

DISCOVERIES IN PHARMACOLOGY

Volume 1

Psycho- and Neuro-pharmacology

edited by
M.J. Parnham and J. Bruinvels



ELSEVIER

VOLUME 1

PSYCHO- AND NEURO-PHARMACOLOGY

edited by

M. J. PARNHAM

A. Nattermann & Cie. GmbH
Pharmacology Research
Nattermannallee 1
5000 Cologne 30
West Germany

J. BRUINVELS

Department of Pharmacology
Medical Faculty
Erasmus University Rotterdam
P.O. Box 1738
Rotterdam
The Netherlands



33

Y077937



ELSEVIER
AMSTERDAM · NEW YORK · OXFORD

© Elsevier Science Publishers B.V., 1983

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the copyright owner.

ISBN Series: 0-444-80492-7

ISBN Volume: 0-444-80493-5

PUBLISHED BY:

Elsevier Science Publishers B.V.
P.O. Box 211
1000 AE Amsterdam
The Netherlands

SOLE DISTRIBUTORS FOR THE U.S.A. AND CANADA

Elsevier Science Publishing Company Inc.
52 Vanderbilt Avenue
New York, N.Y. 10017
U.S.A.

Library of Congress Cataloging in Publication Data

Main entry under title:

Discoveries in pharmacology.

Contents: v. 1. Psycho- and neuro-pharmacology.

1. Pharmacology--History--Collected works. I. Parnham,

Michael J., 1951- . II. Bruinvels, J.

RM41.D57 1983 615'.1'09 83-8867

ISBN 0-444-80492-7 (U.S. : set)

Printed in The Netherlands

DISCOVERIES IN PHARMACOLOGY



DISCOVERIES IN PHARMACOLOGY



Preface

The use of drugs for medicinal or ritual purposes extends back into the mists of antiquity. The scientific study of drugs, however, may be traced back to the pioneers of experimental medicine of the middle nineteenth century, Magendie, Bernard, Bucheim and Schmiedeberg. This marked the dawn of pharmacology as a discipline, the scientific study of the mechanisms of drug action. The drugs which were first subjected to scientific investigation, though, were, to a large extent, those which had long been known to exist by native populations. The introduction of synthetic compounds in the twentieth century, while revolutionizing therapeutics, was also a direct result of the structural analysis of well-known folk remedies. Thus, while pharmacology as a scientific discipline is relatively new, its foundations were built on the accumulated knowledge of previous centuries.

The use of drugs in antiquity and folk remedies has been an essential ingredient of all important histories of medicine. However, the more recent scientific development of drugs has either been considered too modern to be history or too scientific to be discussed in relation to medicine. This is a sad state of affairs since the history of pharmacology, both ancient and modern, is strewn with interesting stories of accidental discoveries, fortunate coincidences and perseverant scientific detective work. How often do we go to the pharmacist to obtain a prescription not realising that the bottle of pills we obtain represents the end product of a chain of discovery and patient hard work?

The existence of this first volume of *Discoveries in Pharmacology*, itself, is the direct result of a casual conversation over a cup of coffee from a university coffee machine! We were both fascinated by the often surprising means by which pharmacological discoveries have been made and regretted that no comprehensive study of this field has been made. Two readable monographs on this topic have appeared. *Readings in Pharmacology* by Holmstedt and Liljestrand (reprinted by Raven Press, New York, 1981) provides a series of annotated quotations from different sources which highlight important drug discoveries and offers interesting biographical information on the scientists who have helped to develop pharmacology. *A History of Pharmacology up to the Twentieth Cen-*

ture by the late Chauncey D. Leake covers in a scholarly and readable manner the development of pharmacology until its rapid growth and maturity as a science during the twentieth century. It is this rapid growth over the last 50 – 70 years which now makes a comprehensive history of pharmacology an interesting proposition. Most of the scientists who were involved in the early discoveries in the various fields of pharmacology are still alive and are thus able to provide a personal perspective on these discoveries, as well as giving interesting anecdotes, aspects which no objective historian is able to cover. Of course, in some fields, such as general anaesthesia, all the major discoveries were made too long ago for any living person to offer any personal recollections. Such topics are dealt with here by authors with expert knowledge of this early work. Indeed, we have been fortunate enough to obtain the co-operation of a star-studded group of authors, acknowledged experts in their fields, who have brought to this volume the personal, human touch which we believe is essential to a true understanding of the means by which pharmacological discoveries are made.

In planning this series of monographs we have sought to be as comprehensive as possible, covering most major fields of pharmacology. However, each author has had freedom to write as he wishes. This has inevitably meant that some chapters have been slanted in a particular direction. Thus, on the one hand, some topics have intruded into two or more chapters, while, on the other hand, some topics have slipped through the net. While we cannot, therefore, guarantee that everyone will find in this series everything he would like to find, we offer this work as an introduction to the intriguing, surprising, sometimes complicated, but rarely boring history of pharmacology.

For the preparation of this first volume, we gratefully acknowledge the time and effort given by all the contributing authors. Mr. James Drake of Elsevier has continued to offer good advice as well as showing patience with the inevitable delays which arise with such a multi-authored monograph. Finally we thank Miss Sylvia Griebeling for coping with the mass of correspondence needed to bring this work to fruition.

MICHAEL J. PARNHAM
JACQUES BRUINVELS
June, 1982

List of contributors

- Z. M. BACQ Université de Liege, Faculté de Médecine, Laboratoire de Biochemie Appliquée, Boulevard de la Constitution, 32, 4020 Liège, Belgium.
- C. D. BINNIE Instituut voor Epilepsiebestrijding Meer en Bosch/De Cruquiushoeve, Achterweg 5, 2103 SW Heemstede, The Netherlands.
- I. L. BONTA Department of Pharmacology, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.
- W. C. BOWMAN Department of Physiology and Pharmacology, University of Strathclyde, 204 George Street, Glasgow G1 1XW, Scotland, U.K.
- A. CARLSSON Department of Pharmacology, University of Gothenburg, P.O. Box 33031, S-40033 Gothenburg, Sweden.
- P. DENIKER University Clinic of Mental Health and Therapeutics, Hôpital Ste.-Anne, 100 – 102 rue de la Santé, 75674 Paris, France.
- D. DE WIED Rudolf Magnus Institute of Pharmacology, University of Utrecht, Vondellaan 6, 3521 GD Utrecht, The Netherlands.
- K. M. GARRETT Department of Pharmacology, School of Medicine, University of California at San Francisco, San Francisco, California 94143, U.S.A.

- S. GAUTHIER Montreal Neurological Institute, 3801 University street, Montreal, P.Q., Canada H3A 2B4.
- W. HAEFELY Pharmaceutical Research Department, PF/1 – Bldg. 69/412, F. Hoffmann-La Roche & Co. Ltd., Grenzacherstrasse 124, CH-4002 Basel, Switzerland.
- P. HOLZER Institut für experimentelle und klinische Pharmakologie der Universität Graz, Universitätsplatz 4, A-8010 Graz, Austria.
- P. A. J. JANSSEN Janssen Pharmaceutica, Turnhoutseweg 30, B-2340 Beerse, Belgium.
- N. S. KLINE Rockland Research Institute, Orangeburg, New York 10962, U.S.A.
- T. KOPPANYI Department of Pharmacology, Georgetown University, School of Medicine, 3900 Reservoir Road NW, Washington, D.C. 20007, U.S.A.
- J. C. KRAMER Department of Psychiatry and Human Behavior, College of Medicine, University of California, Irvine, California 92717, U.S.A.
- H. E. LEHMANN Department of Psychiatry, Division of Psychopharmacology, McGill University, 1033 Pine Avenue West, Montreal, P.Q., Canada H3A 1A1.
- F. LEMBECK Institut für experimentelle und klinische Pharmakologie der Universität Graz, Universitätsplatz 4, A-8010 Graz, Austria.
- A. LIVINGSTON Department of Pharmacology, University of Bristol, The Medical School, University Walk, Bristol BS8 1TD, U.K.
- J. W. A. MEIJER Instituut voor Epilepsiebestrijding Meer en Bosch/De Cruquiushoeve, Achterweg 5, 2103 SW Heemstede, The Netherlands.

- H. MEINARDI Instituut voor Epilepsiebestrijding Meer en Bosch/De Cruquishoeve, Achterweg 5, 2103 SW Heemstede, The Netherlands.
- M. D. MERLIN Department of General Science, University of Hawaii at Manoa, Honolulu, Hawaii 96822, U.S.A.
- R. MISHRA Tennessee Neuropsychiatric Institute, Vanderbilt University, School of Medicine, Nashville, TN 37232, U.S.A.
- T. L. SOURKES Department of Psychiatry, McGill University, 1033 Pine Avenue West, Montreal, P.Q., Canada H3A 1A1.
- F. SULSER Tennessee Neuropsychiatric Institute, Vanderbilt University, School of Medicine, Nashville, TN 37232, U.S.A.
- J. P. TOLLENAERE Janssen Pharmaceutica, Turnhoutseweg 30, B-2340 Beerse, Belgium.
- E. L. WAY Department of Pharmacology, School of Medicine, University of California at San Francisco, San Francisco, California 94143, U.S.A.
- E. A. ZELLER Research Laboratories, Shriners Hospital for Crippled Children, 2211 North Oak Park Avenue, Chicago, Illinois 60635, U.S.A.

Contents

PREFACE	v
LIST OF CONTRIBUTORS	vii
INTRODUCTION	
Folklore, druglore and serendipity in pharmacology	1
<i>I. L. Bonta</i>	
CHAPTER 1	
The use of psychoactive drugs in the ancient old world	23
<i>J. C. Kramer and M. D. Merlin</i>	
CHAPTER 2	
Chemical transmission of nerve impulses	49
<i>Z. M. Bacq</i>	
CHAPTER 3	
Peripherally acting muscle relaxants	105
<i>W. C. Bowman</i>	
CHAPTER 4	
The suppression of psychotic behavior	
PART 1 — Discovery of the clinical use of neuroleptics	163
<i>P. Deniker</i>	
PART 2 — The discovery of the butyrophenone-type neuroleptics	181
<i>P. A. J. Janssen and J. P. Tollenaere</i>	
PART 3 — Antipsychotic agents: elucidation of their mode of action .	197
<i>A. Carlsson</i>	

CHAPTER 5

Antidepressants

PART 1 — Clinical discoveries with antidepressant drugs	209
<i>H. E. Lehmann and N. S. Kline</i>	

PART 2 — Monoamine oxidase and its inhibitors in relation to anti-depressive activity	223
<i>E. A. Zeller</i>	

PART 3 — The discovery of tricyclic antidepressants and their mode of action	233
<i>F. Sulser and R. Mishra</i>	

CHAPTER 6

Levodopa and dopamine agonists in the treatment of Parkinson's disease	249
<i>T. L. Sourkes and S. Gauthier</i>	

CHAPTER 7

Alleviation of anxiety — the benzodiazepine saga	269
<i>W. Haefely</i>	

CHAPTER 8

Neuropeptides and behaviour	307
<i>D. de Wied</i>	

CHAPTER 9

The problem of pain

PART 1 — Analgesia up to the twentieth century	357
<i>P. Holzer and F. Lembeck</i>	

PART 2 — The history of narcotic antagonists	379
<i>K. M. Garrett and E. Leong Way</i>	

CHAPTER 10

The sleep of innocence	395
<i>A. Livingston</i>	

CHAPTER 11

Sleep and hypnotics	423
<i>T. Koppanyi</i>	

CHAPTER 12

The development of antiepileptic drugs	447
<i>J. W. A. Meijer, H. Meinardi and C. D. Binnie</i>	

INDEX	489
-------------	-----

INTRODUCTION

Folklore, druglore and serendipity in pharmacology*

Ivan L. Bonta

CONTENTS

1. Introduction	2
2. Interactions between folklore and druglore	3
3. Some of today's remnants of druglore	10
4. Serendipity in pharmacology	13
5. Is serendipity rewarding?	18
6. Acknowledgements	20
7. Sources of further entertainment	20

* This article is dedicated to the memory of the late Pavel Stern, onetime Professor of Pharmacology in Sarajevo. He was a pioneer researcher into the role of substance P in the brain. Those who knew him will agree with me that Pavel was not only a warm hearted person, but also had a great sense of humour, and used to pour out anecdotes in abundance. He could have written this article much better than the present author.

'Si no è vero, è molto ben travato'
Italian proverb

1. INTRODUCTION

The main scope of this article is to entertain rather than to present documented historical information on some of the developments and discoveries in pharmacology. I shall try to provide the reader with a somewhat loosely connected collection of partially anecdotal oddities, which, actually or seemingly, have contributed to the present state of the art in pharmacology. The above *motto* means, according to my own (rough) translation, 'even an untrue event may be very pertinent'. I should be rather reluctant to recommend this principle as a guideline for (young) scientists who are engaged in writing a research paper. However, at the outset of the present article, I felt that this motto would serve well to indicate that some of the 'stories' which I intend to recount, while not being (entirely) true, are such that they *could have been true*. Several of these stories I have drawn from the literature; where occasionally I found more than one version of the same event. For the purpose of the present article, I have in some cases deliberately chosen the more colourful and, for that matter, possibly less authentic version. I shall also pass on certain anecdotal versions, which I never read, but only learned by hear-say from colleagues whom I came across during my long occupation with pharmacology. Such anecdotes are not only amusing, but have the additional value that they characterize in a very telling way, a person or a certain situation. In the latter context, I am occasionally impressed by the fact that some of the very important earlier discoveries in pharmacology (or in any other area of the life sciences) were made under experimental conditions which would not withstand the rigorous requirements presently stipulated by research grant-awarding agencies. Funds are usually distributed to 'promising' and very well planned programmes. But wholly original, initial observations are not usually planned in advance. Yet such observations form the basis of the majority of premeditated research projects. In further conjecturing on grant awards, I am inclined to believe that subsidized research provides developments rather than discoveries. Since, however, developments require teamwork, in contrast to discoveries, which are usually made by individuals, this fact emphasizes further the value of stories about such individuals.

When the editors asked me to contribute to this volume, I consented because I felt that writing this article would be an enjoyable task. However, I underestimated one particular difficulty with which I would be faced: my thesaurus in English is far too limited to point out colourfully the gist of the kind of stories I had in mind, originating from non-English-speaking countries. To illustrate my problem, let me tell a non-pharmacological anecdote. I read it in the literary memoirs of the Viennese fiction writer Frederic Torberg, a close

friend of the Hungarian playwright Francis Molnár, whose comedies at one time led to queues at box offices not only in Budapest but in Broadway theatres as well. The Nazi regime compelled both writers to escape from their native countries. After already having lived for some time in New York, the two friends chatted (in German) about the emigrant's main difficulty, the barrier of language. Torberg complained that sometimes the limitations of the English language were, for him, such that he was forced to say what he *could* rather than what he *wanted* to. Having sadly agreed, Molnár's answer was: 'Indeed, it happened to me occasionally that halfway through a sentence I had to reverse my ideology'. My own linguistic difficulties have never gone so far, at least not when drafting a research paper: a table or a diagram would always demonstrate that a phenomenon, possibly emerging from my confused text as an increase, was in reality a decrease. Tables or diagrams would even unmask my deliberate efforts in the discussion to attach opposite interpretations to an observation. But now with this article, to which I committed myself inconsiderately, there is neither a table nor a graph which would substitute for my lack of eloquence in English. To start with, I am hardly capable of reflecting in translation the profound truism of the pun, which by changing one single letter in the Hungarian term for pharmacology, reverses the meaning of this word from the science of drugs to the science of dung!

Since this article is, anyway, somewhat unconventional, both in scope and style, I felt it appropriate not to complicate the matter with the conventional way of indicating the references directly in the text. Instead, I provide the reader with a list of books or articles which served me as sources of verifiable information. For the benefit of the reader, I wish to add that some of the listed sources are considerably more amusing than this article.

2. INTERACTIONS BETWEEN FOLKLORE AND DRUGLORE

Folklore is as old as mankind and so is druglore. Episodes related to drugs have played a prominent role both in true folklore and in epic poems derived from folklore, as well as in all kinds of religious scripts. According to Sir William Osler's classic saying '... man has an inborn craving for medicine. . . and the desire to take medicine is one feature which distinguishes man the animal from his fellow creatures'. But it is probable that, since drugs are in fact useful poisons, our ancestors' preoccupation with the toxic aspects of chemicals took them in the opposite direction to that followed by the safety-conscious modern governmental health authorities. Acquisition of food obviously meant hunting and this, in prehistoric society, was a matter of survival. Accordingly, the use of arrow poisons could well be seen as the cradle of pharmacology, while the medical use of drugs was, at that period, likely to have been of minor impor-

tance. The pathway from the Amazonian tribes' arrow heads, through Claude Bernard's classic experiments with curare, to the steroidal muscle relaxant pancuronium, is told elsewhere in this book (Chapter 4). Somewhat less known is the episode which took place 15 years before Sir Thomas Fraser's discovery of the digitalis-like action of the African arrow poison obtained from the seeds of *Strophanthus hispidus*. In 1865, during the African journey of David Livingstone, the famous Scottish missionary, a member of the expedition, a certain Mr. Kirk, heard from the natives that their teeth were kept in good shape because they were rubbed with the powdered seeds of the plant which they also used to decoct their arrow poison. Led by the desire to conserve his own teeth, Kirk put some of the powder on his tooth brush and, a short while after, noticed marked bradycardia as a side effect of his oral sanitation exercise. Kirk decided that the benefit-risk ratio for his own dental and cardiac conditions did not warrant this practice, which he thus abandoned, though telling Livingstone about his experience. The *Strophanthus*-derived arrow poison was included in Livingstone's report, obviously read by Frazer. The above version I read in a booklet edited by the producers of a toothpaste. This company boasted of the safe use of their product by saying that cardiac patients would now not enjoy the beneficial action of ouabain if Kirk had had access to the company's toothpaste! As with many other 'if . . .' references to historical anecdotes, there is no way to prove or disprove the authenticity of this story. But this means of advertising is a peculiarity of our times, a paradoxical negative statement on a milestone medical discovery being used to remove the fear of the public from side effects of a cosmetic product.

When skilled use of poisoned arrows yielded an abundance of food, disorders of bowel function, both negative and positive, must have frequently been the consequence. Many of the purgatives (aloes, manna, senna, prunes etc.) and anti-diarrhoeals (tannin and some other bark extracts) still used today can be traced back to prehistoric druglore among the various tribes clustering around the Mediterranean basin and other centres of growing culture. However, laxatives, now only used for medical purposes, were, in prehistoric times, probably also used for ritualistic purging by certain tribes. The two-fold, physical and mystical, meaning of *catharsis* in Greek mythology is a semantic relic reflecting the habit of using purgatives for ritual purposes. This dual use of purgatives is also reflected in the Bible: the Jewish priests used *hyssop* for the sacred ritual of sprinkling, whereas its recommendation as a cathartic agent is found in Psalm 51: 'Purge me with hyssop and I shall be clean'. Because decayed hyssop was the natural culture medium on which the growth of the mold *Penicillium notatum* was first recognized (by Westling, a Swedish chemist), Sir Alexander Fleming suggested that through hyssop the Bible makes (indirect) mention of penicillin.

The social habit of ritual purging has long since been abandoned. However,