

Preface

Introducing the first edition of *Signal Transduction*, we asked the question, for whom had this book been written, and the simplest response was that it had been written for ourselves. We added the pious hope that it might also be instructive and entertaining for students and professionals at many levels. So why a second edition? The main reasons must be that we have not only been spurred on by the enormous progress in the field but also encouraged by a number of very favourable reviews and letters of appreciation that have offered constructive criticism and new ideas for the development of the text.

In the intervening period (around seven years), the general territory covered by the expression 'signal transduction' has spread inexorably wider, but with the passing of time, not just one, but now two of the authors (BDG and PERT) have gone beyond the age at which it is normal, in British universities at least, to close up their labs and depart their desks. So at the outset, it is beholden on these two greybeards to acknowledge the major contribution of IJsbrand Kramer who undertook the drafting of most of the second half of this new edition. Without him, there would be no second edition. Yet, as before, the aim throughout has been to create a single text as if conceived by one mind, written by one hand. In this way, we hope that it avoids the worst excesses of the skimpily edited texts compiled from articles by multiple specialist authors.

Although we have touched the leading edges of the subject, we have also endeavoured to provide an elementary basis with some historical background to all the topics covered. There has been no attempt to be comprehensive and we are aware that many important topics that well qualify for inclusion are conspicuous only by their absence. However, the omissions in the new edition are not the same as those of the first. Gone now are the major sections on the cell cycle and apoptosis; instead we have new chapters covering nuclear receptors, development, and cancer therapy. As previously, we have been the main beneficiaries as students of our own subject. As we learned more, we were encouraged to challenge, or at least to re-examine, some of the well-established dogmas. We have also learned to respect the wisdom of our forebears, whose freedom of thought and sometimes serendipitous discoveries in the 19th and early 20th centuries led to the creation of the modern sciences of physiology, pharmacology, biochemistry, and cell biology, and related clinical fields, especially endocrinology and immunology.

The book conveniently divides in two parts. The first nine chapters provide the nuts and bolts of what might be termed 'classical' signal transduction.

They concentrate mainly on hormones, their receptors, and the generation and actions of second messengers, particularly cyclic nucleotides and calcium. It was the advances in this area, particularly the discovery of the G proteins, that originally gave rise to the expression 'signal transduction', although the word 'transduction' was stolen from elsewhere (see definitions, below). Chapter 10 extends the paradigm, dealing with the intracellular receptors that, in the nucleus, influence transcription. Then, in Chapters 11–23, attention is concentrated on processes set in action by growth factors and adhesion molecules, particularly through the covalent modification of proteins and inositol-containing lipids, for example by phosphorylation, dephosphorylation, cleavage or ubiquitylation. An important, though not exclusive, impetus to research in this area has been the quest to understand the cellular transformations underlying cancer, with the hope of devising effective therapeutic procedures. Finally, Chapter 24 reflects back on a theme that runs throughout the book. It deals with the concept of protein structural domains and illustrates their central importance in signalling mechanisms.

In preparing the book, we have had the benefit of advice and opinions from many friends and colleagues. These include John Blenis (Boston), Alex Bridges (Ann Arbor), Zhijian Chen (Dallas), Jean Dessolin (Bordeaux), Elisabeth Genot (Bordeaux), John Kuriyan (Dallas), Michel Laguerre (Bordeaux), Patrick Lemaire (Marseille), David Litchfield (London, Ontario), Alfonso Martin-Arias (Cambridge, UK), Joan Massagué (New York), Juan Modolell (Madrid), Alexandra Newton (La Jolla), François Schweisguth (Paris), Pat Simpson (Cambridge, UK), Nick Tonks (Cold Spring Harbor), Colin Ward (Parkville), Xuewu Zhang (Dallas). Geoffrey Strachan advised on the translation of French and German texts into contemporary (19th century) English.

Many others, too numerous to name individually, have given us the benefit of their knowledge and understanding. In acknowledgement of their contribution we offer the following quotation by one of the pioneers of signal transduction:¹

Of course, the authors of this paper would themselves never have recognized the expression 'signal transduction' and it would be a further 100 years before it made its appearance in the biological literature. The sensations brought about by pituri, an alkaloid that according to Ringer and Murrell induces some of the pharmacological effects of atropine (courage, infuriation, frustration, and headaches), are not dissimilar to those experienced by us in the writing of this book. Indeed, they will be familiar to any students and investigators in this and other fields of research. However, we should not take this too far. When Ringer tested the effects of the application of pituri on four men,² he noted that it also caused drowsiness, faintness, pallor, giddiness, hurried and superficial breathing, dilatation of the pupils, general weakness with convulsive twitchings and in large doses copiously increased salivary secretion.

ON PITURI. By SYDNEY RINGER, M.D., and WILLIAM MURRELL, M.R.C.P., *Lecturer on Practical Physiology at the Westminster School of Medicine, and Assistant Physician to the Royal Hospital for Diseases of the Chest.*

QUITE recently a student of University College, London, whose name we have unfortunately forgotten, gave us a small packet containing a few twigs and broken leaves of the powerful and interesting drug Pituri. These we placed in Mr Gerrard's hands, and he kindly made first an extract from which he obtained a minute quantity of an alkaloid, and with this he made a solution containing one part of the alkaloid to twenty of water.

Baron Mueller, from an examination of the leaves of pituri, is of opinion that it is derived from *Duboisia Hopwoodii*. Pituri is found growing in desert scrubs from the Darling River and Barcoote to West Australia. The natives, it is said to fortify themselves during their long foot marches, chew the leaves for the same purpose as Cocoa leaves are used in Bolivia. Dr G. Bennett in the New South Wales Medical Gazette, May, 1873, says Pituri is a stimulating narcotic and is used by the natives of New South Wales in like manner as the Betel of the East. It seems to be a substitute for tobacco.

It is generally met with in the form of dry leaves, usually so pulverized that their character cannot be made out.

The use of pituri is confined to the men of a tribe called Mallutha. Before any serious undertaking, they chew these dried leaves, using about a tea-spoonful. A few twigs are burnt and the ashes mixed with the leaves. After a slight mastication the bolus is placed behind the ear (to increase it is supposed its strength), to be again chewed from time to time, the whole being at last swallowed. The native after this process is in a sufficiently courageous state either to transact business or to fight. When indulged in to excess, it is said to induce a condition of infuriation. In persons not accustomed to its use pituri causes severe headache.

It also antagonized the action of muscarine on the heart. This has not been our experience, which leads one to wonder who, among their students, colleagues, and servants may have offered themselves up as willing – or perhaps less than willing – guinea pigs in the furtherance of scientific research. Ringer and his friends apparently eschewed membership of the very honourable brotherhood of self-experimenters of which the more famous members include Sir Humphry Davey, who breathed nitrous oxide as well as other more noxious gases; John Scott Haldane, who too inhaled lethal gases; and more recently Barry Marshall, who swallowed a culture of *Helicobacter pylori* to show that it caused stomach ulcers and who with Robin Warren was awarded the Nobel Prize in Physiology or Medicine in 2005. Another member of this

fraternity, Charles Edouard Brown-Séquard, figures prominently in the first chapter.

References

1. Ringer S, Murrell W. On pituri. *J Physiol.* 1878:377-383.
2. Ringer S. On the action of pituri on man. *Lancet.* 1879:290-291.

From the Shorter Oxford English Dictionary (3rd edition, 1994, with corrections 1977, © Oxford University Press:

Transduction (trans,dv'kʃən). *rare.* 1656. [ad. L. *tra(ns)ductionem*, *tra(ns)ducere*; see **TRADUCE.**] The action of leading or bringing across.

Traduce (trādīū's), *v.* 1533. [ad. L. *traducere* to lead across, etc.; also, to lead along as a spectacle, to bring into disgrace; f. *trans* across + *ducere* to lead.] †1. *trans.* To convey from one place to another; to transport -1678. †b. To translate, render; to alter, modify, reduce -1850. †c. To transfer from one use, sense, ownership, or employment to another -1640. †2. To transmit, esp. by generation -1733. †b. *transf.* To propagate -1711. †c. To derive, deduce, obtain *from* a source -1709. 3. To speak evil of, esp. (now always) falsely or maliciously; to defame, malign, slander, calumniate, misrepresent 1586. †b. To expose (to contempt); to dishonour, (dis)grace (*rare*) -1661. †4. To falsify, misrepresent, pervert -1674.

1. b. Milton has been traduced into French and overturned into Dutch **SOUTHEY**. 2. Vertue is not traduced in propagation, nor learning bequeathed by our will, to our heires 1606. 3. The man that dares t., because he can With safety to himself, is not a man **COWPER**. b. By their own ignoble actions they t., that is, disgrace their ancestors 1661. 4. Who taking Texts... traduced the Sense thereof 1648. Hence **Traducement**, the, or an, action of traducing; defamation, calumny, slander. **Traducingly** *adv.*

From the Oxford English Dictionary (2nd edition, 2008 © Oxford University Press) online:

transduction

(trænsˈdʌkʃən, træns-) [ad. L. *transduction-em* (usually *traductionem*), n. of action f. *tra(ns)ducere*: see **TRADUCE**.]

1. The action of leading or bringing across. *rare*.

1656 BLOUNT *Glossogr.*, *Transduction*, a leading over, a removing from one place to another. **a1816** BENTHAM *Offic. Apt. Maximized, Introd. View* (1830) 19 In lieu of *adduction*, as the purpose requires, will be subjoined *abduction, transduction*, and so forth.

2. The action or process of transducing a signal.

1947 *Jrnl. Acoustical Soc. Amer.* XIX. 307/1 It is rather interesting...that the direct method of electronic transduction, instead of the indirect method of employing a conventional transducer and then amplifying the output with a vacuum tube, has not been developed. **1970** J. EARL *Tuners & Amplifiers* iv. 87 Low impedance pickup cartridges...using the moving-coil principle of transduction. **1975** *Nature* 17 Apr. 625/1 The transduction of light energy into neural signals is mediated in all known visual systems by a common type of visual pigment.

3. *Microbiology*. The transfer of genetic material from one cell to another by a virus or virus-like particle.

1952 ZINDER & LEDERBERG in *Jrnl. Bacteriol.* LXIV. 681 To help the further exposition of our experiments, we shall use the term transduction for genetically unilateral transfer in contrast to the union of equivalent elements in fertilization. **1960** [see F III. 11]. **1971** *Nature* 18 June 466/1 It has been suggested that transduction of genes by viruses was an important mechanism in evolution for spreading useful mutations between organisms not formally related. **1977** *Lancet* 9 July 94/2 These were derived by selection of sensitive variants from gentamicin-resistant strains or by transduction of this resistance to sensitive strains.

Hence **transductional** *a.*, of or pertaining to (genetic) transduction.

1956 *Genetics* XLI. 845 (*heading*) Linear inheritance in transductional clones. **1980** *Jrnl. Gen. Microbiol.* CXIX. 51 Transductional analysis revealed that one of the four mutations carried by strain T-693 was responsible for constitutive synthesis of both isoleucine and threonine biosynthetic enzymes.