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Inflammopharmacology

OBITUARY

Dr. Stewart Sanders Adams (16 April 1923 to 30 January 2019)

Pioneer in the discovery of ibuprofen, that from meagre beginnings to become world's best-selling pain-killing drug.

It is with much sadness that we record the death of Dr Stewart Sanders Adams aged 95. He has become known as the 'father of ibuprofen', having been leader of the team in Boots Research Department, Nottingham, that discovered and developed ibuprofen, the popular world-wide drug for the treatment of inflammation, pain and fever. Initially, the drug was developed for treating rheumatoid arthritis and later other arthritic and painful conditions. After proof of its safety it later became a popular non-prescription analgesic. Readers of this journal will observe that aspects of the therapeutics, mechanisms of action and side-effects ibuprofen has frequently been reported (see Publications below) (Fig. 1).

Stewart was born in Byfield (a town in the English midland county of Northamptonshire) on 16th April 1923, the son of a railwayman and was educated at Doncaster and March Grammar schools (Yorkshire). He left in 1939 age 16 to begin an apprenticeship in the local Boots pharmacy. After 3 years in retail pharmacy he decided his future was in biological research and he graduated BPharm from the University College Nottingham in 1945. His first job was in Boots penicillin production unit in the early days of the development of penicillin. It was produced by surface culture in which the penicillium mould was grown in quart milk bottles. The work though important, was rather routine, so Adams in 1947 moved to the Pharmacology Division of the Research Department. His first research interest was in the anticoagulant heparin, and in 1948 he developed a unique assay for heparin much superior to that then employed, which became the recommended method in the British Pharmacopoeia. He developed an interest in the anti-lipaemic (fat-reducing) properties of heparin and aimed to develop a heparinoid with maximal anti-lipaemic and minimal anticoagulent properties for use in patients with heart disease. A series of such compounds were produced by sulphating polysaccharide extracts from Laminaria seaweeds was investigated. However, the best of these was found to be too toxic in early clinical trials and was hence abandoned.

Other studies with heparin led him to believe that heparin and histamine co-existed in the mast cell and he continued these and related studies in the pharmacology department at Leeds University where he obtained a PhD.

In 1952 he re-joined Boots Research Dept to work on rheumatoid arthritis. The pharmacology division was housed in a group of rambling buildings on the outskirts of Nottingham having moved there at the beginning of WW2 from the city centre as a precaution against bombing; this proved a wise move since part of the research department was destroyed in an air raid in 1941. The first 6 years of his research (1953–1959) was carried out under challenging conditions since his laboratory was one of the two front rooms of a terraced house in West Bridgford. He began with one technician (Colin Burrows, who became a life-long colleague). In 1953, the only drugs of proven value in the treatment of rheumatoid arthritis were cortisone-like, very high doses of aspirin and phenylbutazone. However, these produced side-effects particularly gastric injury, so Adams saw the need for a non-cortisone-like compound but with anti-rheumatic properties that would be well tolerated particularly by the gut. He was one of the first investigators in this field and these compounds later became known and widely used as non-steroidal anti-inflammatory drugs (NSAIDS).

Aspirin was known to be an analgesic and anti-pyretic (pain and fever) but its anti-inflammatory effects were not generally recognised at that time.

Adams became convinced, that the analgesic effects of aspirin were due entirely to its anti-inflammatory properties and began a search for a suitable animal model to demonstrate this specific effect. Eventually, he found a simple type of inflammation model, the UV erythema the guinea pigs (mild "sunburn"), which he discovered could be inhibited by oral doses of aspirin. He showed that there was a difference between paracetamol and aspirin since the former did not possess anti-inflammatory activity and was hence less effective in rheumatic diseases. Although aspirin had been in clinical use since 1900, no analogues had ever been tested for anti-inflammatory action. In a seminal internal report in 1956, Adams outlined his

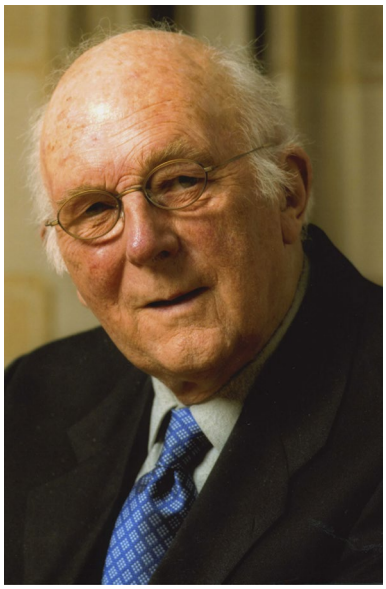

Fig. 1 Stewart Adams in the 1980s

Fig. 2 Stewart Adams receiving the Scroll for the Freedom of the City of Nottingham, with Ian Malcolm, the Sheriff of Nottingham on his right, and Merlita Bryan, the Lady Mayoress of Nottingham on his left

Fig. 3 Stewart with David and Chris Adams

plans for future work which included a chemical programme to explore this. He was joined by the late Dr. John Nicholson an organic chemist and they made and tested over 200 analogues but to their great disappointment none was superior to aspirin. However, these aspirin studies led Nicholson to a group of compounds chemically related to selective weed-killers. The most potent of these possessed high anti-inflammatory activity but failed in clinical trials in rheumatoid arthritis. Hence, the early concept of the primacy of acute anti-inflammatory activity was modified by the inclusion of additional tests for analgesia. Further chemical modification by Nicholson led to new compounds (phenyl acetic acids) three of which were active in clinical trials in rheumatoid arthritis, but unfortunately all had unacceptable side-effects. Studies were performed with radioactively-labelled drugs to determine their biodisposition in dogs. These studies led, to the identification of closely-related propionic acids (phenyl-propionic acids), being a large group of active compounds that might be better tolerated in the liver. Although ibuprofen was not the most active in the group, it was selected for being less toxic. It proved to be effective and well-tolerated in clinical trials and in wider use. Detailed history of the discovery of ibuprofen is shown in Table 1).

After extensive clinical investigations with ibuprofen in rheumatic conditions (as Brufen™) evidence accumulated that it was relatively safe, especially at daily doses of 1200–2400 mg/day. It was introduced in the UK as a prescription anti-rheumatic in 1969. A major development then proceeded in 1983, after further additional studies and safety data, as it was the first NSAID to be approved in the UK and next year in the USA as an over-the-counter (OTC) non-prescription drug for treatment of mild to moderate pain and fever. Much of the efforts in enabling the drug to be accepted as an OTC drug goes to Dr Mervyn Busson, who as Director of Medical Services was responsible for clinical development of OTC ibuprofen. Now over 20,000 tons of drug are produced world-wide annually where it is marketed in a variety of formulations and trade mark names. The success of ibuprofen in being developed in so many formulations is in many ways due to its unique chemistry. It's relative safety is undoubtedly also related to its special chemical properties. Today the fact that it is used as a basis for comparison with newer anti-inflammatory drugs and natural products gives credence for it being regarded as a 'bench-mark' for comparison. Many of these advances would never have been realised back in the early years of the discovery by Adams and his team and would not have been possible without his unending perseverance and determination.

The propionic series was investigated further resulting in the development of a more potent propionic acid, the NSAID flurbiprofen (Froben™) in 1977. It was launched on a rather crowded NSAID market somewhat late, but has been useful in various painful conditions, including bone pain. It has been explored for potentially unique pharmacological properties among them certain cancers.

Table 1 Brief summary of the history of the discovery of ibuprofen and subsequent world-wide development From: Rainsford (2011). Reproduced with permission of Springer (Basel) AG

1953	Dr Stewart Adams at Boots; plans search for replacement for aspirin
1955	Development of guinea pig UV erythema as a potential screening assay for new compounds with anti-inflammatory activity
1956	Initiation of chemical development programme by the late Dr John Nicholson. Initially, screening of > 200 salicylate compounds – proved no better than aspirin (Adams & Cobb, 1967)
1960	Phenoxy-acid, RD 8402, in clinical trial. New strategy: search for analgesic and antipyretic with anti-inflammatory activity
1961	Phenyl acetic acid, RD 10355, active in clinical trials in RA, but rash in 5/12 patients led to it being abandoned. Anti-erythemic activity of ibuprofen discovered. UK Patent application Feb 1961; final specification Sept 30, 1964.
1962	Iso-butyl-phenyl acetate, Ibufenac, active clinically in RA, with no rash. In 1968 withdrawn in UK because of liver toxicity, but this was not found in Japanese patients. Liver toxicity related to accumulation of radiolabelled drug in liver.
1964	Ibuprofen, a phenyl propionic acid, made product candidate: Compared with aspirin 16-32x more potent as anti-inflammatory, 30x more potent as analgesic (Randall Selitto assay) and 20x more potent as antipyretic. Little accumulation of radiolabelled ibuprofen and low GI toxicity in dogs.
1969 (Feb)	Ibuprofen launched in UK as Brufen®
1970	First Symposium on Ibuprofen at Royal College of Physicians, London
1974	Ibuprofen developed as product candidate in 1967 by Upjohn Co (USA) approved by FDA and launched in USA as **Motrin®**
1983	**Ibuprofen** approved by the UK CSM for Over the Counter (OTC, or non-prescription) sale. Launched by Crookes Products Ltd (Boots subsidiary) as Nurofen® August 8th 1983
1984	Ibuprofen approved by US FDA for OTC sale on grounds of proven gastric safety. Whitehall Laboratories (Division of American Home Products, now part of Pfizer Inc) by arrangement with Boots, later marketed **ibuprofen** as **Advil®**
Present Day	OTC Ibuprofen approved for marketing in over 80 countries world-wide

Adams retired in 1983, but continued with his interest in ibuprofen and lectured widely on this and related topics.

He was appointed OBE in 1988 and awarded an honorary doctorate of science by the University of Nottingham in 2008. He was made an Honorary Freeman of the City of Nottingham in 2013 (Fig. 2). The only other Boots employee to be so honoured was Jesse Boot himself. His work undoubtedly contributed to the Boots Company.

He had been a keen sportsman and rugby player and was a member of Nottingham County Cricket Club and Nottingham Forest Football Club. He read widely with a special interest in modern European history and politics, and was most knowledgeable in these fields.

In 1950 he married Mary Harvey a fellow researcher in the Boots Research Department, who died in 2010. They had two sons one of whom (David) is a Pro-Vice Chancellor and Dean of Research at the University of Nottingham and an international expert on liver disease, while the other (Chris) is a successful solicitor in Nottingham (Fig. 3).

On a personal note, I should like to record my sincere appreciation to Stewart for his long-standing help, advice and guidance on matters related to the discovery and development of ibuprofen. He was a humble person, had great humanity, and recognized the contributions of many others both in the Boots Company as well as collaborators and those who published widely on the drug as well as on inflammatory processes.

Publications on the discovery, development and uses of ibuprofen

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