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History and Development of Ibuprofen

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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

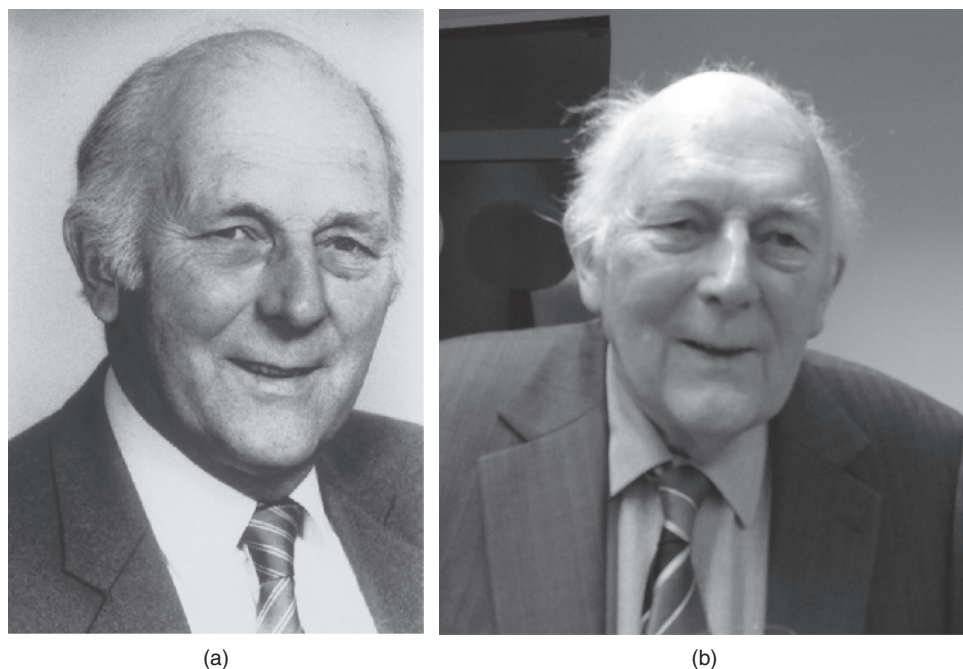


Figure 1.1 A photograph of Dr Stewart Adams taken in 1987 (a) and a recent photograph taken in 2012 (b).

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-inflammatory 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.

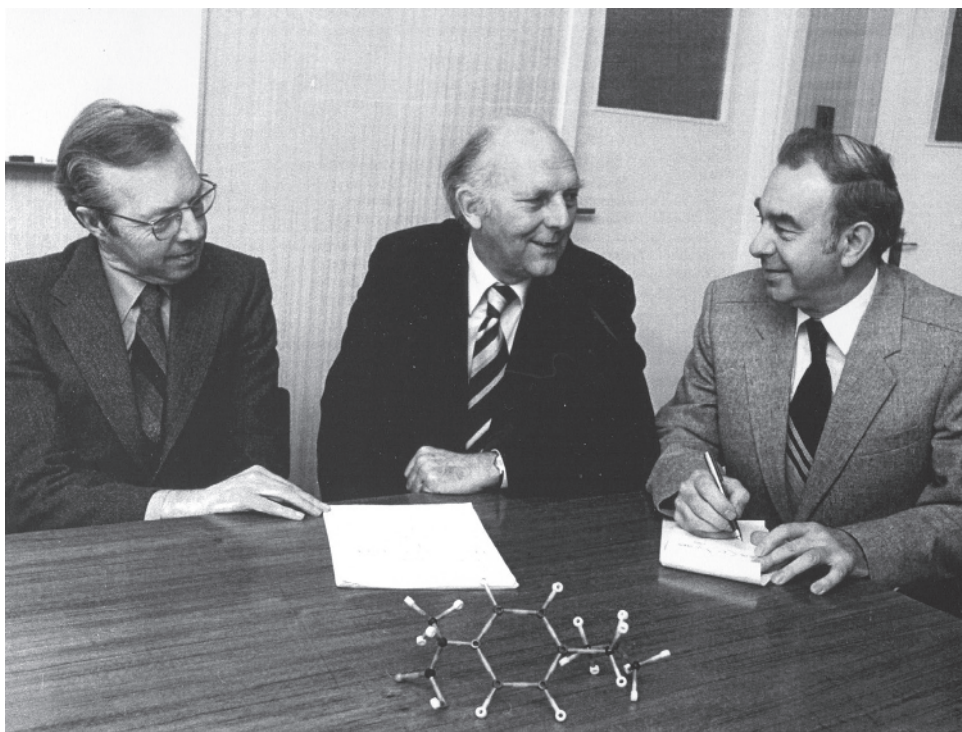


Figure 1.2 The 'ibuprofen team' comprising Stewart Adams (centre) with his technician, Colin Burrows (right) and John Nicholson (left).

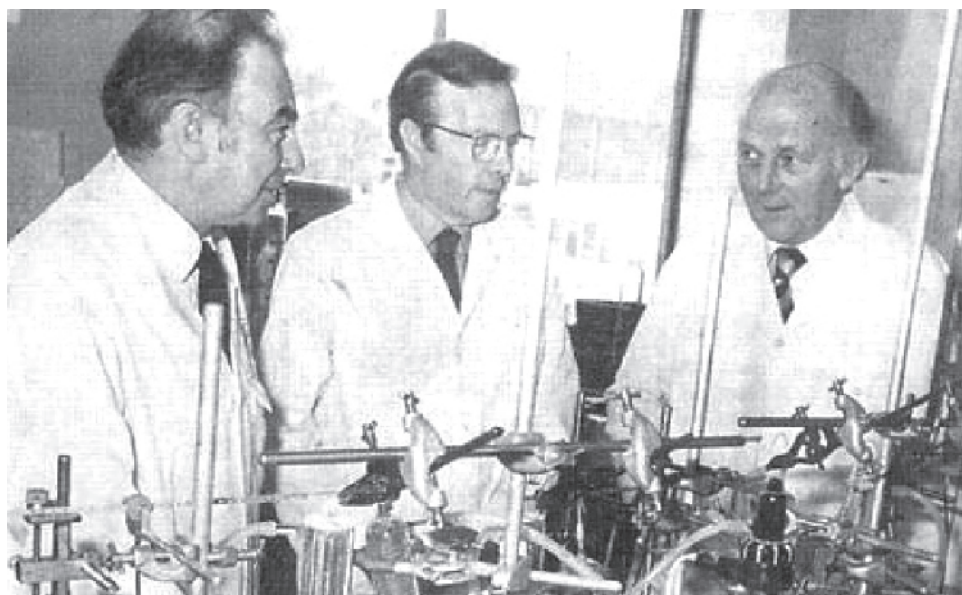


Figure 1.3 Stewart Adams with John Nicholson, Colin Burrows (right) in the mid-1960s.



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 accidentally 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

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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

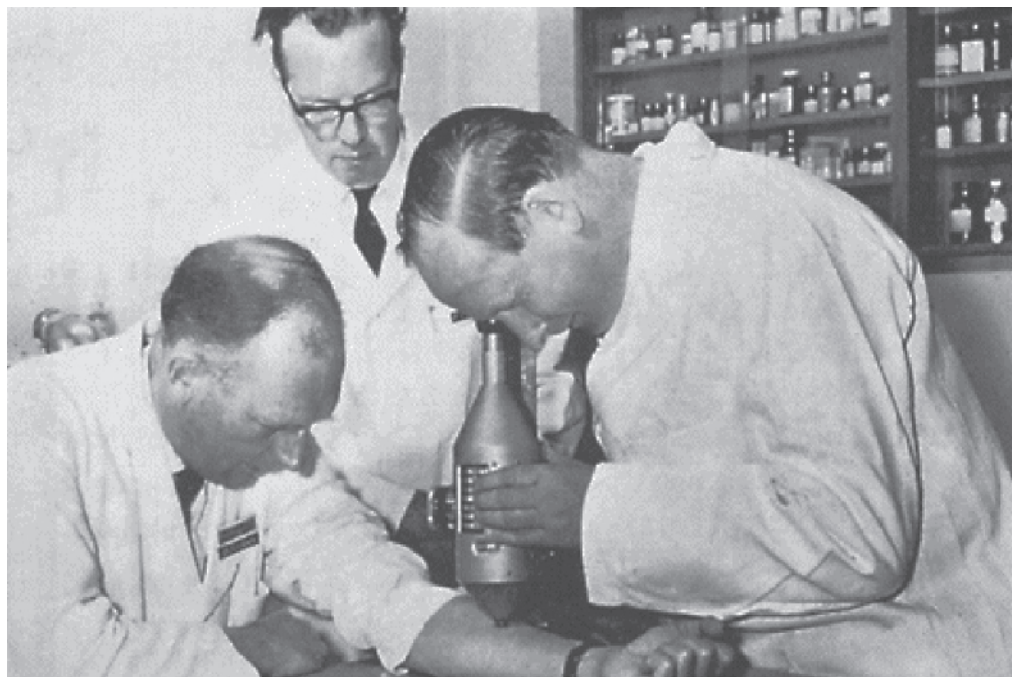


Figure 1.6 Application of the Trafuryl erythema assay on the volar surface of the forearm. Left to right: Adams, Nicholson and Cobb.

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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 P.M. 2229

Animal.	Wt.	Vol	RD number	mg/kg	Result	Animal	Wt.	Vol	RD number	mg/kg	Result
RH	780	3.0	RB 1448	160	2 1	YHT ²⁵	790	1.44	RP 1	80	1 0
RHT	770	3.08		160	0 2	YHT ²⁶	650	2.60	RP 1	160	1 1
RHT	710	0.71	Aspirin	40	1 3	GH ²⁷	650	2.60		160	0 0
RHT	750	1.50	RB 1472	10	0 0	GH ²⁸	650	2.68	Aspirin	160	0 0
RHT	570	1.14		10	0 0	GH ²⁹	710	2.82	RB 1461	20	3 3
RHB	690	2.76	RB 1472	20	0 0	GH ³⁰	700	1.40	RB 1461	10	4 4
RHB	690	2.76		20	0 0	GH ³¹	700	2.82	RB 1461	20	4 4
RHB	620	2.48	Aspirin	160	2 3	GH ³²	630	2.52	RB 1461	20	4 4
BH	760	1.52	Aspirin	80	1 3	GH ³³	670	1.34	RB 1461	40	3 4
BHT	680	1.36	RB 1472	40	1 1	GH ³⁴	660	1.32		40	1 3
BHT	620	1.24		40	0 0	GH ³⁵	600	1.96	RB 1461	80	1 1
BHT	790	3.16	RB 1472	80	2 1	RT ³⁶	720	2.88		80	2 2
BHT	710	2.84		80	1 0	RT ³⁷	720	2.72	RB 1461	20	2 4
BHB	760	0.76	Aspirin	40	2 4	YR ³⁸	740	0.74		20	1 2
BHTB	830	3.32	S 20	240	3 4	YR ³⁹	820	1.64	RB 1461	40	2 3
BHTB	800	3.20	S 21	240	4 4	RB ⁴⁰	750	1.50		40	0 1
BHTB	630	2.52	13599	80	4 4	RB ⁴¹	630	2.52	RB 1461	80	0 2
BHTB	700	2.80		80	4 4	YR ⁴²	660	2.64		80	1 0
YH	650	2.60	S 22	240	4 4	YR ⁴³	710	2.84	13103	80	4 4
YHT	780	3.12	S 23	240	3 4	YR ⁴⁴	750	3.08	13088	80	3 4
YHT	580	1.16	Aspirin	80	0 3	YR ⁴⁵	580	2.32	13122	40	4 4
YHT	700	0.70	RP 1	40	0 0	YR ⁴⁶	700	2.80	S 11	240	4 4
YHT	750	0.75		40	0 1	YR ⁴⁷	650	2.72	S 13	240	3 4
YHB	630	1.26	RP 1	80	0 0	YR ⁴⁸	600	2.40	S 14	240	4 4
						BTRB	690	2.76	S 15	240	4 4
						BYB	530	2.82	S 16	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.

971700



PATENT SPECIFICATION

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.

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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 e (A 61 k)

COMPLETE SPECIFICATION

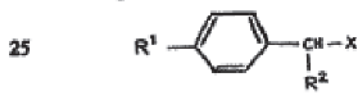
Anti-Inflammatory Agents

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



wherein R¹ represents ethyl, propyl, butyl, alkenyl (C₂—C₆), pentyl (except n-pentyl), alkoxy (C₁—C₆), allyloxy, phenoxy, phenylthio or cycloalkyl (C₃—C₆) optionally substituted by methyl or ethyl in the 1-position, R² represents hydrogen or methyl and X represents the radical COOH, COOR³ wherein R³ represents alkyl (C₁—C₆) or optionally N-alkylated aminoalkyl (C₂—C₆), COOM wherein M represents the ammonium ion or a single [Price 4s. 6d.]

equivalent of a non-toxic metallic cation, COOH.B wherein B represents a non-toxic organic base, CONH₂, CH₃NH₂ or the group CH₂OR⁴ where R⁴ represents hydrogen or lower alkanoyl (C₁—C₆) 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-*i*-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

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).

Table 1.1 Pharmacological activities of some substituted phenoxypropionic, phenylacetic and propionic acids developed by Boots. Activities of the compounds are compared with aspirin rated = 1.

BTS No.	Structure	Activity (Aspirin = 1)		
		Anti-inflammatory	Analgesic	Antipyretic
7268		2		
8402		6–10	1–2	0.4
10335		4	4	2–4
10499		4	10	4
Ibufenac		2–4	2–4	4
Ibuprofen		16–32	30	20

From Adams (1987a). Reproduced with permission of the Editor of Chemistry in Britain.

Adams then postulated that to have anti-rheumatic activity these compounds should have the triad of analgesic, anti-pyretic as well as anti-inflammatory activities, properties that were found in the closely related phenylalkanoic acids (Nicholson, 1982).

Even before the demise of the phenoxyalkanoic acids in the 1960s, Nicholson had moved on to develop phenylalkanoic acids, of which the 4-biphenylalkanoic acids had been found to be very potent (Nicholson, 1982) but also very ulcerogenic in the gastrointestinal tract of dogs. A very interesting decision was made at this point to first develop the somewhat less potent phenylacetic acids rather than the propionic acids because it seemed, in view of toxicological data then available, that a safer candidate product could be selected from this less potent group (Nicholson, 1982). In retrospect this approach, prompted by a concern for safety and the belief that the propionics were more toxic than they eventually proved to be, was a wrong decision that cost several years work.

From the phenylacetic acids that were synthesized by Nicholson, three compounds emerged (Table 1.1) that had the triad of therapeutic activity sought by Adams. The first of these, BTS 10335, proved active in rheumatoid arthritis but was abandoned in the first trial because it produced rashes in 5 out of 12 patients (Adams, 1987a). Unfortunately, the development of skin rashes was not a condition that could have been predicted from animal studies then (though today it might be possible to postulate the occurrence of this based on knowledge of drug metabolism and comparative irritancy studies *in vitro* and *in vivo*).

To be sure that the occurrence of the rashes was not due to manufacturing impurities, three members of the Research Department took highly purified BTS 10335 for one week at twice the dose taken by patients. One of the three subjects developed a severe rash. This clearly established that the effect was inherent in the compound.

1.5 Ibufenac – Almost There, but for Liver Toxicity

The next candidate selected for clinical trial was ibufenac, BTS 11654, a 4-isobutylacetic acid, which proved effective in clinical trials in rheumatoid arthritis and did not produce rashes. Unfortunately, after prolonged use it produced marked liver toxicity in some patients in the United Kingdom (Adams, 1987a). There had been no evidence of liver toxicity in any of the animal studies performed by Dr Barrie Lessel. Curiously, this side-effect did not occur in Japanese people, for reasons that are still not apparent. Indeed, ibufenac continued to be used successfully in Japan for several years after it was withdrawn in the United Kingdom (Adams, 1987a) whereupon it was superseded by ibuprofen in that country.

1.6 More Setbacks

In the meantime another acetic acid, BTS10499, with a cyclohexyl moiety in the 4-position, was found effective in rheumatoid arthritis patients but, again, this compound produced rashes and was therefore discarded (Adams, 1987a).

1.7 More Learning

A key finding emerged from studies carried out by Dr Eric Cliffe on the biodisposition of radiolabelled 4-substituted phenylacetic acids compared with that of the 4-phenylpropionic acids (Adams, 1987a). It emerged that the former were distributed more extensively in the body and accumulated in a number of organs to nothing like the same extent as the 4-phenylpropionic acids (Adams, 1987a). Moreover, some early fears about the gastric ulcerogenicity of the propionics in dogs were allayed when further studies showed that some of these compounds had very long plasma half-lives in dogs. Since it had already been shown by Lessel and Adams that the main ulcerogenic action of these compounds was systemic rather than local (a completely unexpected novel finding), it was possible to predict that the clinical potential of the more potent propionics was better than originally thought.

It was these and later findings of the high toxicity of long half-life phenylpropionics in rats that convinced Adams of the importance of plasma half-life in the safety of NSAIDs, and that one of the major factors relating to the safety of ibuprofen was its short half-life of about 2 h. Many years later, based on these earlier experiences, he published data to show that there is a relationship, clinically, between adverse reactions of NSAIDs and their half-lives (Adams, 1987b, 1988).

1.8 Ibuprofen

It is ironic that eventually there was a surfeit of active phenylalkanoic acid compounds: activity occurred over a wide chemical range. It was necessary, therefore, to perform extensive biochemical and toxicological studies among a number of preferred compounds before ibuprofen, not the most potent, was chosen as being potentially the safest. This decision was based on a whole range of biological data – pharmacological, biochemical and toxicological – that had by then been collected on the phenylalkanoics, and the decision to choose safety rather than potency has proved to be the correct one.

1.8.1 First Clinical Trials

The first clinical trials with ibuprofen (RD 13621, *syn.* BTS 13621) were performed by Dr Tom Chalmers of the Rheumatic Diseases Unit at the Northern General Hospital, Edinburgh in six patients with rheumatoid arthritis. His report of 8 February 1966 describes a randomized trial in which ibuprofen was given at

two dosage levels of 300 mg or 600 mg daily for one week at a time and the results compared with that from one week's treatment with aspirin of 3.6 g/day. The allocation to individual drug treatment was random, but there was no washout period in between. Laboratory investigations were performed at the beginning and end of each week of the trial and included Haemoglobin, erythrocyte sedimentation rate, total leukocyte and platelet counts, liver transaminases, prothrombin activity, serum urate, urine analysis and tests for occult blood. The patients were assessed for grip strength, joint tenderness and joint size each day.

The results obtained are shown in Figure 1.9, from which it can be seen that ibuprofen at both 300 and 600 mg daily produced improvement in grip strength and that there was a trend towards improvement in pressure tolerance (a measure of joint tenderness) with less marked improvement in joint size. One patient on aspirin 3.6 g daily showed faecal occult blood while all the others showed a weak or negative reaction. There were no differences in laboratory parameters observed with any of the treatments. Dr Chalmers noted in his report: 'The pattern of daily measurements [however] shows that throughout the three weeks of trial there was a trend to slight improvement unrelated to the sequence of treatments. This in turn

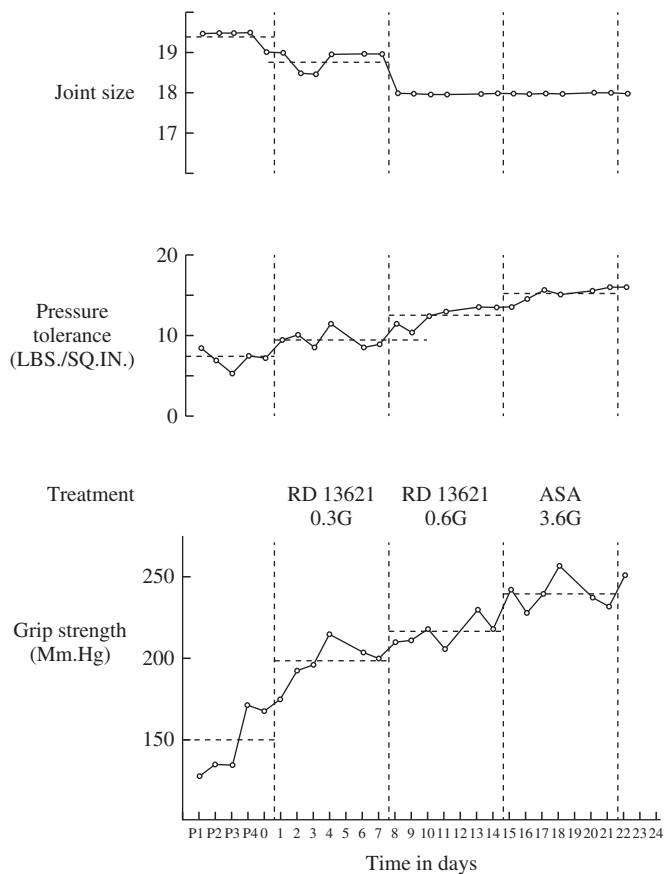


Figure 1.9 Original graphs from the report of Dr Tom Chalmers of the Rheumatic Diseases Unit, Northern General Hospital at Edinburgh, of the responses of a patient to effects of ibuprofen (RD 13621) compared with aspirin.

suggests that RD 13621 was adequate substitution for aspirin in the dosages compared and that there was little difference between the two dosages of RD 13621.'

The side-effects were minor and included one patient having reported flatulent dyspepsia on 300 mg ibuprofen and another on 3.6 g aspirin; significantly, no skin rashes were reported.

In retrospect it is surprising in view of later recognition of the daily dosage of 1200–2400 mg being the most effective range that Chalmers found that 300 and 600 mg/day ibuprofen was as active as 3.6 g/day aspirin. However, these results obtained by Chalmers were a great impetus to the programme.

In fact ibuprofen has never been as potent in humans as the animal data (Table 1.1) suggested (16–32 times that of aspirin), for clinical potency is more in the region of three times that of aspirin (see Chapter 6).

Ibuprofen was originally launched in the United Kingdom in 1969 for the treatment of rheumatoid arthritis at a daily dosage of 600–800 mg, but the results were disappointing. Some clinicians, on the basis of their own experience of good safety, increased this dosage to 1200 mg/day. Later, following extensive clinical trials, the recommended dosage was raised to 1200 mg/day and later to what is now the approved prescription dose in the United Kingdom of 1200–2400 mg/day. In 1974, ibuprofen was launched by Upjohn in the United States as Motrin™ at a daily dose of 1200 mg/day with eventually a top level of 3200 mg/day.

However, there were still disappointments from some of the earlier clinical investigations at the low dosages of 600–900 mg/day of ibuprofen. Thus, Dr Peter Boardman, Dr (now Professor) George Nuki and Dr Frank Dudley Hart (1967) reported that daily dosage with 900 mg ibuprofen failed to produce significant improvement in 20 patients with rheumatoid arthritis, or in 19 patients with osteoarthritis given 600 mg ibuprofen daily (Boardman, Nuki and Dudley Hart, 1967).

Additionally, in a more extensive series of rheumatic patients, including 5 who were in a single-blind pilot study, 43 in a double-blind trial and 51 with rheumatoid arthritis in an open-label investigation, Thompson, Fox and Newell (1968) found that (a) 600 mg ibuprofen daily was effective in relieving pain and morning stiffness; (b) in a controlled clinical trial 600 mg ibuprofen daily was superior to 3 g daily paracetamol; and (c) ibuprofen given to 55 patients for up to a mean of 38 weeks even up to dosages of 1000 mg daily was effective and without any significant side-effects. This trial was important since it was the first to indicate that ibuprofen could be given to patients unable to take aspirin or other preparations because of dyspepsia.

While there were later reports of variable effects of 300 and 600 mg ibuprofen (Symposium, 1970) it was clear that the drug was safe in these low dosages. In later trials it emerged that higher doses were more effective as well as being relatively safe, especially in the gastrointestinal tract (see the review in Chapter 6).

A summary of the history of the development of ibuprofen is shown in Table 1.2.

1.8.2 Gastrointestinal Safety

Gastrointestinal safety was always a concern in both the pharmacological and clinical studies. In the early clinical trials of 600–900 mg/day ibuprofen only a few subjects had evidence of faecal occult blood and this was much lower than observed in patients who received anti-inflammatory doses of aspirin (Wallden and Gyllenberg, 1970). Cardoe (1970) had noted that 42 arthritic patients who had a history of peptic ulcer disease tolerated ibuprofen when given for 1–24 months, averaging 11 months in all. In this study 34 patients showed 'excellent tolerance' with no indigestion, 3 others had a good response, while 5 others had exacerbation of ulcer symptoms. In 45 patients with a history of gastric intolerance, Cardoe (1970) found that there was excellent tolerance in 34, in 5 it was good (only requiring antacids or 'alkalis') while in 6 it was poor in those patients who received the drug for 3–24 months. These results are impressive in highlighting the gastrointestinal safety of ibuprofen in patients with susceptibility to ulcer disease even though the doses employed were relatively low by present-day standards. The gastrointestinal blood loss from 800–1800 mg/day ibuprofen was also found by Thompson and Anderson (1970) to be no different from

Table 1.2 Summary of the history and developments of the anti-inflammatory project at Boots.

1953	Initial thoughts and discussions on a search for aspirin-type drug
1955	UV erythema in guinea-pig; began preliminary investigations
1956 (Mar.)	Report No. 848 on UV erythema technique, with recommendations for a chemical programme of work
1958 (Aug.)	First inhibitors discovered of UV erythema: phenoxy acids
1958 (Nov.)	RD 8402 (a phenoxy acid) made
1960	RD 8402 in clinical trial
1960	RD 10335, RD 10499 and ibufenac made
1961 (Jun.)	RD 10335 active clinically, but rash in 50% of patients
1961 (Dec.)	Ibuprofen made
1962 (May)	Ibufenac active clinically, no rash
1963 (Mar.)	Clinicians' meeting on ibufenac
1964	RD 10499 in clinical trial; active, but rash in 20% of patients
1964 (Apr.)	Ibuprofen made product candidate
1964 (Aug.)	Ibufenac started in clinical trials in Japan
1966 (Feb.)	Ibuprofen shown to be active in clinical trial
1966 (Apr.)	Ibufenac on UK market
1967 (Nov.)	Clinicians' meeting on ibuprofen
1968 (Jan.)	Ibufenac withdrawn from UK market because of liver toxicity
1968 (Mar.)	Ibufenac marketed by Kakenyaku Kako Company Ltd (Kyoto and Tokyo) in Japan; superseded later by ibuprofen
1969 (Feb.)	Brufen™ (ibuprofen) launched
1970	First Symposium on Ibuprofen at the Royal College of Physicians, London
1983	Approval for ibuprofen OTC in UK (Nurofen™ launched 8 August 1983)
1984	Approval for ibuprofen OTC in USA

that with paracetamol or placebo, whereas that from calcium aspirin was appreciable. These studies must have given considerable encouragement to those at Boots that at last they had found a replacement for aspirin in rheumatic therapy with much improved gastrointestinal tolerance.

1.9 Achievements and Rewards at Last

Throughout this programme of drug discovery involving the examination of over 1500 compounds made specifically for the project, the failure of four clinical candidates, and 15 years' hard work on animal model development and drug synthesis, it was sheer perseverance that led to the development of ibuprofen. Much of the credit for this success must go to Stewart Adams, the Project Leader, and his small team. His original report in 1956 outlining his hypothesis and proposals for a chemical programme was the foundation on which the whole of the future project was built. The progress with this research and discovery was dotted with successes and many failures. At times the likelihood of the programme proceeding must have been threatened. These days many programmes of this kind might be closed down or lost in the numerous company amalgamations that proceed. However, it is to the credit of the senior management of the Research Department of Boots Pure Drug Company that this research progressed without interference despite what appeared to be frequent failures.

To the people involved, therefore, go our congratulations and admiration. First, to Stewart Adams who studied pharmacy at the University of Nottingham (BPharm, 1945) and later gained a PhD degree in pharmacology at the University of Leeds. He was made a Visiting Professor at the University of Nottingham in 1977 and awarded the Order of the British Empire in 1987 in recognition of his research culminating in

the discovery of ibuprofen. Recently, at the age of 90 years he was made a Freeman of the City of Nottingham in recognition of the outstanding contributions he has made to the pharmaceutical industry, pharmaceutical sciences and pharmacology from his fundamental discovery of ibuprofen as well as the related drug, flurbiprofen, both of which set the foundations for the extensive developments of the large number of non-steroidal anti-inflammatory drugs (NSAIDs) that have been produced since.

The late John Nicholson was another key figure who worked closely with Adams for 20 years. He was a quiet, thoughtful and highly experienced organic chemist. A graduate and postgraduate of Oxford University, he was a precise and talented chemist with a prolific output. It was Nicholson who made the critical decision to move from the phenoxy to phenyl acids and with his colleagues in the Chemistry Division eventually synthesized specifically for the project over 1500 compounds, of which approximately 450 were alkyl-substituted phenylalkanoics. It is a pity that through premature and untimely death he was denied any recognition for his considerable insight and talents in his synthetic efforts and the development of ibuprofen.

On a personal note, Dr Adams has expressed his particular indebtedness to two people. First, to Colin Burrows – just the two of them began these studies. He supervised the work in Adams' laboratory with great skill and worked closely with him over the next two decades. Second, to Ray Cobb (Figure 1.10) of the Medical Department with whom, particularly in the critical early days when struggling to find a way forward, Adams had many invaluable discussions that continued for many years afterwards.



Figure 1.10 A recent photograph of Ray Cobb who was a much valued collaborator of Dr Adam's and with whom he published studies on the structure–activity relationships of aspirin, salicylate and benzoic acid analogues as well as the properties of anti-rheumatic agents (Adams and Cobb, 1958, 1963, 1967).

The Head of the Medical Department, Dr Eric V. B. Morton, gave much valued enthusiastic support and motivation in the early years of the project and made introductions to a number of leading UK rheumatologists. The key element of personal contact emerges in the philosophical basis and development of ibuprofen. Dr Morton had known Professor J.J.R. (Ian) Duthie, who a leading rheumatologist at that time and was the Director of the Rheumatic Diseases Unit at the Northern General Hospital in Edinburgh where the first clinical trial of ibuprofen was performed by Dr Chalmers. As can be gleaned from the report by Stewart Adams in 1956, Professor Duthie, then a leading authority on the rheumatic diseases, had given much good advice. His support for the idea of a 'super' aspirin and that aspirin had something 'special', strongly backed by Dr Morton, meant that the plea for chemical support in report No. 848 was accepted and shortly afterwards John Nicholson joined Adams. These personal aspects were obviously of great significance as well as serving to create the basis for the expansion of the project. The enthusiastic participation of physicians, coordinated by Dr J. Warwick Buckler, in the early clinical trials in the United Kingdom should also be noted, among them Drs John Golding (Harrogate), Malcolm Thompson (Newcastle), Neil Cardoe (Norwich), Frank Dudley Hart (Westminster) and Watson Buchanan (Glasgow), to name a few. At a very early stage in the life of ibuprofen, Dr Thompson suggested its potential as an OTC alternative to aspirin.

1.10 Ultimate Recognition of Safety – OTC Status

The recent history of ibuprofen has now progressed to this drug having been approved for non-prescription or over-the-counter (OTC) use in many countries throughout the world, for over a decade and a half in many. This has been a major landmark for the drug in that granting of OTC status has been recognition of its well-established safety record (Paulus, 1990; Rainsford, Roberts and Brown, 1997; Rainsford and Powanda, 1997; Rainsford, 2011, 2013a, 2013b).

The Boots Company initially applied to the UK Department of Health and Social Security (DHSS), in August 1978 to have ibuprofen, on the basis of its safety record, allowed for non-prescription sale for the treatment of muscular and rheumatic pain, fever and backache with a unit dose of 200 mg and a maximum daily dose in adults of 1200 mg (Adams and Marchant, 1984). This application was made with no supporting studies. However, the Committee on the Safety of Medicines (CSM) of the DHSS provisionally concluded in May 1979 that on the grounds of safety it was unable to recommend to the Ministry to grant a product licence.

A small group under Dr Colin Lewis then proceeded to collect all the data on the safety of ibuprofen and initiated further studies on this aspect. The data thus obtained from 19 000 patients in clinical trials conducted/sponsored by Boots, retrospective analysis of 1957 patients in the United States and adverse drug reaction reports were incorporated in a revised application submitted to the DHSS in April 1982. Dr Mervyn Busson (Figure 1.11), a medical graduate from the University of Bristol (1958) who had been experienced in a number of hospital specialties including general practice was initially appointed as a medical advisor in the Marketing Department at Boots, trained as a pharmaceutical physician and was subsequently appointed as Director of Medical Sciences responsible for clinical development worldwide. During the period around the 1980s it appears that the Medicines Division of the UK Department of Health made policy changes in recognition of the increasing realization of the importance of 'self-care' and that medicines for patients self-medicating would have to be proven to be safe. Dr Busson proceeded to set up clinical trials to compare ibuprofen (BrufenTM) in comparison with other NSAIDs with emphasis on safety. In particular, his focus was to adopt a new innovative approach for the problem of switching medications from prescription only (POM) to sales supervised by pharmacists (P) or alternatively for general sales outside pharmacies (GSL). The issues that confronted progression of ibuprofen from POM to P status in the 1980s and harmonization across the European Economic Community of the pioneering OTC requirements for efficacy and safety of ibuprofen have been reviewed by David Carter, the Head of Product



Figure 1.11 Dr Mervyn Busson, Director of Medical Services at Boots who was responsible for clinical developments of OTC ibuprofen worldwide.

Registration at Boots (Carter, 1988). The Medicines Division subsequently published the complete programme (MLX 133) as a directive for future OTC applications. This directive has since been adopted around the world as more ethical products are licensed for OTC sale.

The CSM decided in December 1982 to consult with interested bodies regarding the possibility of changing the status of ibuprofen from prescription-only to pharmacy sale. Those organizations that were consulted included the Pharmaceutical Society of Great Britain, The Proprietary Association of Great Britain, the medical profession and The Consumers Association. From these consultations, discussions were undertaken in January 1983 between the DHSS and Boots concerning the conditions of licensing the drug for non-prescription use.

These discussions included: (a) the indications for use of ibuprofen OTC should not exceed those for aspirin, (b) there should be a warning that the drug should not be taken by patients with stomach ulcers, (c) all advertising material should be submitted to the DHSS for approval and (d) pharmacists should be advised about the product prior to advertising. Adams and Marchant (1984) noted in regard to the warning for gastric ulcer patients that this was not then required for aspirin! The licence was enabled by the amendment to the prescription-only medicine (POM) order on 31 July 1983 (Adams and Marchant, 1984).

Initially the indications for use of the drug in treating dental pain, migraine, period pain and other painful states were approved in the 1970s for prescription use. Later, as safety and efficacy were proved, these indications were extended to OTC use.

Nurofen™, the trade mark brand of ibuprofen, was launched by the Boots subsidiary, Crookes Products Ltd, on 8 August 1983. A year later ibuprofen was given approval by the US Food and Drug Administration for OTC sale on the grounds of proven safety, efficacy being accepted (Paulus, 1990). A submission to the FDA was made by Whitehall Laboratories Division of American Home Products (New York, NY, USA) in association with Boots, and Whitehall Laboratories later marketed ibuprofen as Advil™ under arrangements with Boots.

From the UK and US government viewpoints the granting of OTC status for ibuprofen was a landmark decision. The major issue for the drug regulatory authorities of both governments was the safety of the drug. As one of the earliest prescription drugs to move ('switch') to OTC status, its success and good safety record as an OTC product must have had a significant influence on the decision of health authorities to deregulate many other NSAIDs and other prescription medications.

1.11 Worldwide Developments

Boots had a long-standing research agreement with The Upjohn Company (Kalamazoo, MI, USA), who in 1967 took up their option and accepted ibuprofen as a product candidate for clinical trial. They proceeded to carry out the necessary additional laboratory and clinical studies for eventual FDA approval in the United States and this was granted in 1974. Thereafter they marketed ibuprofen under the trade mark Motrin™. Upjohn made a valuable contribution to the success of ibuprofen, not to its discovery or development, but on the clinical side where, with their large clinical resources, they were able to explore new indications and higher dosages to an extent that Boots' own limited clinical resources could not have done.

In the 1970s and 1980s both Brufen™ and Motrin™ rapidly found wide acceptance by the rheumatologic and other specialists and family/general practitioners as what has probably been regarded as a 'first-line' treatment of pain and inflammation in a wide variety of muscular-skeletal and other conditions. Today Brufen™ is marketed by Abbott Laboratories Inc. following the sale of this brand by Boots (and later BASF). Motrin™ is now marketed by McNeil Consumer Healthcare. Numerous other companies now market ibuprofen for OTC and prescription use under a whole range of brand names. Appendix A shows a list of the immense range of ibuprofen products and brand names for the drug that are now available worldwide (the list is by no means complete but does illustrate this point). The extensive commercial development and applications of ibuprofen are a tribute to the pioneers who struggled to develop the fundamental pharmacology and medicinal chemistry leading to ibuprofen, The Boots Company who persevered with research and development, and the medical and scientific community who studied the efficacy, safety and actions of the drug.

1.11.1 Evolving Applications of Ibuprofen

Much of this chapter has dealt with those involved in the early years of the development of ibuprofen, but it must be remembered that as a drug candidate progresses towards being a product many others become involved. There were increasing demands on those involved in toxicological, metabolic, pharmaceutical and clinical studies (and in the case of ibuprofen for 20 years after its launch), as well as in the development of new synthetic processes for large-scale production (now thousands of tons). Indeed, a completely new factory using the latest technology was designed and built at Boots for what was a fairly complicated eight-stage manufacturing process.

Among the tributes to the scientific and technical originality and clinical success of Brufen™ and the Research Department of the Boots Company was the highly prestigious Queen's Award for Technological Achievement, which was given to the company in 1985. By this time over 100 million people had received treatment with ibuprofen in 120 countries throughout the world. It has recently been estimated that there are over 54 million users of the drug worldwide. Annual sales amount to over \$3 billion. From the IMS Health database it is estimated that there are in excess of 50 marketed forms of ibuprofen (e.g. different oral and topical formulations). With about 10 000 original research publications in which research and clinical studies have been reported using this drug, notably also as a standard of comparison, it can truly be considered to be a well-established standard representative of the class of NSAIDs.

Acknowledgements

I should like to specially thank Prof Stewart Adams for his generosity and invaluable help in compiling this chapter, for Figures 1.1 to 1.9 and for extracts from laboratory notes and reports that were used to compile the history of the development of ibuprofen. My thanks to Dr Mervyn Busson, Dr Paul and Mrs Diane Bresloff, Dr John Turner, Dr Ray Cobb, Professor Ian Hunneyball and many other colleagues at the Boots Company for additional insights into the various stages in the development and marketing of ibuprofen at Boots and other companies.

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