

## **Professor Michael John Rand**

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This being the first ASCEPT-only Annual Scientific Meeting since Mike Rand died in May, 2002, the meeting is dedicated in his honour. ASCEPT Council and members welcome Mike's wife, Ilse, to the meeting.

Professor Michael John Rand was one of the founders and most respected members of the Society. Although Mike had been seriously ill for some time, the news of his death still came as tremendous shock. Indeed, the medical research community in Australasia and pharmacologists throughout the world would have been saddened to hear of his passing. Australasia has lost one of its most outstanding medical research scientists and academics, and the world has lost one of the most influential pharmacologists of current times.

Michael John Lewes Allan-Rand was born at Mildenhall, Suffolk, England in August 1927. It was only recently that I learnt from Mike's long-time colleague, Bill Bowman, that Mike originally had a hyphenated surname, which he quickly dispensed with. Bill also advised that Mike maintained that 'Lewes' was the name of the place where he was conceived!

Mike migrated to Australia in 1941 with his mother and brother Stephen. Both boys were enrolled as boarding students at Ivanhoe Grammar School in Melbourne. Subsequently, Mike commenced studying for an undergraduate degree at the University of Melbourne. In an autobiography published in 1993, he confesses that during his undergraduate years, he more or less drifted into the biological sciences, claiming that his studies in physiology and biochemistry 'did not require any mental effort that could have interfered seriously with involvements in left-wing student politics, the free-thought movement, or the lighter side of undergraduate student life in Melbourne in the postwar period' (2). By this time Mike well and truly considered himself to be Australian. He subsequently became a naturalised Australian citizen.

After completing his bachelor degree, Mike was accepted into a Master of Science (M.Sc.) program in the University of Melbourne's Department of Physiology. He acknowledged that, before commencing his M.Sc., he had not given much thought to a career in science, leave alone pharmacology. However, the encouragement and guidance he received from his supervisor, George Reid and the tragic nature of Reid's untimely death were major influences in the determination of his ultimate career direction. Mike soon came to regard Reid as a mentor and friend. At the time, George Reid was investigating the then unknown vasoconstrictor principle released from platelets during blood clotting. In 1952, after the identification of serotonin as the active vasoconstrictor substance, Reid and Rand published the first comprehensive account of its pharmacology (3). Reid's death from malignant hypertension, at a time when effective antihypertensive drugs were not readily available, was a significant factor in Mike's decision to concentrate his research in the field of autopharmacology.

Mike took out a Ph.D. in Pharmacology at the University of Sydney in 1957. His supervisor was Professor Roland Thorpe. Mike's project was concerned with the interactions between cardiac glycosides and adenylyl compounds, including adenosine, AMP, ADP, and nicotinamide adenine dinucleotide. He notes in his autobiography that his findings with these adenylyl compounds later led him to suggest to his colleague Geoff Burnstock that such compounds were possible candidates for the unknown transmitter of non adrenergic-non cholinergic nerves (2).

After finishing his Ph.D., Mike secured an appointment as Departmental Demonstrator to

work with one of the most eminent pharmacologists of the time, Professor J.H. Burn at the Department of Pharmacology, Oxford. After 12 months he was awarded an Australian & New Zealand Life Insurance Medical Research Fund Fellowship, which allowed him to continue working with Burn for a further 18 months. Mike considered the two and a half years in Burn's laboratory as one of the most formative and productive periods of his career. The collaboration resulted in a major advances in the understanding of autonomic neuro-effector function. For example, their work with reserpine led to the concept of the indirect action of certain sympathomimetic amines (4) and their studies with cocaine revealed the existence and operation of the monoamine uptake mechanism at noradrenergic nerve terminals (5). It is clear that such outcomes had a major influence on the subsequent rapid expansion of knowledge of noradrenergic function and, indeed, on the development of new classes of therapeutically useful drugs, particularly for the treatment of hypertension.

Another outcome of the collaboration between Burn and Rand was the hypothesis that acetylcholine was an intraneuronal intermediary in the release of noradrenaline from noradrenergic nerves (6,7). Although ultimately abandoned as a plausible concept, the proposal stimulated an enormous amount of research, the outcomes of which also greatly advanced the understanding of autonomic neurotransmitter mechanisms. Mike himself continued to seek evidence for the cholinergic link hypothesis, briefly with coworkers at the University of Sydney, and then at the University of London's School of Pharmacy. Although not producing the definitive evidence he sought, his work continued to advance the broader body of knowledge of noradrenergic and cholinergic transmission. For example, collaboration with Bill Bowman on the actions of triethylcholine on cholinergic transmission led to the notion of false or surrogate transmitters (8). This was subsequently extended to noradrenergic transmission when he and Michael Day proposed that the formation of methylnoradrenaline within noradrenergic nerve terminals from exogenous methyl dopa, might explain the antihypertensive action of methyl dopa (9).

In 1964, whilst at the London School of Pharmacy, Mike took study leave to work with Geoff Burnstock at the University of Melbourne. It seems that this visit to his undergraduate 'home' encouraged him to apply for the Chair of Pharmacology at the University of Melbourne, which had become vacant after the retirement due to illness of the inaugural Professor of Pharmacology, Frank Shaw. In late 1965 Mike took up the Chair, a position he was to occupy for twenty-seven years.

Mike's time at the University of Melbourne was characterized by a commitment to scholarship in the broadest sense. He worked tirelessly to transform his new Department from one which at the time of his appointment was at a low ebb, to one of great strength and influence in pharmacology, nationally and internationally. Through his dedication to scholarship, his seemingly tireless efforts and his undoubted intellectual brilliance, he was an inspiration to undergraduate students, graduate research students, postdoctoral fellows and, not least, to his academic colleagues. He truly led by example and encouragement. Many of those who were fortunate enough to have had benefit of his mentorship and guidance went on to establish prestigious careers for themselves in academia, industry and public service.

At Melbourne, Mike continued to pursue his interest in autonomic neuroeffector transmission. Together with his colleagues, Marian McCulloch and David Story, he made a major contribution to the concept of feedback inhibition of noradrenergic transmission (10,11) and, more generally, to the modulation of transmitter release from noradrenergic nerves by neurotransmitters, local hormones, hormones and drugs acting through receptors on nerve terminals (12). Although several other groups around the world were active in the area, the concept that a transmitter at a peripheral neuroeffector site, in addition to its action at post-junctional receptors, might also act back on nerve terminals to modulate

subsequent transmitter release, was considered by many to be completely implausible (see 13). However, the role of prejunctional receptors in autonomic neuroeffector function is now generally accepted.

Mike's major contributions to scholarship as Professor of Pharmacology were recognised by the University of Melbourne by conferring on him the title of Professor Emeritus. After his retirement he was invited to join some of his University of Melbourne colleagues who had relocated to another university in Melbourne, RMIT University. Since this provided an opportunity to continue his research, and to continue mentoring graduate students, he enthusiastically took-up the offer and was appointed as an Adjunct Professor in what was to become the Faculty of Life Sciences at RMIT University.

Shortly before the end of his time at the University of Melbourne, Mike, working with his graduate student Chun Guang Li, became interested in a new form of neuroeffector transmission, mediated by an unknown substance, which was subsequently identified as nitric oxide (14,15,16). Mike coined the term nitrenergic transmission to describe this form of transmission, and, reminiscent of his obsession with the cholinergic link hypothesis in the early stages of his career, pursuit of the mechanisms by which the nitric oxide acted as a transmitter became a new research passion for him. He continued to work on nitrenergic transmission at his new research laboratories at RMIT. From the work of Mike and his colleagues and of several other groups around the world it soon became clear that nitrenergic transmission played an important role in many physiological functions. Until his death Mike remained an international leader in this area, making significant contributions to knowledge of the mechanism of release of the nitrenergic transmitter. His enthusiasm for this work, after a lifetime of teaching and research in pharmacology, was astonishing. He supervised doctoral students right up until his final days.

Mike's involvement in ASCEPT was significant. Prior to the establishment of ASCEPT the discipline of pharmacology was represented in Australia largely by the Australian Physiological Society; however, many pharmacologists and, in particular clinical pharmacologists, considered that a new society was needed to provide for effective representation and interaction between basic and clinical pharmacological sciences, and a society which had an Australasian as opposed to an Australian focus. Mike, together with several other academic pharmacologists from Australian and New Zealand and several Medical Directors of pharmaceutical companies, were instrumental in establishing such a society, ASCEP (later to become ASCEPT). After much consultation and planning, the Department of Pharmacology at the University of Melbourne hosted the first meeting of the Society in November 1967. The venue was the Woodruff Lecture Theatre in the University's Microbiology Building (which also housed the Department of Pharmacology) and Mike Rand was the Local Secretary.

Mike was always an enthusiastic supporter of ASCEPT, seeing it not only as providing an important forum for the dissemination and discussion of the latest research findings in pharmacology, clinical pharmacology and toxicology, but also as means of promoting these disciplines to government, industry, academia and the public. Mike was a member of the inaugural Council of ASCEP (from 1967 to 1969) and was its President on two occasions, 1973 and 1987. The 1987 term was held in conjunction with his presidency of the International Congress of Pharmacology, which was held that year in Sydney (see below).

The staff and graduate students of Mike's department were always well represented at the Society's AGMs and, through numerous rehearsals, he ensured that they were always prepared. Even senior academic staff, to their dismay, often had to make major revisions to their presentations which frequently involved remaking photographic slides, a tedious and time-consuming task in the days before computer graphics.

Mike was well known for his involvement in the formal discussion of presentations at scientific meetings. His questions were incisive and, to the dismay of presenters, frequently seemed to come from 'left field'. However, he had the ability to 'cut-through' highly technical matters to identify critical issues that needed to be addressed. Many of our now senior researchers will recall from their early days their trepidation in presenting to an audience in which Mike Rand was present. However, Mike's motives were always to ensure that experimental findings were logically interpreted, effectively integrated with the broader range of knowledge, and that they provided a basis for the formulation of new hypotheses amenable to experimental investigation. Indeed, he considered these essential characteristics of good scientific investigative processes.

At the time of Mike Rand's retirement as Professor of Pharmacology at the University of Melbourne in December 1992 the Council of ASCEPT decided to establish an award in his name. Since 1993, the Michael Rand Medal has been awarded biennially (or as otherwise determined by Council) to a member of ASCEPT who has been judged to have made an outstanding contribution to the disciplines of clinical or experimental pharmacology or toxicology. The Michael Rand Medal is fitting acknowledgement of Mike's enormous contributions to ASCEPT and to pharmacology and related disciplines.

Mike Rand was committed to advancing the development of pharmacology and related disciplines internationally. During the 1970s, together with the late Professor Koroku Hashimoto of Tohoku University in Japan, he was a driving force in bringing together pharmacologists throughout Asia and the Pacific regions for the first Southeast Asian/Western Pacific Regional Meeting of Pharmacologists. There have been seven subsequent highly successful such regional meetings.

Mike Rand was also a strong advocate for the International Union of Pharmacology (IUPHAR) and of the international congresses hosted by IUPHAR. At the Eighth International Congress of Pharmacology, in Tokyo, he led a successful Australian bid to host the Tenth International Congress in Sydney in 1987. Under Mike's leadership as Chairman of the National Organising Committee and as the Congress President, the Sydney meeting is still regarded as one of the most successful ever, both in terms of scientific content and socially, bringing together pharmacologists and toxicologists from many countries in a convivial and collegiate environment. It is also worthy of mention that the Sydney Congress was also a financial success, returning substantial profits to both IUPHAR and ASCEPT. In fact the financial return from the Congress allowed ASCEPT to establish an investment portfolio, which continues to support the Society in the pursuit of its mission.

Rand's pre-eminence in pharmacology and toxicology was recognized by his appointment to many consultative positions and extra-mural committees. He served on several national expert committees dealing with drug and poisons regulation. He was a Commissioner on the Australian National Food Authority, a statutory authority whose task is to establish uniform food standards throughout Australia. At an international level, for many years Mike was a member of the World Health Organisation Expert Advisory Panel on Food Additives and Contaminants, during which time he served on several Joint FAO/WHO Expert Committees on Food Additives. In 1984 he was Vice Chairman of the Joint FAO/WHO Expert Consultation on Residues of Veterinary Drugs in Foods.

In addition to his extensive original journal publications, Mike was the author of numerous reviews in journals and monographs. Indeed, he was a skilled scientific writer and a true artisan of the English language, with a formidable knowledge of grammar and syntax. In 1968, Mike Rand, with Bill Bowman and Geoff West, published the Textbook of Pharmacology. This work, which underwent major revision in 1980 (Bowman and Rand), was considered internationally as a major textbook of pharmacology. Tragically a third edition of this work was twice aborted, firstly in the late 1980s when his extensive drafts

were lost in a fire which destroyed his home, and now by his death (with Bowman, he had been working on it up until his final weeks). Sadly, Bill has indicated that Mike's death puts paid to the revision once and for all.

Throughout his career Mike served as a member of the Editorial Board of many international journals of pharmacology and he was the founding Editor-in-Chief of the Journal, Clinical & Experimental Pharmacology & Physiology (CEPP). As with all of his professional endeavours, he took on the task of fostering the development of the new journal with commitment and enthusiasm. His endeavours and those of the late Professor Austin Doyle ensured that the CEPP soon became recognised as a major international journal for the disciplines of pharmacology and physiology.

The diversity of Mike Rand's skills and the breadth of his accomplishments are truly amazing. He was a born researcher, with an insatiable thirst for knowledge that extended well beyond his own areas of investigation. As an academic, he embraced an integrated model of scholarship, in which generation of new knowledge through research and the integration, dissemination and application of knowledge were each essential components. Next to his passion for discovery, ranked his enthusiasm for encouraging others, particularly his students, to achieve their maximum potential.

In his 1993 autobiography Mike stated that, if he was able to live his life again, he would have given serious consideration to working in the pharmaceutical industry, where he may have had the opportunity to be involved in the development of therapeutically useful drugs (2). Whilst he expressed this desire frequently during his career in academia, he probably did not fully appreciate the enormous influence that his achievements have had on therapeutic drug discovery and application. Moreover, despite his yearnings for a different career path, Mike clearly derived satisfaction from the course that he followed. At a speech he made on his retirement from the University of Melbourne, and repeated in his autobiography, he asked: "Can anyone ask more than to have as a job what one would willingly do as a hobby?"

There is no doubt that Mike Rand lived a rich and satisfying life, one of the final episodes of which had nothing to do with pharmacology. In 2000 Mike and his wife Ilse adopted Bonnie, Ilse's three-year-old granddaughter from a former marriage. Mike was devoted to Bonnie. One small testament to this is an elaborate well-designed and elaborately constructed tree house, 'Bonnie's Tree House Cubby', built by Mike as a labour of love, and completed less than five months before his death.

As his kidney failure worsened, and complications developed, Mike decided that enough was enough. After discussions with Ilse, he refused further dialysis and medication. He quickly fell into a coma and died shortly afterwards.

Those of us who have had an association with Michael Rand as friend, colleague, mentor or teacher have been privileged indeed. His intellectual stimulation, academic insightfulness, encouragement and camaraderie will be sorely missed.

**David Story**  
**Faculty of Life Sciences**  
**RMIT University**  
**Melbourne**

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