HYPOTENSIVE DRUGS -- HARRINGTON

HYPOTENSIVE DRUGS

Proceedings of a symposium on hypotensive drugs and the control of vascular tone in hypertension, held in London on April 5th and 6th, 1956 at the Wellcome Foundation

Edited by

M. HARINGTON
M.B., M.R.C.P.

Published by The Pergamon Press
*4 & 5 Fitzroy Square, London, W.*1

Printed in Great Britain by Page Bros. (Norwich) Ltd.

LIST OF SPEAKERS AND OPENERS OF DISCUSSIONS

PROF. C. BARTORELLI, Viale Piare 20, Milan, Siena, Italy.
MR. J. W. BILLINGHURST, Wellcome Research Laboratories, Beckenham, Kent.
DR. H. BLASCHKO, Department of Pharmacology, University of Oxford.
J. CONWAY, Charing Cross Hospital Medical School, Department of Physiology, London.
R. S. DUFF, Department of Cardiology, St. Bartholomew's Hospital, London.
M. A. FLOYER, Medical Unit, The London Hospital Medical College, Turner Street, E.1.
B. FOLKOW, Department of Physiology, University of Gothenburg, Sweden.
MR. A. F. GREEN, Wellcome Research Laboratories, Beckenham, Kent.
SIR CHARLES HARRINGTON, F.R.S., National Institute for Medical Research, Mill Hill, London.
DR. M. HARINGTON, University College Hospital, London.
DR. B. HOOD, Medical Clinic I, University of Gothenburg, Sweden.
DR. H. R. ING, F.R.S., Department of Pharmacology, University of Oxford.
J. M. LEDINGHAM, Medical Unit, The London Hospital Medical College, Turner Street, E.1.
PROF. H. MCILWAIN, Biochemical Department, Institute of Psychiatry, Maudsley Hospital, S.E.5.
J. MCMICHAEL, Postgraduate Medical School of London, Ducane Road, W.12.
DR. W. S. PEART, Medical Unit, St. Mary's Hospital, London.
PROF. G. A. PERERA, Department of Medicine, Columbia University College of Physicians and Surgeons, New York.
PROF. F. H. SMIRK, Department of Medicine, Otago University Medical School, Dunedin, N.Z.
DR. J. TRIPOD, Ciba Ltd., Basle, Switzerland.
DR. MARTHE VOGT, F.R.S., Pharmacology Department, University of Edinburgh.

DR. J. G. WIDDICOMBE, Department of Pharmacology, St. Bartholomew's Hospital, London.
PROF. C. WILSON, Medical Unit, London Hospital.
DR. ELEANOR ZAIMIS, Department of Pharmacology, Royal Free Hospital School of Medicine, London.

CONTENTS

OPENING REMARKS

SIR CHARLES HARINGTON, F.R.S.

I ASSUME that I have been asked to say a word or two in opening this symposium primarily because I happen to be chairman of a committee of the Biological Council, at whose instance the idea of this symposium was first mooted. This committee, which owes its existence in the first place to the initiative of our chairman at this morning's session, Professor BERGEL, has assumed the task of examining the general field of research on drug action, and suggesting from time to time subjects within that field which are ripe for general discussion, and subjects which require for discussion the members of more than one scientific society. It is, of course, the hope of the committee that such discussions will not only be informative of the present state of development, but will point the way to further progress.

The suggestions that are put forward by this committee can only be brought to fruition through the action of the relevant scientific societies, and it is most encouraging that in so many cases the suggestions that have been made have in fact proved acceptable to one or another society.

It has been most gratifying also that, when there has been need for help in the organization of these symposia beyond the scope of the scientific societies, this help has been forthcoming. This is, I think, the third occasion on which the Wellcome Foundation has shown the greatest generosity in offering hospitality, without which neither this meeting nor the previous ones on histamine and anticholinesterase could have been so pleasantly and so satisfactorily arranged; we must all feel deeply grateful to the foundation for their action. We can only hope they will feel rewarded by the scientific value of the discussions which are to take place.

The fact that it has been thought worth while to organize this particular meeting is an illustration of the advances that have been made in this particular branch of pharmacology and therapeutics, and also of the urgency of the medical problem of the control of vascular tone in hypertension.

The actual programme illustrates well the present state of affairs, in which some progress has been made towards the solution of the

problem, but in which still more remains to be done. After all, it is only within the last ten years or so that drugs have been discovered which are of real clinical value in the control of hypertension. But, as so often happens when a discovery of this sort is made and a new field is opened up, the number of drugs with therapeutic possibilities in this direction is now rapidly increasing.

I, personally, welcome the invitation to say a word or two on this occasion for two reasons; the first is that it gives me an opportunity of referring to the development of the earliest practically useful drugs, namely the methonium series, which took place largely in the National Institute for Medical Research, and in doing so of paying a tribute to the memory of my former colleague and friend, HAROLD KING, whose death we have had recently to mourn. At the same time I am enabled to ride one of my own hobby horses, in that the story of the development of the methonium drugs, in so far as it concerned the National Institute, seems to me to be a model example of the way in which things ought to happen but do not always happen in research institutes.

In saying this of course, I do not for a moment mean to suggest that the credit for the development of the methonium drugs belongs entirely to the National Institute of Medical Research; on the contrary, much is owed to the work of others, and particularly to that of Dr. ING and his colleague, Dr. BARLOW, who themselves synthesized a series of polymethylene bisquaternary ammonium salts, their interest lying chiefly in the possible so-called curare-like action of such salts. It was however the work of KING on the curare alkaloids which I think really opened the way to the systematic pharmacological work that has proved so profitable. KING's research on curare was a masterly series of investigations extending over many years, and leading from the isolation of d-tubocurarine in the pure state to the determination of the constitution of this alkaloid. This research might well not have been undertaken by him but for the inspiration of the interest in substances affecting nervous conduction and neuromuscular transmission which existed in Sir HENRY DALE's laboratory in the institute for so many years. It was certainly this interest which led KING to speculate on the possibility of reproducing curare-like activity in simple synthetic compounds, and hence to encourage Dr. ZAIMIS to synthesize a long series of polymethylene bisquaternary ammonium iodides. It was again the same interest that ensured that these compounds received a thorough pharmacological investigation by KING's colleagues, particularly by Dr. PATON in collaboration with Dr. ZAIMIS herself, which revealed

the unexpected and powerful ganglionic blocking action of the hexamethylene salt, and it is this discovery which is the real basis for this symposium.

The point I wish to make is, I think, a fairly obvious one; KING's work on curare, wherever and with whatever object it had been done, would have stood in its own right as a considerable scientific achievement; under less favourable circumstances, however, this work might have remained on record only as a classical exercise in organic chemistry. Similarly, a pharmacological investigation of the methonium series restricted to the search for compounds with muscle-relaxing properties would have concentrated attention on decamethonium and, although this might in turn have led to the interesting physiological synthesis of the mode of action of this drug which Dr. ZAIMIS carried out with such skill, the more important properties of the hexamethonium salt might well have passed unobserved. It was only the sharing of the particular kinds of chemical and pharmacological interest and knowledge between colleagues in the same building that produced the result which emerged on a basis of systematic research and in a reasonably short space of time. I can assure you that it is events such as this which gladden the hearts of those who have to direct research institutes.

I have spoken only in terms of methonium compounds because, as I have said, it is the work of these drugs that has made it worth while to hold this symposium. However, we are now seeing the discovery of many other types of compound which are finding important places in the pharmacological control of vascular tone, and the contributions to the pharmacology of reserpine that we shall hear will be particularly welcome. Moreover, we need not doubt that the views of the clinical members of the symposium on the practical usefulness of the various drugs now available will certainly be interesting, and may be salutary to the pharmacologists.

In conclusion I should like to reiterate my hope that this symposium will do more than present a synopsis of current knowledge in the field of discussion. We are most fortunate in the distinction of the members of the symposium who are to make scientific contributions. These contributions will give an authoritative statement of the present position, and should also bring out clearly the weaknesses of the situation and the aspects on which more work is required. With good fortune they may also produce some ideas on the directions which further work should follow, and as to the best means of attack on the outstanding problems. If the symposium attains these objects, those who have been responsible for organizing it will be well rewarded.

1ST SESSION

(MORNING)

THURSDAY, APRIL 5TH.

Chairman: Professor F. Bergel

CHEMICAL AND BIOCHEMICAL ASPECTS

STRUCTURE-ACTION RELATIONSHIPS OF HYPOTENSIVE DRUGS

H. R. ING

IN a recent review article Dr. ZAIMIS (1955) referred to acetylcholine as a masterpiece among molecules because it activates so many different receptors; I do not think that I can emulate this versatile molecule and elicit appropriate responses from all the members of so diverse an audience. I may hope to activate some receptors by my remarks but I fear I may fail to excite, and may even depress, others.

Hypotensive drugs are of many types, differing both chemically and pharmacologically, so that if I am to fulfil the wishes of the organizing committee, I must hop as gracefully as I can from one group to another. Moreover, since I cannot deal fully with all the different groups, the amount of space I devote to each group will be dictated by my personal interests.

I will start with the veratrum alkaloids, not because I have anything useful to say about their structure-action relationships, but because of the intrinsic interest of the mechanism of their hypotensive effect, the clue to which was discovered by VON BEZOLD and HIRT (1867) nearly a century ago. At least seventeen alkaloids have been isolated from *Veratrum* spp. or from sabadilla seeds (the commercial source): four alkamines, two alkamine glucosides and eleven alkamine esters. All the alkamines, whether occurring naturally or obtained by hydrolysis of glucosidic or ester alkaloids, contain 27 C atoms, 1 tertiary N atom, and 2–9 O atoms; they are steroid alkamines containing six ring structures with the solitary N atom, so far as we know, common to two rings. The structure of none of the alkamines is known with certainty, although considerable advances have been made in elucidating the structure of the cevine group. The ester alkaloids are the most potent of the group. Veratridine ($C_{36}H_{51}O_{11}N$) is a typical example; it is hydrolysed at 0° to veratric acid ($C_9H_{10}O_4$) and veracevine ($C_{27}H_{43}O_8N$), and the latter is converted by less mild treatment with alkali, first into cevagenine and then into cevine, both isomeric with veracevine.

The main interest of these alkaloids for my purpose lies in the

mechanism of their hypotensive action which, together with slowing of the heart and respiration, is produced reflexly by stimulation of afferent nerve endings in the heart and lungs (KRAYER and ACHESON, 1946); and in the fact that this reflex mechanism is not confined to the veratrum alkaloids but is displayed by what DAWES and COMROE (1954) have called "a weird collection" of chemical substances, such as adenosine triphosphate, 5-hydroxytryptamine, and certain amidines. It would be as absurd to seek for structure-action relationships between such diverse substances as it would be to do so between saccharin and sucrose because they both taste sweet, but the amidines at least do show some consistent relationships among themselves.

Table 1 gives the names, formulae, and activities of eight of the most active among some thirty to forty compounds of fairly simple structure, all containing one unsubstituted amidine group, which DAWES and MOTT (1950) and DAWES and FASTIER (1950) found to

Table 1

Vasodilator amidine derivatives

Name	Formula	Depressor activity*
Guanidines		
p-chlorophenylguanidine	4-Cl.C_6H_4NH.C(:NH)NH_2	1·0
Diguanides		
phenyldiguanide	C_6H_5NH.C(:NH)NH.C(:NH)NH_2	1·0
o-chloro ,,	2-Cl- ,,	2·5
p-chloro ,,	4-Cl- ,,	1·5
o-methyl ,,	2-CH_3- ,,	1·5
Iso*thioureas*		
2-α-naphthylethyl*iso*thiourea	α-$C_{10}H_7CH_2CH_2$S.C(:NH)NH_2	2·2
m-chlorobenzyl*iso*thiourea	3-Cl$C_6H_4CH_2$S.C.(:NH)NH_2	1·1
cis-3-bromo*cyclo*hexyl*iso*-thiourea	3-BrC_6H_{10}S.C(:NH)NH_2	1·1

* In terms of phenyldiguanide

elicit a reflex fall in blood pressure and heart rate in the cat by an action on afferent nerve endings in the heart (the Bezold reflex); they also elicit a similar depressor reflex by an action on afferent endings in the lungs. The approximate depressor potencies are given (Table 1) in terms of phenyldiguanide, which is itself about 1/5th to 1/10th as active as pure veratridine. All these amidines produce their depressor effects in doses of 1 mg/kg or less in the cat.

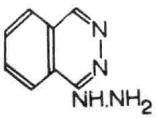
The activity appears to depend upon an intact amidine group, since substitution of aryl or alkyl groups on one of the N atoms of the amidine unit abolishes it. A terminal aryl nucleus enhances activity but is not essential; e.g. 3-bromo*cyclo*hexyl*iso*thiourea is as potent as phenyldiguanide. Activity is also enhanced by the substitution of halogen or methyl into certain positions of the aryl nucleus. Finally, it may be noted that amidines are strong monoacidic bases and will exist at physiological *p*H's as cations ($-C(:NH_2)NH_2^+$).

At this point it is convenient to mention some other vasodilator amidine derivatives which do not, however, contain an unsubstituted amidine unit.

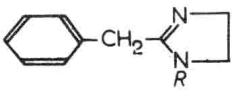
Hydralazine or 1-hydrazinophthalazine (I) belongs to a small group of phthalazine compounds which includes its 4-methyl, 4-phenyl and 4-hydrazino derivatives, all of comparable activity. The integrity of the hydrazino group appears to be essential since its replacement by amino or substituted amino groups reduces activity drastically. The mechanism of the hypotensive effect is obscure; it develops gradually and is remarkably persistent (GROSS, DRUEY, and MEIER, 1950).

It would be interesting to investigate the pharmacological properties of related compounds, e.g. 2-hydrazino-pyridine or -quinoline and 1- or 3-hydrazino*iso*quinoline, all of which would contain the amino-amidine unit ($\cdot N{:}\dot{C}\cdot NH\cdot NH_2$).

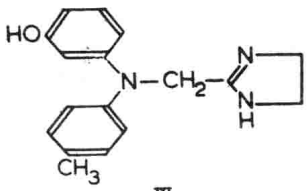
Hydralazine has some antiadrenaline action but much less antinoradrenaline action. Tolazoline and phentolamine are more effective antagonists of adrenaline.



I



II



III