

IN MEMORIAM

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How do you describe a giant? As a person of abnormally great stature; above the usual size; or someone with much greater powers than the average person? Abraham Guz ('Abe') was not a tall man, but he was a scientific giant with an absolute desire to understand and find the scientific truth. This drive led him to make many original contributions in respiratory and cardiovascular physiology. Indeed, a simple literature search produces over 250 peer reviewed papers spanning some 50 years, the top 25 of which have been quoted over 2500 times. Moreover, most of his outstanding work was published in *The Journal of Physiology*, and we received it with gratitude because it was always insightful and ahead of its time. Many will argue that counting citations is a poor measure of scientific endeavour and I suspect Abe himself would certainly agree. However, this approach did provide us with a place to start when faced with the task of bringing together Abe's huge and varied scientific contributions.

**The early years: cardiovascular and respiratory physiology**

Abe's first published study was carried out while he was a House Officer at Charing Cross Hospital. The paper describes the effect of noradrenaline bitartrate infusion in six patients post cardiac infection, and

provides a glimpse of the clinical scientist he would become (Smith & Guz, 1953). Having completed his medical training Abe became a Fellow with the inspirational Dr Julius Comroe at the Cardiovascular Research Institute of the University of California San Francisco carrying out a series of important studies on blood volume regulation (Wilcken *et al.* 1964; Hoffman *et al.* 1965). Comroe regarded Abe as the brightest trainee to visit the CVRI (J. H. Mitchell, personal communication), and that experience in San Francisco clearly shaped what was to come.

In 1961 Abe returned to the UK, publishing his MD thesis in 1967 entitled 'Studies on vagal afferent nerves in man: their role in the control of breathing and respiratory sensation in normal and dyspnoeic subjects'. His work accelerated and it came as no surprise when in 1973 he was elected to the Chair of Medicine at the Charing Cross Hospital Medical School, London. Throughout this period Abe continued his research in cardiovascular physiology and, as his MD title suggests, he also began to study the role of the vagus nerve in respiratory control and sensation, inspired by his time at the Cardiovascular Research Institute. These studies included the pioneering vagal (/glossopharyngeal) blockade experiments in anaesthetised and conscious humans (Guz *et al.* 1964, 1966a,b). In his summary of 'how it really happened' (Guz, 2001) Abe recalls that little was known about the role of the vagus in breathlessness at that time. It was also the early days of heart–lung transplantation surgery and vagal nerve damage was thought to be the cause of death in many of the first operations in animals. The early studies highlight key differences between man and other mammals in the functional significance of cardiorespiratory reflexes as well as implicating afferent activity in the vagus as the genesis of visceral respiratory sensations (Guz & Trenchard, 1971). Contemporaneous studies in dogs during cardiopulmonary bypass provided further insights into the role of vagal feedback in modulating central respiratory rhythmogenesis (Bartoli *et al.* 1973, 1974).

During a sabbatical at Delhi University with A. S. Paintal in 1970, Abe's interest in the vagus was extended to the role of 'J receptors' (Paintal *et al.* 1973).

Thereafter he undertook ground-breaking studies on the effect of airway/alveolar anaesthesia (Cross *et al.* 1976; Winning *et al.* 1985) and later that of heart–lung transplantation on respiratory control and sensation (Shea *et al.* 1988; Banner *et al.* 1989). These studies generally supported the view that spontaneous respiratory control and the genesis of dyspnoea in humans did not depend crucially on vagal afferent information. They also established a life-long pattern of utilising patients and clinical interventions to better understand physiology, and using physiology to better understand patients.

Much of Abe's early work is summarised in the classic Hering–Breuer Centenary Symposium (Porter, 1970). This highly influential Ciba Foundation Symposium took place in 1967 and one quarter of the research papers/chapters in the subsequent publication were co-authored by him synthesising and driving forward research in respiratory control. Attendees were physiologists and clinicians; many were both. Indeed, the distinction between being a physiological researcher or a clinician was not as separate then as it is today. Many participants would have identified themselves as being both, and puzzled over the apparent distinction. Abe would have been one of those identifying himself as both a physiologist and a clinician in equal measure. He had a staggering thirst for knowledge and an absolute desire to understand the cause(s) of the diseases his patients suffered. This can be seen from his very first publication (Smith & Guz, 1953) all the way through to some of his most important studies on the mechanisms of breathlessness and respiratory sensations (Cross *et al.* 1976; Adams *et al.* 1985a; Elliott *et al.* 1991).

Studying dyspnoea and exercise

In the 1980s, Abe initiated the approach of studying the genesis of dyspnoea by using established psychometric techniques to measure the symptoms directly (e.g. Adams *et al.* 1985a,b) rather than the ability of humans to detect and quantify experimental respiratory perturbations. These studies were important in shaping the view that exertional dyspnoea is predominantly a perception of central respiratory-related neural activity. *Pari passu* with this work,

Abe was active in trying to understand the enigma of exercise hyperpnoea (Katona *et al.* 1982) and his work using electrically stimulated muscle contraction in paraplegic individuals, indicating that neither 'central motor command' nor peripheral muscle afferents were obligatory for the exercise response (Adams *et al.* 1984*a,b*). Indeed, the cardiopulmonary aspects of exercise were some of the last studies he carried out with students and colleagues in Oxford (Thornton *et al.* 1998, 2001; Green *et al.* 2007). As an emeritus professor Abe would make the daily trip to Oxford on the bus from Harrow. The net result was stimulating debate and discussion. But more importantly, the outcome was insightful experiments in human physiology using PET, hypnosis, and then functional neuro-surgical techniques that unravelled putative circuits involved in the neural control of the cardio-respiratory system. The University Laboratory of Physiology certainly became a richer place given his presence, not only intellectually, but also a generation of young physiologists and medical students got the Abe 'experience' on how to do science! They kept him young and he kept them enthralled with stories about the wonders of physiology.

The sleep team

The 1980s saw Abe establish one of the first respiratory Sleep Laboratories in the UK, initially to study breathing when behavioural/conscious control was separated from automatic breathing. This was an amazingly productive period with many outstanding achievements, for example the first phenotypic descriptions of breathing during wakefulness and sleep in healthy humans, and in patients with cardiopulmonary disease (Shea *et al.* 1988, 1989, 1993*b*; Shea & Guz, 1992). Abe and his team then turned their attention to the emerging condition of obstructive sleep apnoea, identifying the actual site of upper airway obstruction during sleep in patients with obstructive sleep apnoea (Horner *et al.* 1989*b*). This paper was one of the first to use non-invasive imaging in this patient group, and also identified variability between patients in the sites of obstruction, which has important implications for treatment. Another first for the group was the identification of the excess fat surrounding the pharynx in obstructive sleep apnoea patients, compared

to weight-matched controls (Horner *et al.* 1989*a*). This finding explained (at least in great part) the link between obesity and obstructive sleep apnoea.

In a subsequent series of papers, Abe's sleep team was the first to systematically characterise reflex pharyngeal dilator muscle activation in humans using sub-atmospheric airway pressure as the stimuli (Horner *et al.* 1991*b*), the afferent nerves mediating this reflex (Horner *et al.* 1991*a*), and the suppressant effect of sleep on this reflex response (Horner *et al.* 1994). Further studies identified the central *versus* reflex control of the tongue musculature (Innes *et al.* 1995; Kobayashi *et al.* 1996), and also the impact of sleep on central respiratory control (Morrell *et al.* 1993, 1995). The genioglossus muscle of the tongue was investigated in these studies because it is an important pharyngeal muscle whose activation maintains an open airspace for effective breathing and lung ventilation; depression of activity in the genioglossus is a critical component of upper airway closure and a key factor in the clinical syndrome of obstructive sleep apnoea, along with how breathing is controlled centrally at the sleep-wake transition. This work, especially that involving upper airway imaging, and the physiological studies of upper airway control, stimulated work in many laboratories around the world.

The ideas were many and varied

Abe was fascinated by, and therefore always on the lookout for, new ideas, new techniques, new ways of conceptualising things. In the early 90s he spearheaded the use of the newly available methodology of functional brain mapping to extend our understanding of the role of suprapontine neural networks in human respiratory control (e.g. Colebatch *et al.* 1991; Ramsay *et al.* 1993; Corfield *et al.* 1995). These studies revealed new insights into the behavioural control of breathing during volition, exercise, speech, adaptation to added respiratory loads and even hypnosis. Abe's excellence as a clinician meant that he was able to recognise the importance of supplementing such laboratory studies with careful observations in relevant patient populations as exemplified by the respiratory reaction to an emotional event in an individual with locked-in syndrome (Heywood *et al.* 1996), and

the robust ventilatory response to exercise in individuals lacking ventilatory chemosensitivity (Shea *et al.* 1993*a*) as well as the sleep-wake control of breathing in lateral medullary syndrome (Morrell *et al.* 2001).

Abe believed in others, although his ways of leading and motivating were unusual, and sometimes challenging to the individuals involved. He was always passionate about 'the team' and 'the students'. He inspired enormous loyalty and affection from those who worked with him. He considered it a priority to educate the next generation, and to encourage them in their careers. As a result his Alumni are many and varied. An example of this was his integration of molecular and lung cell biology into his physiology group at a time when this was not common. In one experiment described here they wanted to know the acute effect of cigarette smoking on the antiprotease defences in the lung secretions, as peripheral lung proteases were hypothesised to cause emphysema and there was much controversy regarding the role of locally secreted antiproteases. Ethical approval was obtained (after heated discussions) to lavage healthy volunteers using a unique peripheral lung lavage technique to sample (wash) the alveolar respiratory units where emphysema occurs and where the reduced antiprotease balance was thought most likely to occur.

Volunteers stopped smoking for at least 12 h prior to the investigation. A small portion of their peripheral lung was then washed to collect secretions. They then smoked two cigarettes to a pre-determined protocol, which is quite a high dose of cigarette smoke. The opposite lung was then washed post-smoke exposure. An important and subsequently controversial procedure, suggested by Abe, was the use of trans-tracheal cocaine to negate the discomfort and allow continued communication between the volunteers and bronchoscopists. In some subjects this resulted in a significant degree of hyperactivity, which had to be managed during the course of the study! Abe was very keen to determine whether any of the subjects had emphysema; consequently they also underwent CT scanning. Unexpectedly, two subjects had emphysema and, significantly, one had no locally produced, epithelium-derived antiproteases, whilst in the other, the locally produced antiproteases did not work, suggesting that locally produced antiproteases (i.e. SLPI and elafin) are important in emphysema (Tetley *et al.* 1989).

The iconoclast

Many people have contributed in putting together this Memoriam. In particular one of Abe's former students described him as 'always iconoclastic'. He never (or almost never) fell in love with his own ideas. His experiments were not about confirming with reasonable confidence that his prior beliefs were correct, or confirming conventional or accepted wisdom. In an age where the title Professor is now commonplace in British universities, Abe professed something worthwhile. He wanted his science to be about testing his ideas to destruction. This meant that, crucially, he was happy to change direction completely if it looked more likely to provide a better, or more complete, insight into the truth. This also meant that he was not afraid. He was not afraid to challenge others. He was not afraid to challenge himself. He was not afraid of being challenged. And he was not afraid of radical experiments. He was a professor's professor and a fabulous mentor!

The future

The bedrock that provided the foundation for all of the studies described or referenced in this memoriam was Abe's passionate belief in science. He was obsessed about standards in all senses of the word – standards in calibration, standards in experimental design and standards in analysis. He encouraged the publication of data testing techniques and methods (Adams *et al.* 1985a; Innes *et al.* 1987). He also stressed standards in professional scientific conduct, and giving credit where credit was due. He epitomised scientific rigour. And his most defining question was: 'But what is the mechanism?' Even in the rarefied field of academia Abe was unique, both volatile and eccentric, but his eccentricities never obscured his intellect, and his volatile nature never obscured his love for his colleagues and students. Simply put, the world was a more interesting place with Abe in it. He lives on in the science we do every day, as well as in our hearts.

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Additional information

Competing interests

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