Aspirin and the Salicylates

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Foreword 1

Where would we be without the salicylates? These convenient-to-use drugs, so freely available for self-medication — even by those who shun the products of the pharmaceutical manufacturers and prefer to use salves, intinctions and other herbal extracts — have been almost indispensable aids to living amongst the literate world for at least two millenia, wherever the fear of pain, the malaise of an infection and restricted movement of joints or muscles were not accepted fatalistically as being beyond relief. That life is so tolerable for so many for much of their allotted timespan is largely because of that bottle of aspirin in the family's medicine cabinet, to tide them over the next bout of toothache, muscular sprain or the 'flu.

The sheer tonnage of aspirin consumed each day and the number of its formulations in the market place are indeed remarkable statistics. Couple this with the widespread use of other salicylates as flavourants, preservatives, 'rub-on' medications etc. and we really see how indispensable this family of drugs and natural products have become for our modern way of life. Yet here, as in several other contexts, to be newer is not necessarily to be better. Drugs promoted as successors to aspirin have never really displaced it in popular acceptance. We are rediscovering some of the virtues of the less gastroirritant salicylates favoured by our forefathers before aspirin became an article of commerce. We are even told in the newspapers that cheap plain aspirin has desirable properties in controlling some forms of diarrhoea, diminishing the risk of thromboembolisms or preventing sickle-cell crises, that place this humdrum drug in the forefront of modern preventive medicine — holding a place in competition with many far more expensive, less safe, prescription-only proprietary drugs.

With this almost overwhelming popular interest in aspirin, it is still amazing how little interest has been shown in this drug by professional pharmacologists (be they biochemical, clinical, neurochemical or otherwise). I well remember the dismay I felt when I wanted to know the structure–action relationships for one of the outstanding biochemical properties of its principal metabolite, the salicylate anion. An answer to this question, I thought, required a couple of hours or so in the library looking up the classical texts or review journals in pharmacology. I ended up by having to purchase many, beg several and synthesize not a few more, chemical variants of this very simple aromatic acid and then test 80 or more of these congeners before I could begin to answer my own question. That was less than 20 years ago. Even 10 years ago, I was still being allotted only 50 minutes to lecture on aspirin and all the non-steroid anti-inflammatory/anti-pyretic/uricosuric drugs together with the treatment of salicylate

overdosage, in a well-established course in modern pharmacology (supported by its own textbook) in an otherwise very enlightened American Medical School. [The brevity of this consideration of non-prescription aspirin and all its successor prescription drugs at that time was further emphasized by including three lectures devoted to gallamine and strychnine, agents hardly encountered in a clinical context!] Fortunately, the academic 'respectability' conferred upon aspirin a decade ago, as a tool to probe the involvement of prostaglandins in many regulatory processes (then commanding the attention of experimental physiologists) has now 'washed over' into investigations of its efficacy, toxicity and clinical interactions with other drugs.

Research on the properties of salicylates manifest in different clinical contexts today proceeds at such a pace that we are now being threatened with another form of ignorance — this time as to what is *in* the literature, there being so much of it — as this volume amply testifies. This book is a timely and worthy successor to those classic reviews of the salicylates by Gross and Greenberg (1949) and the two Smiths (1966), and faithfully reflects the division of interest among different areas of research activity embracing aspirin and the alternative salicylates. That the coverage of some aspects may seem disproportionate *vis-á-vis* others is a strength of this great work in honestly reflecting the *status quo* concerning our wisdom and ignorance as it embraces these long-tried, but perhaps still undervalued, drugs. Matters requiring further investigation are alluded to continually. Critical insights are provided which elevate this book well above a literature compendium; but for even providing that alone, we shall all long be indebted to the author.

An old Chinese proverb says 'Without going out of the door, one can know the whole world.' Certainly this book, which is principally about aspirin, affords considerable enlightenment about topics as diverse as analytical chemistry and paediatric medicine, taxonomy and cartels, enzymology and toxicity, renal functions and rheumatology, to merely name a few. Neglected areas are brought into focus. All that we needed to know about such daunting topics as the many pathways of arachidonate transformations or the complexities of gastric proton secretions are thoughtfully provided herein to illuminate the principal topic under consideration, namely the efficacy and safety of salicylates as always with a promising future, as well as a distinguished record in history, for ameliorating so many of our ailments. *Floreant Salicylatia.*

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Foreword 2

The resilience of aspirin, both as a domestic remedy and a serious drug, evokes mixed feelings amongst scientists and clinicians. There are its detractors who alternately deride it as a weak non-specific pain-reliever and condemn it as a dangerous toxin causing widespread, if low grade, gastrointestinal bleeding and, on occasion, frightening attacks of bronchial asthma. In the middle range are the untold millions of lay people who take it for mild headaches and as an antipyretic and the clinicians who prescribe it as an effective and often first line anti-inflammatory agent in conditions such as active rheumatoid arthritis.

At the other end of the spectrum are the aspirinophiles. Sometimes these are research workers who have used aspirin as a test material in a laboratory system and have been intrigued by the variety and complexity of its effects on biological systems. They are seduced to explore both its history and literature and quite soon become addicted. One of the cardinal signs of such a condition is the production of a monograph on aspirin and its chemical relatives. It is no surprise to see this has now occurred with Kim Rainsford since he has already contributed many useful and original observations to the aspirin story.

Nevertheless it is a pleasure to welcome a work of real scholarship showing an enviable capacity to make sound and critical judgements in a frequently contradictory and confusing welter of facts and opinions. It is made clear that there is much more to the salicylate group of drugs, than aspirin itself. In particular, those aspects of its action, which depend on its ability to acylate biomolecules by non-enzymatic reactions, are recognized and distinguished as being confined to acetylsalicylate. This leads to a consideration of successful and effective drugs recently developed from salicylate, rather than from aspirin.

The main themes of the book are that salicylates are polycompetent drugs in that they influence a large number and variety of biological processes. Their multifactorial actions, in relation to the known therapeutic and toxic effects are clearly described. Secondly, there is a refreshing multidisciplinary approach to the subject covering the whole gamut from chemical to clinical aspects. Finally, the author is very conscious of the pathological basis of disease processes and the effects of these processes on drug metabolism and actions. In short, it is a careful stimulating and up-to-date account of this fascinating and ancient family of drugs written by a discriminating enthusiast.

M. J. H. Smith

Preface

The salicylates are a fascinating group of drugs. Despite their apparent chemical simplicity, they have an immense array of therapeutic properties. We are also now just discovering that they have many exciting new applications.

My interest in this group started some 16 years ago when I went to London to do my PhD with Professor Mervyn Smith on the gastric mucosal reactions to the salicylates. In one sense this may have been regarded as a negative introduction to the salicylates, for by analysing the side-effects of a drug one can all too readily become somewhat engrossed in these aspects and develop a feeling that the drugs have nothing more than untoward effects with little therapeutic value by comparison. I soon learned that this was not the case with the salicylates — in fact they are a remarkably safe group of therapeutic agents. We are, however, faced today with a numerically greater number of reports of side-effects of the salicylates relative to those of other drugs, simply because they are the oldest of the anti-inflammatory/analgesic drugs and so, on statistical grounds, would be expected to have received more attention than some of the newer agents.

It was through Professor Smith's experience that I soon saw the immense diversity of actions of these drugs and also gained biochemical insight into their modes of actions. I quickly learned from my own experiments that the organs of the body respond to these drugs in many diverse ways. They present a true intellectual challenge, for in studying the actions of these drugs one has to know the intricacies of the physiological, cellular and molecular organizations one is working with to see how the drug perturbs the complexities of these systems. Moreover, the most important thing to remember is that, as with all drugs, the salicylates are employed to treat pathological conditions and so it is imperative to know what molecular and cellular events are occurring in the pathological states to appreciate how the drug influences these processes. Regrettably most of the literature on the actions of the salicylates is from studies performed *in normal* animals, tissues or even man. We must often, of necessity, make extrapolations and await the experiments in the particular pathological state we are anxious to treat. Unfortunately, these kinds of experiments are becoming increasingly difficult to perform with concern over both animal and human experimentation. This book is an attempt to bring together diverse concepts about the actions of the salicylates and also their therapeutic developments and applications. In one way, this may help in bringing together a very diverse array of literature and experiences of previous investigators. We

need a basis to develop newer concepts for testing to make the best use of our knowledge and benefit by new applications of different members of these drugs, especially to improve their safety.

This book would not have been possible had it not been for the help and encouragement of people to whom I would like to express special gratitude. First, Mrs Veronica Rainsford-Koechli who typed practically all the manuscript drafts, helped in faithfully translating many German and French papers and provided immense encouragement. My colleague and friend, Dr Michael Whitehouse who, from close association over the past decade, has been an immense stimulus to me in my understanding of the anti-inflammatory drugs and their actions in inflammatory states. He and Dr Brian Hasleman of Addenbrookes Hospital Cambridge also critically reviewed the manuscript in detail. Professor Mervyn Smith and other colleagues, among them Dr Bill Dawson and colleagues at the Lilly Research Centre Ltd, and also those at King's College Hospital Medical School London, Professor Kay Brune and colleagues at the Biozentrum of the University of Basel and Dr Lyndsay McLeod of the University of Tasmania, provided immense stimulation and support in my research work and understanding of the actions of salicylates and other anti-inflammatory drugs.

This book is in appreciation to these people for their help over the years.

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Abbreviations and Nomenclature

The term 'Aspirin' is used in accordance with its widespread generic use throughout the world as the name for the chemical, acetylsalicylic acid. In some European countries this name is still protected by Trademark (to Bayer AG). Its use in this book recognizes its convenience and widespread use in the scientific and medical community, and is in no way intended to denote use of the Trademark.

'Salicylates' is used to denote all drugs having the 2-hydroxybenzoic acid structure. When used in a general sense, it implies that, based on the current state of knowledge, it seems reasonable to employ this name to cover actions or properties of all these compounds.

Caution should, however, be expressed in such an extrapolation and the reader should be mindful of this. Standard chemical, biochemical and pharmacological abbreviations are employed and where necessary are defined where first used in the text.

Standard abbreviations are defined when first introduced in the text and have, where possible, been derived from those detailed in *Units, Symbols and Abbreviations* (1979) Ed. D. N. Baron, Royal Society of Medicine, 1 Wimpole St., London W1M 8AE.

The enzyme nomenclature employed is that described in *Enzyme Nomenclature: Recommendation of the Nomenclature Committee of the International Union of Biochemistry* (1978), Academic Press, New York, with the exception that the word 'synthetase' is employed instead of 'synthase' in accordance with common usage.

The following list of abbreviations is provided for convenient usage:

A23187 = calcium ionophore (Lilly) (= calimycin)
acetyl-SCoA = acetyl-(S)coenzyme A
ADP = adenosine diphosphate
AMP = adenosine monophosphate
Ang = angiotensin
ASA = aspirin (2-acetoxybenzoic acid = acetylsalicylic acid)
ATP = adenosine triphosphate
AUC = area under the plasma concentration curve
B-cell = bone-marrow-derived lymphocytes
BW = 755c = 3-amino-1-[*m*-(trifluoromethyl)phenyl]-2-pyrazoline
CuDIPS = copper 3,5′-diisopropylsalicylate
cyclic AMP = adenosine cyclic 3′:5′-monophosphate
cyclic GMP = guanosine cyclic 3′:5′-monophosphate

DEAE = diethylaminoethyl
diplosal = salicylsalicylic acid (i.e. salicyl ester of salicylic acid)
ED_{10} = effective dose required to produce 10 lesions to the gastric mucosa
ED_{50} = effective dose required to produce a response in 50 per cent of animals
EDTA = ethylethenediamine tetraacetic acid
Ent. cell = enterochromaffin cell
ER = endoplasmic reticulum
ESR = erythrocyte sedimentation rate
ETYA = 5,8,11,14-eicosatetraynoic acid
GAGs = glycosaminoglycans
G-cell = gastrin cell
gentisic acid = 2,5-dihydroxybenzoic acid
GPs = glycoproteins
GSH = glutathione
GTP = guanosine triphosphate
H_1, H_2 = histamine type 1 and 2 receptors, respectively
Hb = haemoglobin
HETE(s) = Hydroxyeicosatetraenoic acids (variously substituted)
HHT = 12-L-hydroxyheptadecatrienoic acid
HPETE(s) = hydroperoxyeicosatetraenoic acids (variously substituted)
HPLC = high-performance (or pressure) liquid chromatography
IC_{50} = inhibitory concentration required to produce 50 per cent reduction in response
IgG = immunoglobulin G
log *P* = logarithm of the partition coefficient between *n*-octanol and an aqueous mixture
LTs (C_4, D_4, E_4) = leukotriene(s) (C_4, D_4, E_4, respectively)
MK-447 = 2-aminomethyl-4-*tert*-butyl-6-iodophenol
MOPS = multisubstrate oxidizing peroxidases
NDGA = nordihydroguaiaretic acid
NSAI = non-steroidal anti-inflammatory (drugs)
$O^{\bullet}_2^-$ = superoxide ion
$[O]^{\bullet}_x$ = hypothetical oxygen radical species deriving from peroxidation of PGG_2 or HPETEs
$OH^{\bullet}$ = hydroxyl radical
PAF = platelet aggregating factor = 1-*O*-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine
PCO_2 = partial pressure of carbon dioxide
PGDH = prostaglandin 15-hydroxydehydrogenase
PO_2 = partial pressure of oxygen
pyrocatechoic acid = 2,3-dihydroxybenzoic acid
γ-resorcyclic acid = 2,6-dihydroxybenzoic acid
RNA and DNA = ribonucleic and deoxyribonucleic acids
SA = salicyclic acid (2-hydroxybenzoic acid)
Sal = salicylate (anion)
salicylazasulphapyridine = salazapyrin; sulphasalazine; 2-hydroxy-5-{[4-[(2-pyridinylamino)sulphonyl]phenyl]azo}benzoic acid

salol = phenol ester of salicylic acid
salophen = phenetsal = paracetamol ester of salicylic acid
serotonin = 5-hydroxytryptamine
SGOT = serum glutamate–oxaloacetate transaminases
SGPT = serum glutamate–pyruvate transaminases
SLE = systemic lupus erythematosus
SRS-A = slow-reacting substance(s) in anaphylaxis ($= LTC_4 + LTD_4$)
T-cell = thymus-derived lymphocytes
TX(A_2, B_2) = thromboxanes (A_2, B_2)
UDP = uridine diphosphate
V_D = volume of distribution

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