Preface

There are not many small molecules about which a whole book could be written. Rather unexpectedly, at least to those who studied chemistry and biology before 1987, the simple diatomic molecule nitric oxide (NO)* is one such species. That it progressed from being a nasty pollutant in the air we breath to being designated 'molecule of the year', because of its biological role, by the journal *Science* in 1992 has been said and written so many times that it would be tedious to dwell on this again. That said, it is still a remarkable story.

The dramatic change in our perception of NO came about when it was discovered that it is part of mammalian physiology, firstly as a messenger molecule in controlling the dilation of blood vessels and subsequently in a whole host of tissues and organs. The story is still unfolding. The literary theme is not inappropriate as the scientist-turned-author Carl Djerassi has written a novel entitled *Nitric Oxide*. However, there was an 'NO story' before its physiological role was discovered: it has an interesting chemistry and plays a crucial part in the nitrogen cycle in soil and in smog formation. In an effort to rid the world's cities of smog the chemistry of NO was fully explored by the oil companies as they struggled to find ways of reducing NO levels in car exhausts to keep ahead of the demanding legislation that was being enacted. Much of that work was, of course, commercially sensitive and received little publicity. The news that NO plays a part in controlling blood flow, and hence blood pressure, was publicized through scientific journals and brought fame, and a Nobel prize, to some of those involved. What has been truly amazing is the subsequent proliferation of roles for NO in animal physiology. As this subject has been under intensive scrutiny by scientists for over 150 years it is astonishing that no-one before had seriously suggested that animals make NO as part of normal physiology. There is, to our knowledge, not even a hint of this

* Although not strictly correct usage, it is customary to refer to nitric oxide as NO, using the chemical formula as an abbreviation. Biologists often put a dot after the formula to indicate that it is a radical but we have not felt this to be necessary.

in the pre-1987 scientific literature. Perhaps the reasons are rather prosaic: NO is a very small molecule, it has a very short lifetime in tissue (how short depends on whom you ask but it rarely exceeds 30 s) and it is difficult to detect chemically at the concentrations at which it occurs (less than 1 μM).

In this book we have written about many areas of chemistry and biology and, in order to keep the book to a reasonable length, some topics have been greatly simplified. This could lead to misunderstandings and we trust that experts in these areas will not be too critical. At the same time we do apologize for any errors and omissions, and hope that the message of the book ('Look at what one simple, diatomic molecule can do') comes through in spite of our shortcomings. Shakespeare described Cleopatra as having 'infinite variety' and the same might be said of NO. That infinite variety is a result of its very special chemistry and we hope that we have written something that makes sense of the NO story in terms of its chemistry.

When NO was first publicized as a cellular messenger molecule, some biologists saw that it is a radical (a species with an unpaired electron) and assumed that it must be highly reactive, like other biologically significant radicals. Chemists, of course, knew that NO, although a radical, is not particularly reactive. If you understand chemical bonding the reason for the lack of reactivity is easy to understand but try explaining it to a cardiologist in a hurry. From school chemistry we may know that NO reacts readily with oxygen to give brown fumes of NO_2. Open a gas jar of NO to the atmosphere, an act now probably forbidden by EU regulations, and the reaction appears to be instantaneous. However, at the concentrations of NO and oxygen found in tissue the reaction is much slower, a nice example of the law of mass action. Immunologists are not always sensitive to the finer points of reaction kinetics and it is not easy to explain why the formation of NO_2 is generally unimportant to the biological role of NO. For a time there were problems discussing NO with some medical doctors because of confusion with nitrous oxide (N_2O), with which they were familiar because of its place in anaesthesia ('laughing gas').* Now that inhaled NO is used therapeutically let us hope that this confusion has been overcome.

We have not written this book because the NO story is now coming to an end but, as so much progress has been made, it is not a bad time to take stock. Anyone who has written a scientific review knows that

* Sir Humphry Davy discovered laughing gas but its effect on respiration was first investigated by a physician, Peter Mark Roget, later to achieve greater fame as a compiler of a thesaurus of the English language.

one of the most demanding and time-consuming aspects of such writing is keeping track of all the references. We have refrained from giving references in the text, partly to make the text easier to read and partly to shorten the book. Our selection of names for mention has been arbitrary. Scientific research can appear very arid and occasionally mentioning a person may remind readers that without people there is no science.

Much of the NO story has still to be fully elucidated. This means that the current status of our understanding in some areas is one of confusion and doubt, particularly concerning the biological role of NO. A recent review of NO in the skin* was subtitled *More questions than answers*. We have tried to avoid emphasizing the confusion because it weakens the impact of the message. Instead we thought that in this preface we would warn the reader that some of the conclusions are stated with a confidence they do not strictly deserve. There are two major sources of confusion: firstly, results obtained from experiments using cultured cells may not apply to whole animals and, secondly, the effect of NO in tissue is often reversed if the concentration is raised. If the conclusions are seen as interim ones then little harm can be done. At the end of each chapter we have given references for further reading for those who wish to know more.

Readers of this book require some knowledge of chemistry and biology but we have tried to explain in the text as many technical terms as possible. A glossary of technical terms has been provided for further help. Some chapters will be easier for the general reader to understand than others. These are probably those at the end of the book rather than at the beginning. Some chapters, such as Chapter 8 and 9, have been included for reference and serious study rather than casual reading.

We have failed to cover all aspects of the chemistry and biology of NO. For example, it plays a crucial role in the development of insulin-dependent diabetes and in influenza and asthma. Also we have only touched on the fascinating co-ordination chemistry of NO. Had we tried to mention everything the book might have been better but it would never have been finished. An issue of the American Chemical Society publication *Chemical Reviews* (April 2002) has a comprehensive account of many aspects of the chemistry of NO by experts and repays study by the serious student of the subject.

Before we conclude we would like to thank some people. We thank the RSC for inviting us to write this book; we hope it will not regret its

* R. Weller, Nitric oxide, skin growth and differentiation. *Clin. Exptl. Dermatol.*, 1999, **24**, 388.

decision. To all those scientists who had the insight to see that NO could do all the things we have tried to describe, and then laboured long and hard in their laboratories to prove their ideas, we tender our heartfelt thanks. We thank a number of experts who read what we have written and made helpful suggestions for improvement: Richard Weller (Edinburgh Royal Infirmary), Ian Megson (University of Edinburgh), David Adams (Heriot Watt University), Keith Sillar (University of St Andrews), William Martin (University of Glasgow), Faisel Khan (Ninewells Hospital, Dundee), Roberta Fruttero (University of Torino), David Cole-Hamilton (University of St Andrews), Lyn Williams (University of Durham), Neil Cape (Institute of Terrestrial Ecology), John Moffett (Needham Research Institute) and Kevin Nolan (Royal College of Surgeons in Ireland). We owe a special debt of gratitude to Eric Flitney (University of St Andrews), for introducing us to the biology of NO in exchange for some information on the photochemistry of nitroprusside.

Finally we thank our spouses, Janet and Hugh, who encouraged us to start the work and rejoice with us at its completion.

Anthony Butler
St Andrews, Scotland

Rosslyn Nicholson
Stavanger, Norway