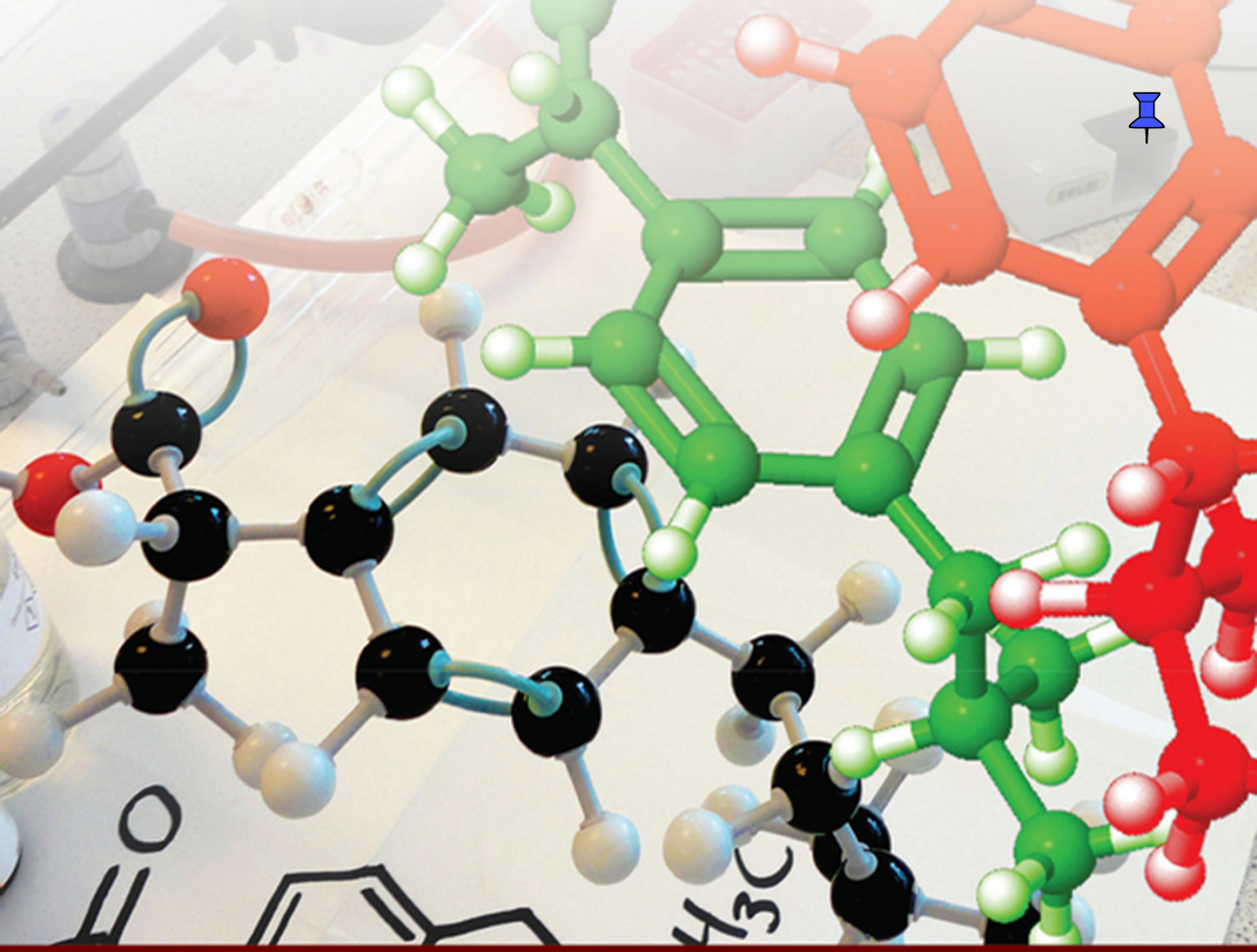


Edited by

K.D. Rainsford

IBUPROFEN

Discovery, Development and Therapeutics

WILEY Blackwell

Ibuprofen

Ibuprofen

Discovery, Development and Therapeutics

EDITED BY

K.D. RAINSFORD
Biomedical Research Centre, Sheffield Hallam University, UK

WILEY Blackwell

Registered Office
John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Offices
9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

Library of Congress Cataloging-in-Publication Data

Ibuprofen (2015)
Ibuprofen : discovery, development and therapeutics / edited by Kim D Rainsford.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-118-74338-6 (cloth)
I. Rainsford, K. D., 1941–, editor, contributor. II. Title.
[DNLM: 1. Ibuprofen–pharmacology. 2. Ibuprofen–therapeutic use. QV 95]
RM666.I17
615.7′83–dc23

2015001065

A catalogue record for this book is available from the British Library.

Set in 9/11pt Times by SPi Global, Pondicherry, India

1 2015

Contents

List of Contributors

Professor K.D. Rainsford, PhD, FRCPEdin, FRCPath, FRSC, FSB, FIBMS, Dr(hc) Biomedical Research Centre, Sheffield Hallam University, UK

Professor David W. Allen, DSc Biomedical Research Centre, Sheffield Hallam University, UK

Professor Ingvar Bjarnason MD, MSc, FRCPath, FRCP (Glasg), DSc Department of Gastroenterology, King's College Hospital, UK

Dr Dion R. Brocks, PhD Faculty of Pharmacy and Pharmaceutical Sciences, Katz Centre for Pharmacy and Health Research, Canada

Professor W. Watson Buchanan, MD, FRCP (Glas, Edin, C) (the late) Sir William Osler Health Institute and McMaster University Faculty of Health Sciences, Canada

Dr Stephen A. Cooper, DDS, PhD Palm Beach, USA

Dr Raymond A. Dionne, DDS, MS, PhD East Carolina University, Brody School of Medicine, Greenville, NC, USA

Dr Sharon M. Gordon, DDS, MPH, PhD School of Dental Medicine, East Carolina University, Greenville, NC, USA

Professor Randall E. Harris, MD, PhD Center of Molecular Epidemiology and Environmental Health, Colleges of Medicine and Public Health, Division of Epidemiology and Department of Emergency Medicine, The Ohio State University Medical Center, USA

Dr Fred Higton, PhD Higton Associates, UK

Professor Fakhreddin Jamali, Faculty of Pharmacy and Pharmaceutical Sciences, Katz Centre for Pharmacy and Health Research, Canada

Dr Judith K. Jones, MD, PhD The Degge Group, Drug Safety Research and Information, USA

Professor Walter F. Kean, MB ChB, MD (Glas), FRCP (Glas, Edin, C) McMaster University Faculty of Health Sciences, Canada

Dr M. Maneno The Degge Group, Drug Safety Research and Information, USA

Dr L.J. Miwa The Degge Group, Drug Safety Research and Information, USA

Dr Kenneth J. Nichol, PhD Kelso, Scottish Borders, UK

Dr Glyn Volans, MD, BSc, FRCP Department of Clinical Pharmacology, School of Medicine at Guy's and St Thomas' Hospitals, UK

Preface

Now over 50 years since the discovery of ibuprofen at the Boots Company in Nottingham (UK), this drug has evolved to be used in a wide range of conditions. It has now become almost a university standard both for assessment of pain and inflammation as well as therapy of these conditions. This book is intended to be a monograph on all the main aspects of the properties, mechanisms of action and therapeutic uses of ibuprofen. An earlier version of this book was published in 1999 and since then there have been considerable advances in research and clinical studies on ibuprofen. This is reflected in a major increase in original research publications during this period in which ibuprofen has been cited and in which it has been compared with other analgesic or anti-inflammatory drugs or in which its mechanisms and efficacy have been studied. Ibuprofen has also now been used clinically for over 50 years and this is a reflection of its widespread use and acceptance in treating many inflammatory and even non-inflammatory states, many of which are reviewed in this volume.

Without doubt, recognition of the relative safety and efficacy of ibuprofen has come from the large-scale mega-trials undertaken in the past two to three decades on newer cyclo-oxygenase-2 (COX-2) selective or preferential drugs in which ibuprofen, like that of the other 'traditional' NSAIDs (tNSAIDs), diclofenac and naproxen, were used as comparator drugs. To the surprise of many the newer COX-2-selective agents proved no more effective in controlling pain and joint inflammatory symptoms in arthritis or acute pain states than the tNSAIDs. Their serious gastrointestinal (GI) adverse events were lower than some tNSAIDs after short-term use at high anti-inflammatory doses but after long-term use (several months) these advantages were lost or less apparent. Moreover, in arthritic patients taking COX-2 selective agents who needed aspirin for cardioprotection the incidence and severity of serious GI reactions became more frequent, so there were no benefits of the COX-2 selective agents compared with tNSAIDs. The added costs of the COX-2 selective inhibitors also outweighed their benefits.

A surprising outcome from the mega-studies of the coxibs was a marked increase in their incidence of myocardial infarction, stroke and rates of death in patients taking these drugs long-term, with a trend evident that these serious cardiovascular (CV) events were more frequent with coxibs than naproxen or ibuprofen; the situation with diclofenac has become less clear in that this drug appears to have a high incidence of CV events.

The serious or severe GI and CV reactions seen with high long-term so-called 'anti-arthritic' doses of coxibs and some tNSAIDs is not evident, or is indeed rare, with short-term non-prescription or over-the-counter (OTC) sale of drugs such as ibuprofen, ketoprofen or naproxen. With ibuprofen it has now become recognized that this is probably amongst the safest of OTC analgesics (including paracetamol (acetaminophen)). Upper GI bleeding and ulceration seen often with aspirin and high-dose tNSAIDs is of relatively low frequency with ibuprofen and is probably comparable with paracetamol, which is less ulcerogenic than tNSAIDs. Evidence in support of the OTC safety of ibuprofen in both adults and children has come from many studies that have appeared in recent years. These studies along with extensive pharmaco-epidemiological data have given confidence for the safe use of short-term dosages of ibuprofen, while at the same time giving insight to the factors underlying the development of side-effects, e.g. GI upsets and asthma in children, of all OTC analgesics including ibuprofen.

Understanding of the molecular and cellular actions of ibuprofen has given a broader view of its mechanisms of analgesia and anti-inflammatory activities. Hitherto, the prostaglandin (PG) era in the 1970s and 1980s had led to focused views that ibuprofen was a week PG synthesis inhibitor and that the actions in

controlling inflammation were attributed to one of the two isometric components (the *S*(+) enantiomer) of the drug. While this is well-recognized and now been found with low OTC doses of ibuprofen it is now becoming recognized that stimulating effects on the production in the brain of endocannabinoids, noradrenergic (nor-epinephrine and 5-hydroxy-tryptamine (serotonergic)) pathways contribute to the central nervous system components of analgesia by ibuprofen, and may also be evident with some other analgesics as well.

Moreover, insight into the molecular and cellular processes affected by ibuprofen on cell inflammation and immunological processes affected in chronic inflammation have diversified understanding of the actions of ibuprofen in these inflammatory states. Observations that these actions may contribute to a lower incidence or severity in elderly patients of Alzheimer's disease or other forms of nerve injury have given rise to the view that long-term, even low OTC, doses of ibuprofen may have wider benefits than just control of pain and inflammation. Perhaps these neurological actions could be considered as 'collateral' benefits, especially in elderly arthritic patients or those requiring ibuprofen for various musculoskeletal painful conditions. While these are interesting observations with possible benefits, more research is needed to gain insight into the mechanisms of action in these neurological conditions as well as answering very important questions on the relative benefits and safety of the drug arising from considerations of when the drug should be taken, at what dose and for how long in different neuroinflammatory states.

The future may be bright for ibuprofen but there are very important developments required for making this relatively safe drug much safer and defining the conditions and uses of the drug in all populations.

My interest in knowledge about ibuprofen has come with my research into the comparative aspects of the pharmacological and therapeutic properties of the non-steroidal anti-inflammatory drugs. This is an exciting area of research and one that is constantly changing, thanks to advances in the understanding of these drugs and their complexities, both from advances in their therapeutic and adverse reactions. Ibuprofen has been at the centre of these advances owing to its long-standing position in the field of pain and inflammation. Emphasis on the pharmacology, therapeutics and adverse reactions in this book has been from a comparative viewpoint so that the reader will be able to appreciate how this drug fits in with the large number of other NSAIDs and analgesics that are available today.

The publication of this book would not have been possible without the enthusiasm, support and efforts of colleagues who have contributed chapters in their specialist areas. Also of immense help have been the valuable discussions I have had with many collaborators over the years, amongst them Professor Walter Kean (McMaster University, Hamilton, Ontario, Canada), Dr Brian Callingham (University of Cambridge, Cambridge, UK), Professor Michael Whitehouse (Griffith University and University of Queensland, Nathan Campus, Brisbane, Queensland, Australia), Professor Ingvar Bjarnason (King's College Hospital, London, UK), Professor Laurie Prescott (University of Edinburgh, Scotland, UK), Emeritus Professor Richard Hunt (McMaster University, Canada, and Radcliff Hospital Oxford, UK), Professor David Haynes and Dr Mel Cantley (University of Adelaide, Adelaide, South Australia, Australia), Professors Audrejs Skesters and Maije Eglite, Dr Tija Zvagule and colleagues (Riga Stradins University and Institute of Occupational and Environmental Health, Paul Stradins Hospital, Riga, Latvia), Professor Stewart Adams OBE (formerly of Boots, Nottingham Research, Nottingham, UK) as well as colleagues in the pharma-industry (amongst them Reckitt Benckiser, Wyeth, Oxford Pharmasciences, PLxPharma) and other companies who have given valuable advice and insight over the years into pharmaceutical developments associated with ibuprofen.

My special thanks to Mrs Veronica Rainsford-Koechli, Mr Alexander Rainsford and Mr William Rainsford who have provided valuable help in the preparation of the text, figures and tables in this book. I would like to record the valuable advice, editorial assistance and most valuable help in preparation of this book of Mss Nicky McGirr, Celia Carden, Fiona Seymour and their colleagues at John Wiley & Sons, Ltd (Chichester, UK).

This book is dedicated to the discoverers of ibuprofen, Dr (later Professor) Stewart Adams and his colleagues at the Boots Company (Nottingham, UK), the late Professor Watson Buchanan (McMaster University, Hamilton, Ontario, Canada) who inspired and supported many including myself.

Kim Drummond Rainsford
Sheffield (UK)
February 2014

Addendum

The book which I edited and part-authored on *Ibuprofen. A Critical Bibliographic Review* that was published by Taylor & Francis (CRC) in 1999 has formed a basis in part to some chapters in this book. I am grateful to Taylor & Francis for assigning copyright of the first book on ibuprofen to this one.

1

History and Development of Ibuprofen

K.D. Rainsford

Biomedical Research Centre, Sheffield Hallam University, UK

Summary

Ibuprofen was discovered over half a century ago following pioneering approaches by Professor Stuart Adams OBE for the identification of anti-inflammatory properties of drugs related to aspirin and later screening of a range of acidic compounds that were synthesized by the late Dr John Nicholson. The subsequent clinical assessments of the anti-rheumatic activities of ibuprofen were initially as a prescription-only medication for treating rheumatoid arthritis. With extensive trials in various other rheumatic and painful states the drug consistently proved to be effective and relatively safe. By the early 1980s the data amassed on the safety of ibuprofen set the basis for granting by the health authorities in the United Kingdom and United States of America as a non-prescription drug for over-the-counter (OTC) sale by pharmacies at the half-prescription (1200 mg/day) dose for short-term use by the lay public. Later OTC sale was approved by a large number of drug regulatory agencies worldwide and this has since been extended to it being available in stores under the general sales list (GSL) regulations in a large number of countries. Ibuprofen has become amongst the most widely used pain-relieving medication worldwide with its proven safety and efficacy. The drug has also been widely investigated for application in a variety of painful and non-pain inflammatory states including cancer, Parkinson's disease and dementias, reflecting the unique and novel properties of the drug that would never have been foreseen from knowledge of the properties when it was initially discovered.

1.1 Introduction

The history of ibuprofen began over 50 years ago and has been inextricably linked to understanding of the concepts of the pathogenesis of inflammatory diseases and the actions of therapeutic agents used at that time (Rainsford, 2011). The principal initiator of this research leading to the discovery of ibuprofen was

Ibuprofen: Discovery, Development and Therapeutics, First Edition. Edited by K.D. Rainsford.

(a) (b)

Figure 1.1 *A photograph of Dr Stewart Adams taken in 1987 (a) and a recent photograph taken in 2012 (b).*

Dr Stewart Adams (Figure 1.1), a pharmacologist in the Research Department of The Boots Pure Drug Company Ltd at Nottingham, United Kingdom. His aim was to find analgesic drugs with improved efficacy over aspirin. As with all major discoveries, there is an important personal element and what has been attempted here is to bring together information to show what were the most significant events and thoughts that were important for the discovery process. I am most indebted to Stewart Adams for a considerable amount of information and historical detail that enabled me to write this important chapter. I am also especially grateful to him for discussing what have been most interesting historical details and for giving me an insight into those earlier years and the thinking behind the discovery of ibuprofen.

Stewart Adams has written a detailed account of the pharmacological aspects of the discovery of the propionic acids (Adams, 1992). It is worth noting that the discovery of ibuprofen occurred in the period before the discovery by Vane and colleagues in 1971–1973 of prostaglandins as targets for the anti-inflammatory actions of non-steroidal anti-inflationary drugs NSAIDs (Vane, 1971; Flower et al., 1972; Ferreira, Moncada and Vane, 1973; Moncada, Ferreira and Vane, 1973). Thus there was no biochemical or cellular target established that could have been employed in the identification of anti-inflammatory actions of ibuprofen and its precursors. The animal models that were employed in the discovery of propionic acids and other NSAIDs were the only means then available for identifying their anti-inflammatory activity. The late Dr John Nicholson (Figure 1.2), who first synthesized ibuprofen, reviewed in depth the medicinal chemistry of the propionic acids and the chemical discovery process underlying the development of ibuprofen (Nicholson, 1982). It is not proposed to give a total account of what these expert authors have already reviewed in depth. I hope more to emphasize the main thinking at the time and key events involved in the discovery of what has been one of the most successful NSAIDs developed since aspirin.

The standard drugs for treating rheumatoid arthritis and other painful arthritic diseases at the time when Stewart Adams started his research were aspirin and cortisone. The pioneering studies supported by the

Empire Rheumatism Council (later to become the Arthritis and Rheumatism Council) and the Medical Research Council in the United Kingdom had established the efficacy of cortisone and aspirin in the relief of pain and soft-tissue swelling in rheumatoid arthritis. However, the shortcomings of both drugs were becoming strikingly evident even at the time of these reports.

In the 1950s when Boots were beginning this research, only a few other companies had begun research programmes into aspirin-type drugs, notably Dr T.Y. Shen at Merck and Company (Rahway, NJ, USA) and Dr Steve Winder at Parke Davis (Ann Arbor, MI, USA). Before this Dr G. Wilhelmi at J R Geigy AG (Basel, Switzerland) had worked on derivatives of amidopyrine and other pyrazoles. In 1958 Winder and his colleagues published an important paper indicating their thinking about the use of the ultraviolet (UV) erythema technique for determining the anti-inflammatory activity of novel compounds. This assay was similar to that in use at Boots and they had, moreover, obtained similar results with standard drugs (e.g. aspirin). The Parke Davis group eventually produced mefenamic acid, flufenamic acid and other fenamates as a result of the initial testing of compounds in this assay.

Boots, however, started with a distinct disadvantage with their meagre resources as their Pharmacology Department was housed in a group of old rambling buildings attached to a Victorian house located in the outskirts of Nottingham (Figures 1.3 to 1.5). It was moved there at the beginning of the Second World War from the centre of Nottingham as a precaution against bombing – a wise move since part of the Research Department was destroyed in an air raid in 1941. The first six years of the research on new aspirin-type drugs was thus carried out under most unsatisfactory conditions. Adams' laboratory (Figure 1.3) was in one of the 'front rooms' of the house and later he was able to acquire the kitchen and larder (Figure 1.4) as additional accommodation.

Figure 1.2 *The 'ibuprofen team' comprising Stewart Adams (centre) with his technician, Colin Burrows (right) and John Nicholson (left).*

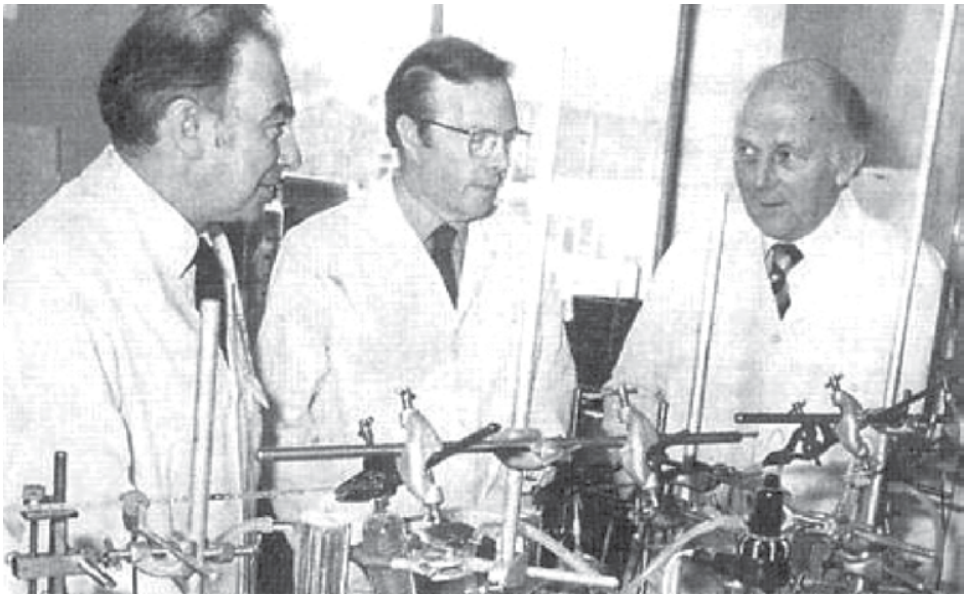


Figure 1.3 *Stewart Adams with John Nicholson, Colin Burrows (right) in the mid-1960s.*

Figure 1.4 *Part of the laboratory ('kitchen') in 1957 showing the Kromayer ultraviolet lamp in the background and guinea-pig holding cages on either side.*

Figure 1.5 *The house where Stewart Adams had his laboratory in Rutland Road, West Bridgford, Nottingham and where the early pharmacological studies leading to the discovery of ibuprofen were performed.*

1.2 Historical Background

It has been said that the road to drug development is a minefield, the path through which is both tortuous and dangerous. One of the leading medicinal chemists in the field of inflammatory drug research, T.Y. Shen, who developed the NSAIDs indomethacin, sulindac and diflunisal at Merck and Company (USA), described the period, 1955–1970, during which the earlier NSAIDs such as ibuprofen and indomethacin were developed as the 'golden era' of Edisonian empiricism (Shen, 1984). Without doubt this era set the stage for the later proliferation of NSAIDs in the 1970s and 1980s, many of which were discovered serendipitously (Shen, 1984) and are considered by some to represent little advance over those drugs developed previously. The mechanisms underlying the development of the rheumatic diseases for which these drugs were intended were little understood. The drugs available for treating pain and inflammation in rheumatic diseases in the 1950s to 1960s included aspirin, the other salicylates, aminophenols (phenacetin) and pyrazolones, which dated from the beginning of the century; phenylbutazone (which was originally used to solubilize aminopyrine and accidently discovered as an effective anti-inflammatory drug); and the corticosteroids discovered in the 1950s (Shen, 1984). Gold salts had also been found in the 1930s to have disease-modifying activity in rheumatoid and related arthropathies, though in the 1950s they were regarded as very toxic.

Thus, with the current remedies for rheumatic diseases being aspirin, corticosteroids, phenylbutazone and, to a lesser extent, gold salts, the need was readily identified in the 1950s for a more potent drug than aspirin, one that would not produce the potentially fatal side-effect of agranulocytosis seen with phenylbutazone or the serious side-effects with corticosteroids. Indeed a report (No. 848 entitled 'The Testing of

Non-hormonal Anti-rheumatic Compounds' by Adams from the Pharmacology and Physiology Division of the Research Department at the Boots Pure Drug Company) dated 5 March 1956 and prepared by Dr Adams noted:

> Apart from cortisone and related steroids, aspirin and phenylbutazone are the only two drugs which are universally used to bring about relief of pain and increased mobility in rheumatoid arthritis. Aspirin, because it is a very safe drug, is usually preferred.

Also,

> From discussions with Dr Duthie [a leading rheumatologist of the time] at Edinburgh [Northern General Hospital], Dr Bywaters [also a leading rheumatologist] at Taplow and Dr Hill at Stoke Mandeville, it is obvious that aspirin and phenylbutazone are the only established non-hormonal compounds in the treatment of rheumatoid arthritis, while aspirin and sodium salicylate are very effective in the treatment of rheumatic fever.

Furthermore,

> We believe that virtually no attempt has been made to investigate thoroughly the anti-inflammatory properties of salicylate-type anti-rheumatics. In view of the widespread use of aspirin and sodium salicylate over the past 50 years this seems to be an amazing omission.

The key to the need to develop a drug that would be superior to aspirin, less toxic than phenylbutazone and without the hormonal associations and side-effects associated with cortisone derives from the following quotes in Dr Adams' report:

> We recently discussed our results [from guinea-pig UV erythema assays with benzoic/salicylic acids and related compounds], with Dr Duthie of the Rheumatism Research Unit, Edinburgh, and he was strongly in favour of the type of investigation [involving the development of a drug to replace existing agents] which is envisaged here. Dr Duthie who is a staunch supporter of aspirin and opposed to cortisone, believes that a 'super' aspirin or non-toxic phenylbutazone would have an immense market.

Moreover:

> The main disadvantage of the compounds of this type [pyrazoles] which have been used clinically, e.g. phenazone, amidopyrine, and phenylbutazone, is that prolonged administration of therapeutic doses may give rise to toxic side-effects including agranulocytosis. This we believe is the main objection to the further investigation of compounds of this nature.

It is important to note that at this stage Adams believed that the analgesic action of aspirin could be explained entirely on its anti-inflammatory properties – a hypothesis that despite some subsequent qualification has proved at least partly valid. This report by Dr Adams is interesting from the insight that it gives to the thinking about anti-rheumatic therapies at the time and the potential for commercial developments. This report was important because it made a plea for chemical support at Boots to enable development of new anti-rheumatic drugs. This plea proved successful as ultimately this chemical development led to the discovery of ibuprofen and so this report represented a major milestone in the development of the drug.

An interesting aspect concerning the use of aspirin and ideas about developing a 'super' aspirin is that no mention was made in the report of the gastrointestinal side-effects of aspirin that were discussed in the literature at the time. The gastrointestinal side-effects of aspirin were recognized by many rheumatologists at that time. Although not mentioned in report No. 848, it was an aim of Adams' group to produce a compound that would be 'well tolerated by the gastrointestinal tract'. Extensive studies were carried out to find those compounds with the best potential in this respect. Over the years this was always a major target in the studies by the group and it is not entirely good luck that ibuprofen is now considered to be the safest of the NSAIDs.

1.3 Initial Stages

This report by Dr Adams in 1956 was making the case for development of a programme for 'non-hormonal' anti-rheumatic compounds; at this time the 'project' team was merely Adams and one technician. Adams and Colin Burrows had already modified the UV erythema assay in guinea-pigs first described by Wilhelmi (1949), who had used this to identify the anti-inflammatory activity of phenylbutazone (Adams and Cobb, 1958). This was later adapted for the assay of skin erythema in humans using Trafuryl as the inflammogen (Figure 1.6). Adams and Burrows later developed a more sophisticated technique requiring only a 20-second exposure to UV without the need to anaesthetize the animal, a feature that not only removed the confounding effects of anaesthesia but also enabled them to test appreciably more compounds each day. Their technique (Dr S.S. Adams, 1998, Figure 1.4, personal communication) was as follows:

> Shaved albino guinea-pigs were dosed orally with aspirin or test compound 30 min before a 20-second exposure to ultraviolet light from a Kromayer lamp. Two hours later the degree of erythema was estimated visually on a scale of 0–4 (maximum = 4) by an observer who was unaware of the dosage schedules. The 2 hr erythema could be completely suppressed by oral doses of 160 mg/kg aspirin and this drug was employed as a positive standard in each day's experiments. In fact there was only suppression of the erythema at 2 hr since it became fully developed after 24 hr.
>
> Adams and Cobb, 1963

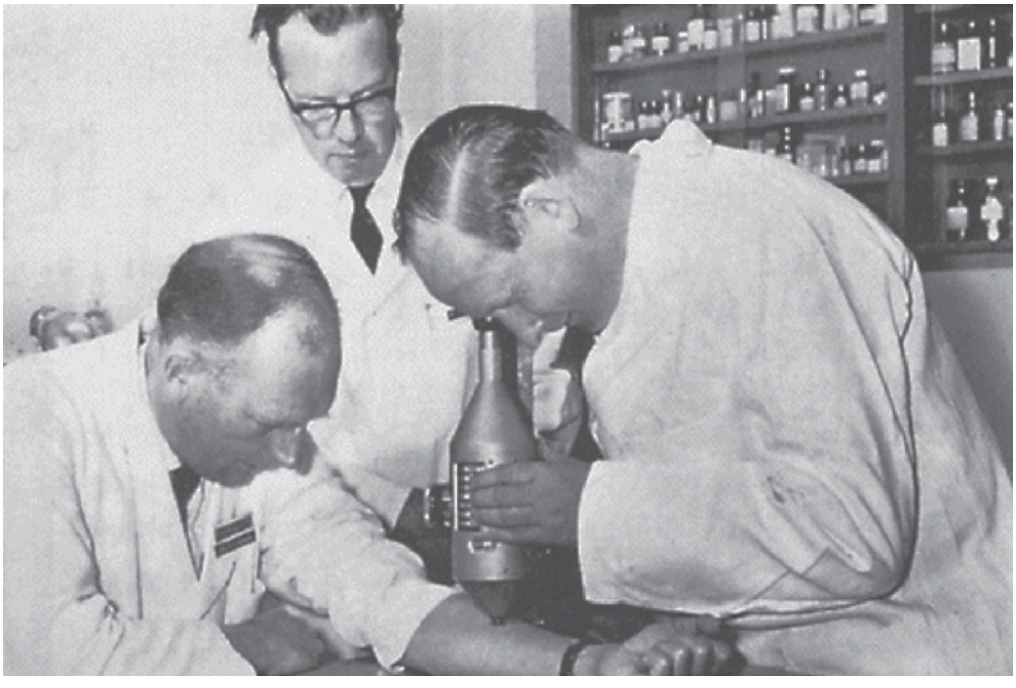
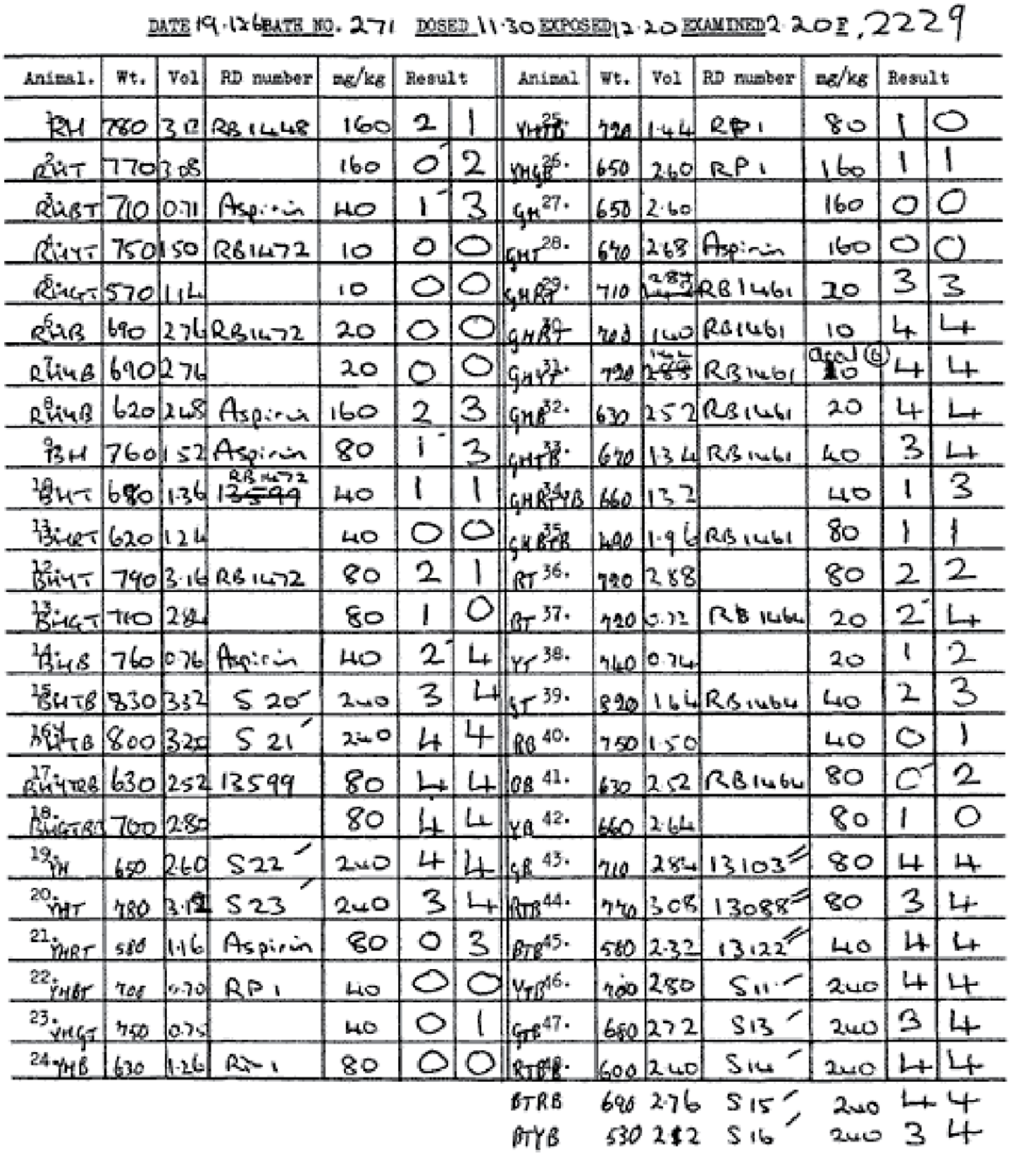


Figure 1.6 *Application of the Trafuryl erythema assay on the volar surface of the forearm. Left to right: Adams, Nicholson and Cobb.*

Using this assay Adams showed that the anti-erythemic activity of compound RB 1472 (later named ibuprofen) was discovered on 19 December 1961 (Figure 1.7). This was quickly followed by filing of a patent, the final specification of which was made on 12 January 1962 (Figure 1.8).



DATE 19.12.61 BATH NO. 271 DOSED 11.30 EXPOSED 12.20 EXAMINED 2.20 E, 2229

Animal.	Wt.	Vol	RD number	mg/kg	Result	
1 RH	780	3.12	RB1448	160	2	1
2 RHT	770	3.08		160	0	2
3 RHBT	710	0.71	Aspirin	40	1	3
4 RHYT	750	1.50	RB1472	10	0	0
5 RHGT	570	1.14		10	0	0
6 RHB	690	2.76	RB1472	20	0	0
7 RHHB	690	2.76		20	0	0
8 RHHB	620	2.48	Aspirin	160	2	3
9 BH	760	1.52	Aspirin	80	1	3
10 BHT	680	1.36	RB1472 ~~13599~~	40	1	1
11 BHRT	620	1.24		40	0	0
12 BHYT	790	3.16	RB1472	80	2	1
13 BHGT	710	2.84		80	1	0
14 BHB	760	0.76	Aspirin	40	2	4
15 BHTB	830	3.32	S 20	240	3	4
16 BHTB	800	3.20	S 21	240	4	4
17 BHYRB	630	2.52	13599	80	4	4
18 BHGTRB	700	2.80		80	4	4
19 YH	650	2.60	S22	240	4	4
20 YHT	780	3.12	S23	240	3	4
21 YHRT	580	1.16	Aspirin	80	0	3
22 YHBT	700	0.70	RP1	40	0	0
23 YHGT	750	0.75		40	0	1
24 YHB	630	1.26	RP1	80	0	0

Animal	Wt.	Vol	RD number	mg/kg	Result	
YHTB 25.	720	1.44	RP1	80	1	0
YHGB 26.	650	2.60	RP1	160	1	1
GH 27.	650	2.60		160	0	0
GHT 28.	670	2.68	Aspirin	160	0	0
GHRT 29.	710	2.84	RB1461	20	3	3
GHBT 30.	700	1.40	RB1461	10	4	4
GHYT 31.	720	1.44	RB1461	dead (B) 10	4	4
GHB 32.	630	2.52	RB1461	20	4	4
GHTB 33.	670	1.34	RB1461	40	3	4
GHRTYB 34.	660	1.32		40	1	3
GHBTB 35.	490	1.96	RB1461	80	1	1
RT 36.	720	2.88		80	2	2
BT 37.	780	3.12	RB1464	20	2	4
YT 38.	740	0.74		20	1	2
GT 39.	820	1.64	RB1464	40	2	3
RB 40.	750	1.50		40	0	1
OB 41.	630	2.52	RB1464	80	0	2
YB 42.	660	2.64		80	1	0
GB 43.	710	2.84	13103	80	4	4
RTB 44.	770	3.08	13088	80	3	4
BTB 45.	580	2.32	13122	40	4	4
YTB 46.	700	2.80	S11	240	4	4
GTB 47.	680	2.72	S13	240	3	4
RTBB 48.	600	2.40	S14	240	4	4
BTRB	690	2.76	S15	240	4	4
BTYB	530	2.12	S16	240	3	4

Figure 1.7 *Extracts from the files showing the first testing of ibuprofen on 19 December 1961. Each figure is the degree of redness (on an increasing scale of 0 to 4) for each individual guinea-pig. Ibuprofen was RB 1472, an early temporary number. The two sets of readings represent observations before and after light 'stroking' of the skin in the erythematous area; the 'stroking' appeared to enhance the sensitivity of detection.*

PATENT SPECIFICATION

971,700

NO DRAWINGS

971700

Inventors: JOHN STUART NICHOLSON and STEWART SANDERS ADAMS

Date of filing Complete Specification: Jan. 12, 1962.

Application Date: Feb. 2, 1961. No. 3999/61.

Complete Specification Published: Sept. 30, 1964.

Index at acceptance:—C2 C(2A2, 2A14, 2R15, 2T16, 3A8A2, 3A8B2, 3A8C3, 3A8K, 3A10A4E, 3A10A4F, 3A10A5A1, 3A10A5A2, 3A10A5E, 3A10A5F, 3A10A5G2, 3A10A5K, 3A10B2C, 3A10B5E, 3A10E3C1, 3A10E4A3, 3A10E5D, 3A10E5E, 3A10E5F1A, 3A10E5F1E, 3A10E5F2A, 3A10E5F3A, 3A10E5F3D, 3A13A3A2, 3A13A3A3, 3A13A3B1, 3A13A3F3); A5 B(1S, 2S)

International Classification:—C 07 c (A 61 k)

COMPLETE SPECIFICATION

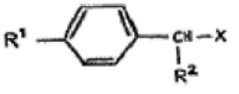
Anti-Inflammatory Agents

We, BOOTS PURE DRUG COMPANY LIMITED, a British Company, of Station Street, Nottingham, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to phenylalkane derivatives. More particularly it relates to novel pharmaceutical and veterinary compositions which comprise as the active ingredient one or more members of a specified group of derivatives of toluene. The invention also relates to the provision of novel members of this specified group of compounds.

It is an object of the invention to provide therapeutic compositions for the relief of pain, fever and inflammation in man and animals which do not suffer from the disadvantages of similar therapeutic compositions based on aspirin, phenylbutazone or adrenocorticosteroids.

We have now discovered that compounds of the general formula I



I

wherein R^1 represents ethyl, propyl, butyl, alkenyl (C_2—C_4), pentyl (except n-pentyl), alkoxy (C_2—C_4), allyloxy, phenoxy, phenylthio or cycloalkyl (C_5—C_7) optionally substituted by methyl or ethyl in the 1-position, R^2 represents hydrogen or methyl and X represents the radical COOH, $COOR^3$ wherein R^3 represents alkyl (C_1—C_4) or optionally *N*-alkylated aminoalkyl (C_2—C_4), COOM wherein M represents the ammonium ion or a single equivalent of a non-toxic metallic cation, COOH.B wherein B represents a non-toxic organic base, $CONH_2$, CH_2NH_2 or the group CH_2OR^4 where R^4 represents hydrogen or lower alkanoyl (C_1—C_2) have valuable anti-inflammatory, analgesic and antipyretic properties.

Furthermore in general the compounds exhibit low toxicity and low irritancy to the gastric mucosa, they do not have other undesirable pharmacological activities which might give rise to unwanted side effects and they are stable in the presence of water.

According to the present invention there are provided therapeutic compositions comprising as active ingredient one or more compounds of the general formula I in association with a pharmaceutically acceptable diluent or carrier.

The following compounds are typical of the active compounds of the general formula I, but do not limit the invention in any way:—

4-*n*-Propylphenylacetic acid
4-Ethoxyphenylacetic acid
4-Isopropylphenylacetic acid
4-propoxyphenylacetic acid
4-Isopropoxyphenylacetic acid
4-*s*-Butylphenylacetic acid
4-Allyloxyphenylacetic acid
4-*t*-Butylphenylacetic acid
4-Cyclopentylphenylacetic acid
4-*iso*butylphenylacetic acid
4-Cycloheptylphenylacetic acid
4-Cyclohexylphenylacetic acid
4-(1-Ethylpropyl)phenylacetic acid
4-Phenoxyphenylacetic acid
4-(1,2-dimethylpropyl)phenylacetic acid
4-Phenylthiophenylacetic acid
α-(4-Cyclohexylphenyl)propionic acid

[*Price 4s. 6d.*]

Figure 1.8 *The Patent Specification for the UK Patent No. 971,700 covering the therapeutic compositions of phenylalkanoic acid derivatives, including ibuprofen, for the relief of pain, fever and inflammation that were developed by Dr John Nicholson and Dr Stewart Adams. The filing of the complete specification was on 12 January 1962.*

One of the factors that was important in the decision to proceed with the use of the erythema technique was the fact that corticosteroids were inactive. Thus the actions of aspirin-type drugs in this assay could be regarded as specific to this class of compounds. Later pioneering studies both of Collier (1963) on the 'antagonism' of kinins by aspirin, phenylbutazone, mefenamic acid and other compounds, and of Vane (Vane, 1971; Flower et al., 1972; Moncada, Ferreira and Vane, 1973) showing that the anti-inflammatory, analgesic and antipyretic effects of aspirin and related compounds are related to their effects on the production of prostaglandins were important in understanding the actions of these NSAIDs. However, it is important to note that the discovery of ibuprofen and other NSAIDs did not proceed with the advantage of knowing how aspirin-type drugs worked.

Adams and his colleagues had assayed the anti-erythemic activity of a number of salicylates that had been proposed or shown to have anti-inflammatory or pain-relieving effects in rheumatic patients, including the hydroxylated metabolites of salicylate, most of which had proved to have low or nonexistent activity. These results on the development of salicylates and other NSAID derivatives at that time have been discussed in an extensive review by Adams and Cobb (1967) and also by Rainsford (1984). The stage was therefore set for developing a 'super' aspirin. The UV erythema assay had been validated and, in general, a number of salicylates/benzoates tested, most of which had been found to also have comparable (in)activity in patients (Adams and Cobb, 1967).

1.4 Compounds in Development

The case for chemical support set out in the report (No. 848) by Dr Adams was successful and the late Dr John Nicholson, an organic chemist (see later), joined Adams and a testing programme was commenced using the guinea-pig UV erythema.

It was clear from report No. 848 that the first compounds to be made would be salicylates and phthalates. There was great optimism, since such compounds had never been investigated before, that agents more potent than aspirin would emerge. This proved to be so, but sadly they were always more toxic than aspirin. This line of attack was therefore abandoned, but the studies proved invaluable since they indicated the importance of the carboxylic group of aspirin for anti-inflammatory activity. It was therefore decided to examine a range of simple compounds with carboxylic acid moieties. Among these a number of phenoxyalkanoics were found to be more active than aspirin in inhibiting the UV erythema. This group of compounds were originally made by Boots as herbicides and were available in the files at that company (Nicholson, 1982).

It is fascinating to note that two plant growth regulators – an indolylacetic acid and a phenoxyalkanoic acid – were the lead compounds at both Merck and Boots. These eventually led to the development of indomethacin and ibuprofen respectively (Shen, 1971; Nicholson, 1982).

John Nicholson was the chemist who led the team involved in the synthesis of the phenoxy compounds and the other progenitors of ibuprofen. After the screening of over 600 phenoxyalkanoic acids made by Nicholson and his colleagues, two compounds emerged in 1958 with potential anti-inflammatory activity: BTS 7268 with twice the anti-inflammatory activity of aspirin and BTS 8402, which was 6–10 times more potent (Table 1.1). The ethyl ester of BTS 8402 was prepared on the basis that this might have less gastric intolerance than aspirin but was found inactive in the treatment of rheumatoid arthritis at 1.8 g daily (Nicholson, 1982). As Adams (1987a) queried: 'Did this mean that after seven years our entire programme had been based on a false hypothesis – and if so, what should we do next?'

The turning point came with Adams adopting a newly published American technique for analgesic activity, the Randall–Selitto assay based on the relief of pain from pressure applied to the inflamed paws of rats. Up to this time there was no method of showing an analgesic action of aspirin in animals at reasonable oral doses. Using this technique and an anti-pyretic assay it was discovered that the analgesic activity of BTS 8402 was only comparable with that of aspirin and that its antipyretic activity was even lower (Table 1.1).