ADVANCES IN
PHARMACOLOGY AND THERAPEUTICS
Proceedings of the 7th International
Congress of Pharmacology

General Editors: J. R. BOISSIER, P. LECHAT & J. FICHELLE

Volume 7

BIOCHEMICAL CLINICAL PHARMACOLOGY

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Editor

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Introduction

The scientific contributions at the 7th International Congress of Pharmacology were of considerable merit. Apart from the sessions organised in advance, more than 2,200 papers were presented, either verbally or in the form of posters, and the abundance of the latter in the congress hall is a good indication that this particular medium of communication is becoming increasingly attractive to research workers, and offers scope for discussions which combine an elaborate, thorough approach with a certain informality.

It would have been preferable to have published the entire congress proceedings within the framework of the reports. That was, however, physically impossible, and the organisers had to adopt a realistic solution by publishing only the main lectures, symposia and methodological seminars. The amount of material presented necessitated the printing of ten volumes, each volume containing congress topics regrouped according to their relevant content and subject areas. This system of division may give rise to criticism on account of its artificiality, and we readily admit that certain texts could have been placed in more than one volume. We are asking the reader to excuse this arbitrariness, which is due to the editors' personal points of view.

I draw attention to the fact that most of the symposia finish with a commentary which the chairmen had the option of including, presenting their personal opinions on one or several points. We think that such an addition will facilitate reflection, discussion, indeed even controversy.

The launching of the scientific programme for this congress began in September 1975 on returning from the last meeting in Helsinki. Long and delicate discussions took place in the Scientific Programme Committee and with the International Advisory Board. Should it be a pioneer, 'avant-garde' congress? Or one laid out like a balance-sheet? Should we restrict the congress to the traditional bounds of pharmacology, or extend the range of papers to cover the finest discipline? The choice was difficult, and the result has been a blend of the two, which each participant will have appreciated in terms of his training, his tastes, and his own research.

A certain number of options, however, were taken deliberately: wide scope was given to toxicology, from different points of view, and to clinical pharmacology, a subject much discussed yet so badly practised; the founding of two symposia devoted

to chemotherapy of parasitic diseases which are still plagues and scourges in certain parts of the world; a modest but firm overture in the field of immunopharmacology, which up until now was something of a poor relation reserved only for clinical physicians; the extension of methodological seminars, in view of the fact that new techniques are indispensable to the development of a discipline.

We have been aware since the beginning that, out of over 4,000 participants who made the journey to Paris, not one could assimilate such a huge body of knowledge. Our wish is that the reading of these reports will allow all of them to become aware of the fantastic evolution of pharmacology in the course of these latter years. If one considers pharmacology as the study of the interactions between a "substance" and a living organism, then there is no other interpretation. Nevertheless, one must admit that there exists a period for describing and analysing a pharmacological effect, and that it is only afterwards that the working mechanism can be specified; a mechanism which will permit these "substances" to be used for the dismantling and breaking down of physiological mechanisms, a process which justifies Claude BERNARD'S term, "chemical scalpel".

The reader will be able to profit equally from more down-to-earth contributions, more applied to therapeutics, and less "noble", perhaps, for the research worker. He will realise then that his work, his research and his creative genius are first and foremost in the service of Man, and will remember this statement from Louis PASTEUR:

> "Let us not share the opinion of these narrow minds who scorn everything in science which does not have an immediate application, but let us not neglect the practical consequences of discovery."

I would like to renew my thanks to my colleagues in the Scientific Programme Committee and also to the members of the International Advisory Board, whose advice has been invaluable. I owe a particular thought to J J BURNS, now the past-president of IUPHAR, who granted me a support which is never discussed, and a staunch, sincere friendship. The Chairmen have effected an admirable achievement in the organisation of their proceedings, and in making a difficult choice from the most qualified speakers. The latter equally deserve our gratitude for having presented papers of such high quality, and for having submitted their manuscripts in good time.

The publisher, Robert MAXWELL, has, as always, put his kindness and efficiency at our service in order to carry out the publication of these reports. But none of it would have been possible without the work and competence of Miss IVIMY, whom I would like to thank personally.

My thanks again to the editors of the volumes who, in the middle of the holiday period, did not hesitate to work on the manuscripts in order to keep to the completion date.

Finally, a big thank you to all my collaborators, research workers, technicians and secretaries who have put their whole hearts into the service of pharmacology. They have contributed to the realisation of our hopes for this 7th International Congress, the great festival of Pharmacology. Make an appointment for the next one, in 1981, in Tokyo.

Jacques R BOISSIER

Chairman

Scientific Programme Committee

Contents

Clinical implications of plasma protein binding of drugs

Subcellular distribution of drugs

Stable isotopes and application to pharmacology

Applications of immunological assays for pharmacology

New physical methods in pharmacology

Biochemical Assessment of Drug Action in Man

The Use of Biochemical Pharmacology in the Assessment of Drug Action in Man

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Pharmacology is a discipline which inherently integrates and mirrors the development in many other sciences. It has emerged from the old knowledge of materia medica generated through thousands of years. Influenced from techniques and concepts in classical physiology and pathology it became an experimental discipline of its own. The classical pharmacologist or general pharmacologist is to-day almost a vanishing species. The smoked drum has been replaced by scintillation counters, electronic amplifiers, computers and mass spectrometers. General pharmacology has evolved largely in two directions. Firstly towards studying biochemical mechanisms of drug actions, creating new subdisciplines such as biochemical pharmacology, with sub-subdisciplines such as molecular pharmacology and receptor pharmacology. Secondly the development of techniques for assessment of therapy in man has resulted in the development of clinical pharmacology. Lastly the impact of drug therapy on society has fostered a new subdiscipline, namely social pharmacology. This science studies patterns of drug consumptions by society, its causes and consequences.

The topic of to-days symposium is to examine the link between biochemical and clinical pharmacology. A scheme showing some of the interrelationships in this border line area is shown in Fig. 1.

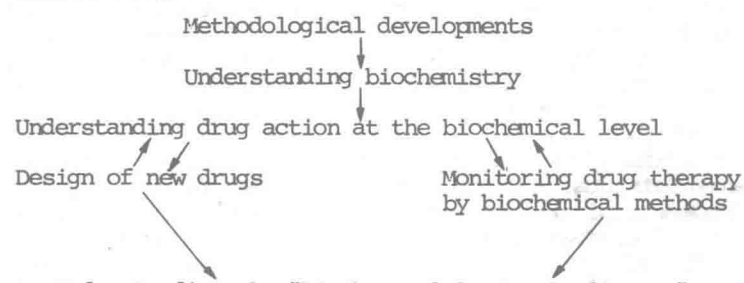

Fig. 1. Relationships between biochemical and clinical pharmacology.

Methodological developments

The expansion of knowledge in biochemical pharmacology has largely been due to the use of new and ever more powerful techniques for the study of life events at the molecular level. Those of us who are a bit older will recall the tremendous impact on biochemistry and pharmacology by the optical spectroscopic methods and by fluorometry. Purification of specific enzymes and the use of radioactive substrates for labelling in radioenzymatic techniques is another example of a useful biochemical technique employed by pharmacologists in the last decade. The availability of compounds labelled with radioactive isotopes has also permitted the development of radioreceptor assays such as that developed by Dr Terenius and others for the opiate receptor, and of radioimmunoassays. The beauty of these techniques are that they are simple, sensitive, inexpensive and yet fairly specific, the specificity being inherent in the macromolecules provided by Mother Nature and characterized by the scientist.

Finally the developments in biochemical separation methods have been a key factor in the generation of new knowledge. The power in the latest separation system, e.g. high performance liquid chromatography (HPLC) and capillary gas chromatography is truly staggering up to 100.000 theoretical plats in one column. With the coupling of gaschromatography with computerized mass spectrometry these superb separation tools are interacted with sophistaceted systems for collecting, and storing structural information of the multitude of separated components. Such systems, although expensive and rather difficult to operate successfully, can on the whole generate information more quickly than most scientists are prepared to receive and digest. Problems which previously could take months or years of a qualified biochemists working life can now be solved in one or two days. The production of new knowledge is almost overwhelming - in Alvin Toflers words a scientific "future shock".

Understanding biochemistry and the "biochemical lesion" of disease

The development of biochemistry has resulted in a more comprehensive and dynamic knowledge of the synthesis, metabolism and function of the body constituents. Of particular interest to the art of therapeutics are the discoveries of a series of novel major bioregulators e.g. the catecholamines, histamine, cyclic nucleotides, peptide and steroid hormones and the prostaglandins. These bioregulators are switches which turn specific part of the biochemical machinery on and off. The knowledge of the structure of these compounds and the nature of their interaction with their sites of action (receptor pharmacology) has permitted the design of new drugs. Examples of new drugs emerging from receptor pharmacology are the β-adrenergic receptor antagonists for the treatment of hypertension, histamine H_2 receptor antagonists for the treatment of peptic ulcer, dopamine receptor antagonists for the treatment of schizophrenia, and dopamine receptor against for the treatment of Parkinson´s disease. Many other examples can be given.

Another aspect of the advances in biochemistry has been a revision of the domination of Pasteurian ideas and anatomical techniques in pathology. It has shown that many diseases originate from some biochemical trouble. The concept of the biochemical lesion of disease was promoted by Sir Rudolp Peters, who coined the name (ref. 1). The earliest examples of such biochemical lesions were the demonstration of avitaminosis and certain inborn errors of metabolism. Current research indicate biochemical lesions in the patophysiology of many diseases. Some of these are listed in Table 1.

TABLE 1. The "biochemical lesion" theory of disease

(Sir R Peters)

Classical theories

Avitaminosis

Poisoning with Lewisite

Inborn errors of metabolism

Developing theories

Hyperfunctioning dopamine system in schizophrenia?

Hyperfunctioning histamine system in peptic ulcer?

Hyperfunctioning renin-angiotensin system in renal hypertension?

Hyperfunctioning prostaglandin system in Bartters syndrome??

Hypofunctioning renal prostaglandin system in low renin hypertension??

To further illustrate this type of development I shall choose an example from my own field. Research in biochemistry has established structure, biosynthesis and metabolism of the prostaglandins. Studies in biochemical pharmacology showed that loading with the PG precursor arachidonic acid was a good way to stimulate the PG system and that aspirin or indomethacin could be used to inhibit the PG syntheses. We applied these observations in a study to determine if the PGs were involved in the mechanism of renin secretion from the kidney (ref. 2). The effect of arachidonic acid was to stimulate release of renin (Fig. 2) and that of indomethacin to depress basal renin release and to inhibit the response of arachidonic

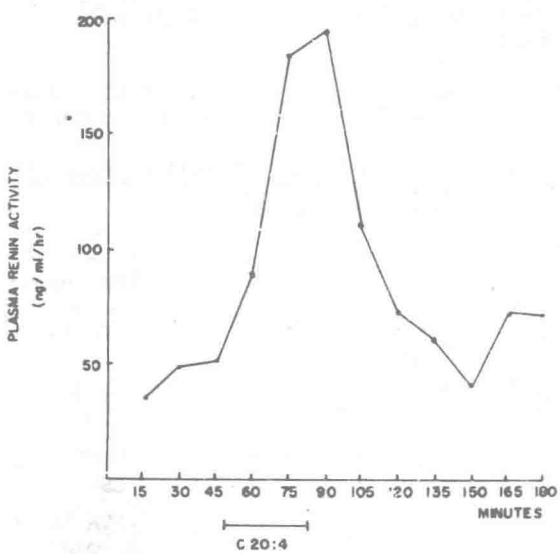

Fig. 2. Plasma renin activity (ng/ml/hr) before and after the infusion of C20:4.

acid. The inhibitory effect of aspirin-like drugs on renin release was later demonstrated in man. This in turn led clinical scientists to try indomethacin in cases of Bartter's syndrome, a disease characterized by hypersecretion of renin, hypertension and disturbancy of electrolyte metabolism. The results so far have been encouraging (ref. 3,4).

Biochemical assessment of drug action in man

In some diseases biochemical assessment of drug therapy is part of the clinical routine. Examples of this are given in Table 2. Since the discovery of insulin

TABLE 2 Some diseases where biochemical assessment of drug therapy is established

Disease	Drug	Biochemical response
Diabetes	Insulin	Glucose, insulin
Thrombosis	Warfarin Hydroxycoumarin	Coagulation tests
Heart failure	Digitalis	Inhibition of Na^+/K^+ transport

by Banting and Best and its use in diabetes, measuring blood glucose has been a major tool to optimize this life saving drug therapy. Other examples are the use of coagulation tests to follow the response of drugs like warfarin and bishydroxy coumarin. Dr A Breckenridge will address himself to this subject in more detail in a following lecture. The discovery that digitalis owes its inotropic effect to inhibition of the Na^+/K^+ stimulated ATP-ase has permitted the development of sensitive biochemical assays for the assay of the action of the cardiac glycosides. My cochairman Dr D Grahame-Smith will describe the recent developments in his field.

In other diseases our knowledge of the role of the detailed aspects of biochemical pathofysiology is a process of rapid development (Table 3). Biochemical

TABLE 3 Some diseases where biochemical assessment of drug therapy is experimental

Disease	Drug	Biochemical response
Renal hypertension	Converting enzyme inhibition	Angiotensin II
Bartter's syndrome	Aspirin	Plasma renin activity aldosteron, K^+
Depression	Tricyclic antidepressants	5-HIAA and HMPG in CSF
Schizophrenia	Neuroleptics	HVA in CSF Prolactin in plasma Platelet function

Biochemical pharmacological and clinical research has together put forward evidence for subtypes in many diseases. Not surprisingly some major disease entities have been found to have multifactorial biochemical etiologies. Thus different forms of hypertension are well known. In major hypertension clinics the diagnostic arsenal involves measurement of plasma catecholamines, plasma renin activity, aldosteron excretion and several other determinant of antihypertensive drug responsiveness. We shall hear more of this subject this afternoon from Dr D. Shand.

Another area, where biochemical techniques are becoming increasingly useful in determining choice of drug as well as drug responsiveness, in psychotic illness. The use of neuroleptic and tricyclic antidepressants results in changes of the levels of the renotransmitter metabolites homovanillic acid, 5-hydroxyindolactic acid and hydroxymethoxy ethylene glycol in cerebrospinal fluids and in plasma levels of certain hormones. This rapidly developing field will be discussed by Dr G. Sedvall.

Other effects of psychotropic drugs involve tissues outside the control nervous system. Since cerebrospinal fluid is relatively unaccessible for routine clinical sampling such responses are useful as indexes of drug action. One such example is the action of neuroleptics and antidepressants on the blood platelet. The platelet behaves in several aspects as a minineuron, at least in its capacity to accumulate, store and release certain neurotransmitters. Thus the uptake of labelled serotonin in platelets suspended in serum from a treated patient has been a fruitful way to determine the response of certain new antidepressants, like Chlorimpramine. Dr D. Boullin will review this area for us.

Finally the discovery of the opiate like peptides, the endorphins have opened new and exciting areas in medicine and biology. Some endorphin analoques with therapeutic potential are already available in experimental pharmacology. Recent research has also indicated that certain diseases are accompanied by changes in endorphin levels in the cerebrospinal fluid and are responsive to treatment with naloxone, a specific opiate receptor antagonist. Although this area still appears to be at a very early experimental stage the development is very rapid. We have asked Dr L. Terenius to give us the latest news.

Benefits of biochemical assessment of drug therapy.

Some of the advantages of biochemical methods in therapeutics are indicated in Fig 1. The first and major advantage is an optimization of drug therapy, both with respect to dose and dosage interval. This is well exemplified by the use of blood glucose measurement in insulin treatment of diabetes. Secondly it gives us a better opportunity for diagnosing and understanding side effects of drugs. examples of this benefit is the discovery of the association between the hypertensive crisis and eating of tyramine rich foods (e.g. cheddar cheese) during treatment with inhibitors of monoamine oxidase inhibitors, prescribed for depressive illness. Thirdly an understanding of a drugs biochemical mode of action by the physician will help him to predict drug interactions. Following a biochemical variable of drug response will also teach him what to expect. Thus psychiatrist with knowledge in psychopharmacology may want to avoid giving a tricyclic antidepressant (which stimulates adrenergic receptors by blocking transmittor uptake) with a neuroleptic (which blocks adrenergic receptors).

The bodys capacity to adapt to biochemical interventions imposed by drug molecules can result in the development of tolerance. The use of an objective drug response will reading pick up such adaptive decreases in drug responsiveness. The physician can then choose between increasing the dose or to go to alternative treatment.

Lastly the careful and well structured use of biochemical techniques together with

other methods of clinical evaluations will greatly add to our knowledge of biochemical mechanisms in human disease.

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