated animals than in a collective group even under otherwise identical experimental conditions. How much more will that be the case in the highly organized and differentiated human being. It is my conviction that this kind of analytical psychology is not only a valuable tool in psychoanalysis and psychotherapy but can contribute to psychopharmacology by deepening our understanding and favouring experimental research in psychic and emotional behaviour. Experimental psychopharmacology, in more or less the same state as experimental psychology, can only profit by considering systematically the integrating procedure of analytical psychology.

Two trends of research have developed in psychopharmacology today. On the one side, the purpose is to find out if psychotropic compounds are able to produce psychic syndromes, similar to those occurring in neuroses and psychoses (psychotomimetics), and on the other, to determine whether psychotropic substances may influence neurotic or psychotic states. These are the psychotropic drugs or tranquillizers; an unprecise definition which I use only for convenience. With regard to the therapeutic benefits of tranquillizers, the answer is easy, as it is undoubtedly positive. It is not my purpose to differentiate between the numerous compounds which have emerged since 1952. Chlorpromazine and reserpine have proved to be valuable drugs in the treatment of psychotic states with pronounced psychomotility. The therapeutic effect of these classical tranquillizers is an empirical fact, inasmuch