PHARMACOLOGY MATTERS

David Bowen 1940-2011

David Bowen was a pioneer in the systematic investigation of the neurochemical basis of dementia through in the use of human brain tissue. David graduated with a BSc in Chemistry and Microbiology from the University of Reading in 1961. He then obtained a PhD from the University of Pittsburgh where he studied the role of nicotinic acid in cholesterol metabolism. He took up a National Institutes of Health funded postdoctoral position at the University of Michigan in the laboratory of Prof Norman Radin, where he studied brain lysosomal enzymes. In 1968, he returned to the UK to take up a position at Unilever. In 1970, his career path returned to the sphere of neuroscience when he joined the newly formed Department of Neurochemistry at the Institute of Neurology in London.

The success of post-mortem studies of the brains of people with Parkinson's disease that provided a basis for effective pharmacotherapy, was an inspiration to David in choosing his area of reaserch. David studies were in collaboration with research-minded neuropathologists and dementia clinicians in the UK who could help supply suitable material and more importantly, provide the clinical information to make sense of the findings. David's approach to research was always rigorous, meticulous and free of the constraints of the boundaries of distinct scientific disciplines. Indeed, he pioneered the multi-disciplinary approach to the study of AD, which is taken for granted today, through the establishments of collaborations between neurologists, neuropathologists, psychiatrists, neurosurgeons, pharmacologists, neuroanatomists and psychologists.

In a landmark study of 38 biochemical markers that involved 20 brain regions of 56 post-mortem brains, David established that one of the most profound changes was reduced activity of choline acetyltransferase (ChAT), the enzyme responsible for the synthesis of the acetylcholine (ACh) (Bowen et al 1976). This finding was rapidly corroborated and extended by other post-mortem studies in Edinburgh and Newcastle and by studies in David's lab showing that both choline uptake and ACh synthesis was reduced in AD brain tissue obtained ante-mortem (Sims et al 1983). These and other data, including data showing that the decline in ACh synthesis in AD correlated with dementia (Francis et al 1985), indicated that dementia associated with AD occurs in part as a consequence of dysfunction of cholinergic neurons. More than twenty five years later, inhibitors of the enzyme responsible for ACh catabolism, acetylcholinesterase (AChE), have become the most successful approach, with three such compounds (donepezil, rivastigmine, and galantamine) now the mainstay in treatment of mild and moderate AD. David was delighted to hear that the National Institute of |Health and Clinical Excellence (NICE) has recently revised its guidance to allow more people with dementia in the UK to benefit from these drugs.

In subsequent studies, David examined the integrity of non-cholinergic neurons in AD and showed loss of monoamine neurons early in the disease process (Palmer et al 1987a; Palmer et al 1987b),. He then provided biochemical evidence to indicate the loss of glutamatergic neurons, supporting previous histological data from collaborators at the University of Manchester demonstrating the loss of pyramidal cells in AD, which is probably the major contributor to the syndrome of dementia (Francis et al 1993; Neary et al 1986; Procter et al 1988). David was driven by a powerful desire to provide the biological basis from which to develop effective medicines to improve both cognitive and non-cognitive behavioural symptoms of dementia.

The results of the studies described above were always the subject of lab discussions to identify the best pharmacological approach. His lasting legacy is evidenced by a series of widely-quoted and influential publications, most often reporting novel biochemical findings in human brain tissue from people with dementia or a carefully considered model system. These were never findings in isolation but the rationale for the study and the interpretation was always dominated by clinical relevance: David was doing translational science before it was fashionable. Even in retirement he was writing to clinicians and whoever would listen within pharmaceutical companies to propose new treatment approaches for fronto-temporal dementia on the basis of his last publication (Bowen et al 2008).

David's laboratory was always lively and productive, with many students obtaining PhDs and scores of colleagues, postdocs and clinicians from around the world training with him. Many benefited from his powerful insight and wealth of ideas and most grew to share his passion for finding new treatments for people with dementia. This was achieved through the force of his very powerful will, coupled with his contagious enthusiasm. Everyone who spent time in David's lab benefited from the experience and a large number now hold leading positions in the pharmaceutical industry, academia and clinical medicine in the UK and overseas. . The importance of David's contribution is reflected in the award of many international prizes, including the Dhole-Eddleston Prize from the British Geriatrics Society in 1980; the J. Allyn Taylor Gold Medal from the Robarts Institute, Canada in 1986; the Luigi Amaducci Memorial Award from the International Psychogeriatrics Association in 2005. In addition, in 1986 he was selected to receive a major academic-industry initiative awarded by Astra (now AstraZeneca) that led to the establishment of a productive drug discovery unit within the Institute of Neurology.

David's scientific career was cut short by a heart attack in late 1993, leading to retirement at age 55. Many of David's friends and colleagues attended a Festschrift in 1996, which led to an issue of Neurodegeneration (volume 5, 1996) devoted to many of the scientific studies he initiated. Like many others, we are deeply grateful for the friendship, leadership and inspiration that David provided. David was a pioneer in the study of the neurobiology of dementia. His legacy endures, but he will be dearly missed by all that knew him.

Paul T Francis, PhD
Professor of Neurochemistry and Director, Brains for Dementia Research. Wolfson Centre for Age-Related Diseases, King's College London

Alan M Palmer, PhD
CEO MS Therapeutics,

Address for correspondence
Professor Paul T Francis
Wolfson Centre for Age-Related Diseases
King's College London
Guy's Campus
St Thomas Street
London SE1 1UL
+ 44 207 848 6269
Paul.francis@kcl.ac.uk

Bowen DM, Procter AW, Mann DM, Snowden JS, Esiri MM, et al. 2008. Imbalance of a serotonergic system in frontotemporal dementia: implication for pharmacotherapy. Psychopharmacology (Berl). 196:603-10
Bowen DM, Smith CB, White P, Davison AN. 1976. Neurotransmitter-related enzymes and indices of hypoxia in senile dementia and other abiotrophies. Brain 99:459-96
Francis PT, Palmer AM, Sims NR, Bowen DM, Davison AN, et al. 1985. Neurochemical studies of early-onset Alzheimer's disease. Possible influence on treatment. N Engl J Med 313:7-11
Francis PT, Sims NR, Procter AW, Bowen DM. 1993. Cortical pyramidal neurone loss may cause glutamatergic hypoactivity and cognitive impairment in Alzheimer's disease: investigative and therapeutic perspectives. J Neurochem 60:1589-604
Neary D, Snowden JS, Mann DM, Bowen DM, Sims NR, et al. 1986. Alzheimer's disease: a correlative study. J Neurol Neurosurg Psychiatry 49:229-37
Palmer AM, Francis PT, Benton JS, Sims NR, Mann DM, et al. 1987a. Presynaptic serotonergic dysfunction in patients with Alzheimer's disease. J Neurochem 48:8-15
Palmer AM, Francis PT, Bowen DM, Benton JS, Neary D, et al. 1987b. Catecholaminergic neurones assessed ante-mortem in Alzheimer's disease. Brain Res 414:365-75
Procter AW, Palmer AM, Francis PT, Lowe SL, Neary D, et al. 1988. Evidence of glutamatergic denervation and possible abnormal metabolism in Alzheimer's disease. J Neurochem 50:790-802
Sims NR, Bowen DM, Allen SJ, Smith CC, Neary D, et al. 1983. Presynaptic cholinergic dysfunction in patients with dementia. J Neurochem 40:503-9