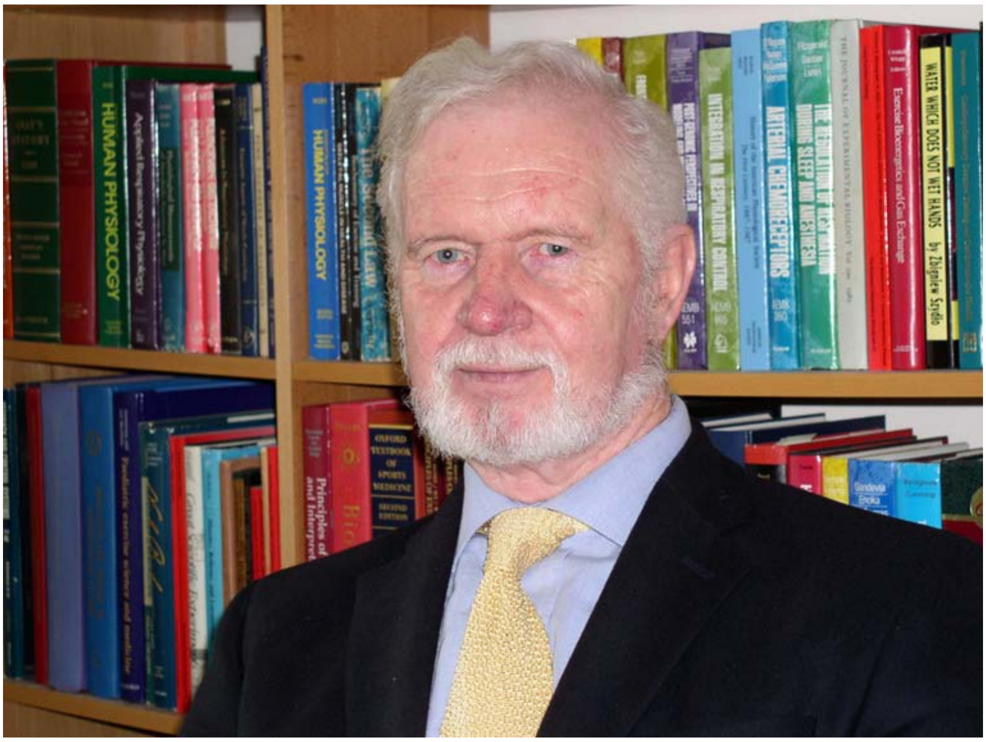
Brian James Whipp, 1937-2011



Brian Whipp was a pioneer of modern exercise physiology, recognized internationally for his contributions both to the determinants of human athletic performance and how particular physiological system failure in disease can provoke exercise intolerance with its sequellae for compromised habitual physical activity. He was a highly accomplished and respected authority on the integrative physiology of exercise, producing defining work in several discrete areas, such as skeletal muscle energetics, pulmonary gas exchange, ventilatory control, and clinical exercise testing and interpretation.

Brian was born and grew up in Tredegar in the South Wales Valleys. He was an accomplished sportsman and, as a schoolboy at Tredegar Grammar School, he was twice Monmouthshire Schools shot-put champion and also represented Tredegar in the Welsh Table Tennis league. During his period of national service, he represented the Royal Air Force at table tennis and athletics; and then, while a physical education student at Loughborough College, he gained University Athletic Union honours in table tennis and was also Welsh Amateur Athletic Association champion for the high hurdles and decathlon. He continued his sporting interests throughout his life, being an avid and accomplished squash player and, in his later years, a keen hill walker.

Having secured teaching credentials from Loughborough College (with First Class Honours), Brian was appointed Lecturer in Physical Education first at Dudley Technical College in 1960 and then at the Prince of Wales College in St. Johns, Newfoundland, Canada in 1961. It was then that he learned that in North America it was possible to study physical education to degree level and beyond. His career consequently took a significant turn in 1962, when he was admitted to the University of Florida in Gainesville. Supported by a Danforth Graduate Fellowship, he was awarded a B.S. and then an M.A. in Physical Education. He was soon thereafter accepted for doctoral studies in the Department of Physiology at Stanford University in Palo Alto, California, gaining a PhD in 1967 under the tutelage of Karlman Wasserman. Brian then moved with Wasserman to the Division of Respiratory Physiology and Medicine at Harbor-UCLA Medical Center in Torrance, California as a National Institutes of Health postdoctoral research fellow, embarking on what was to become an illustrious career in respiratory and exercise physiology. Following a brief period as a Lecturer in the Department of Physiology at University College Cardiff in Wales, he returned to Harbor-UCLA Medical Center and was appointed as an Assistant Professor of Physiology and Medicine in the UCLA School of Medicine - rising rapidly though the academic ranks eventually to become Professor of Physiology and Medicine and Vice-Chairman of the UCLA Department of Physiology. It was fitting that Brian's final promotion at UCLA was as a professorial "scholar and teacher of great distinction". He returned to the UK in 1992 as Head of the Department of Physiology at the University of London's St George's Hospital Medical School, from which he retired as Emeritus Professor in 2001. His retirement was virtual, however, as he continued his academic activities largely unabated, working from his home in Crickhowell in the Brecon Beacons, having affiliations with the Harbor-UCLA Medical Center where he worked with Richard Casaburi and also at the Universities of Glasgow and Leeds where he continued his long-standing collaboration with Susan Ward.

While much of Brian's early research was conducted in collaboration with Karlman Wasserman, he soon emerged as an independent investigator in his own right. Naturally, while a significant proportion of his output constituted "team" efforts, many of these relied heavily on him for not only for their inception but also for their successful prosecution. As such, he and his collaborators have been credited with several key conceptual contributions in human integrative physiology, each of which has provided intellectual and technological impetus for new research avenues. In particular, his early recognition that systems analysis and mathematical control could provide a means of remotely interrogating physiological system function in humans has proved highly influential not only because of its impact on experimental technique (e.g. breath-by-breath pulmonary gas exchange monitoring; dynamic forcing of end-tidal gas tensions; ^{31}P-nuclear magnetic resonance spectroscopy), but also because it has provided a valuable contemporary slant on homeostatic operations as diverse as ATP status in skeletal muscle and pH in arterial blood, and how these are challenged at the limits of performance in health and disease.

As principal author with Karlman Wasserman on the first continuous breath-by-breath description of pulmonary oxygen uptake ($\dot{V}O_2$) kinetics, he demonstrated that these kinetics were not linear over the entire work-rate range as had previously been widely thought, owing to the existence of a "slow kinetic phase" that supplements the fundamental kinetic component - but which is only manifest at work rates associated with a metabolic acidosis (Whipp & Wasserman

1972). There is now no serious challenge to this concept and it is an established feature of modelling studies attempting to assemble defensible systems-analytic hypotheses of muscle oxidative phosphorylation control during exercise and computational strategies for the oxygen deficit at high work rates. And his later research undertaken at St. George's with John Griffiths and the young Harry Rossiter (then a PhD student with Brian) in the late 1990s which, for the first time, allowed the kinetics of intra-muscular high-energy phosphate turnover and pH change to be quantified with high fidelity in concert with $\dot{V}O_2$ kinetics while subjects exercised inside a "whole-body" NMR magnet remains a unique technical feat that others, for well over a decade, were unable to reproduce (e.g. Whipp et al. 1999; Rossiter et al. 2002a & 2002b).

By meticulous documentation of the dynamic co-relationships between ventilation ($\dot{V}E$) and pulmonary gas exchange rates at exercise onset in humans and by means of pharmacological and innovative surgical interventions in animals (including the use of calves with implanted artificial hearts), Brian with younger colleagues such as Richard Stremel, Andrew Huszczuk and Philippe Haouzi, was instrumental in a surge of investigation into the phenomenon of "cardiodynamic hyperpnoea" (Wasserman et al. 1974) - an increase in $\dot{V}E$ mediated in some (still as yet) unspecified fashion by factors closely related to the current level of cardio-circulatory activity (e.g. Haouzi et al. 1995). The notion that the exercise hyperpnoea might be initiated by mechanisms other than the traditionally-espoused views of central and/or peripheral neurogenesis was quite revolutionary at that time, and still – in some minds, at least – remains so.

In parallel with these developments was a "revisiting" of the then traditional "Dejours" view that the medullary and carotid body chemoreceptors largely subserve the later, dominant nonsteady-state phase of the exercise hyperpnoea ("phase 2"). Collaborative work with colleagues such as Richard Casaburi, Norman Lamarra and Susan Ward that employed systems analysis techniques demonstrated that $\dot{V}E$ increased at a substantially slower rate than $\dot{V}O_2$ but only marginally slower than CO_2 output ($\dot{V}CO_2$) when exercise was "forced" dynamically (whether with steps, ramps, sinusoids or impulses). It was argued that the ensuing transient arterial blood-gas perturbations (modest hypoxaemia, slight respiratory acidosis) were not sufficiently large to account for the hyperpnoea through conventional mechanisms of hypoxic and CO_2 responsiveness. These early findings both in humans and in animals were reinforced by demonstrations that $\dot{V}E$ remained tightly coupled to $\dot{V}CO_2$ (but not $\dot{V}O_2$) for a wide range of conditions in which pulmonary CO_2 delivery was experimentally dissociated from tissue CO_2 production: dietary modification; manipulation of body CO_2 stores; pharmacological manipulation of cardiac output; and alteration of mixed venous PCO_2 by intra-venous infusion of CO_2 and (in humans) by modified bicarbonate haemodialysis. This resulted in the formulation of the "CO_2 flow" hypothesis, which purported to link $\dot{V}E$ to the pulmonary vascular CO_2 delivery rate (Wasserman et al. 1977; Whipp 1983), to which Brian had recently added an important refinement: "Such proposals, however, fail to meet the $PaCO_2$-regulatory demands of the control. That is, any such control link will depend not on the rate at which CO_2 is brought to the lung per unit time but that minus the rate at which CO_2 leaves the lung in the pulmonary arterial blood." (Whipp 2008).

A further contribution to our understanding of the control of the exercise hyperpnoea relates to the role of the carotid bodies. Utilizing a unique group of individuals who had previously undergone surgical resection of their carotid bodies by Los Angeles surgeon Benjamin Winter, coupled with techniques for altering carotid body responsiveness in normal individuals (e.g. manipulation of metabolic acid-base and oxygenation status), the carotid body chemoreceptors were demonstrated not only exert an important modulating action on the phase 2 dynamics of the exercise hyperpnoea but also to be responsible for mediating the greater part of the compensatory hyperventilation for the lactic acidosis of high-intensity exercise (Wasserman et al. 1975; Whipp 1994).

With his colleagues at Harbor-UCLA Medical Center in the 1980s, most notably Karlman Wasserman and James Hansen, Brian was pivotal in the development of the clinical paradigm of cardiopulmonary exercise testing and interpretation, which has now evolved into an international "gold standard" of clinical practice. The influential book "*Principles of Exercise Testing and Interpretation*" – first published in 1986, with translations into Japanese, Chinese and Portuguese and now in its fifth edition (Wasserman et al. 2012) - is considered by many to be the "bible" of clinical exercise testing. And with Josep Roca from Barcelona, he led, too, on parallel *European Respiratory Society (ERS)* initiatives (e.g. Roca & Whipp 1997a & 1997b).

Brian was also fascinated in the historical aspects of exercise physiology. In 1992, he published with Susan Ward a provocative Letter to *Nature* (Whipp & Ward 1992) that explored some implications for past and future running performance, based on a chronological analysis of World Records. And he can be credited with introducing to the field the term "Paleo-Bioenergetics" – with stimulating publications on Roman Legionaries (Whipp et al. 1998) and ancient Greek Trireme rowers (Rossiter & Whipp 1998 & 2011).

Brian's work was scholarly in the finest sense, combining an extensive knowledge of physiology and biochemistry with thoughtful and incisive scientific logic; qualities which he imparted over the years to many of the research students, fellows and physicians whom he mentored. He was a gifted lecturer and teacher. His presentations were captivating, drawing not just on the physiological "matter at hand" but illustrated by pertinent "snippets" from philosophy and literature. He had the valuable attribute of being able to make difficult concepts accessible and understandable.

He was generous with his time, serving, for example, on the editorial boards of many journals, including the *Journal of Applied Physiology*, *Medicine and Science in Sports and Exercise*, *European Journal of Applied Physiology* and *Respiration Physiology*. He also served on committees of scholarly societies, such as the *American Physiological Society (APS)*, the *American College of Sports Medicine (ACSM)* and the *American Thoracic Society*. He was a staunch supporter of the *Physiological Society*. Despite living overseas for much of his career, he regularly presented at meetings. He edited the 1987 Study Guide "*Control of Breathing in Man*" and co-edited with Anthony Sargeant the 1999

Teaching Symposium monograph "*The Physiological Basis of Human Exercise Tolerance*". And on his return to the UK, he served on the Committee (1993-1997) and was an Editor on the Board of *Experimental Physiology* (1994-2000).

Brian enjoyed considerable standing within the international physiological community, and received many honours: a Doctor of Science by Loughborough University in 1982; an *ACSM* Citation Award in 1990; Chairmanship of the Respiratory Commission of the *International Union of Physiological Sciences* from 1997-2002; the 2002 Joseph B. Wolffe Memorial Lectureship of the *ACSM*; the 2007 Distinguished Scientist Honor Lectureship of the *American College of Chest Physicians*; the 2008 *APS* Honor Award (Environmental and Exercise Physiology); and, most recently, the 2010 *ERS* J.-C. Yernault Lectureship and the 2010 *ACSM* D.B. Dill Lectureship.

And Brian had other "strings to his bow". He was a serious scholar of Shakespeare, for example, and intensely interested in matters of philosophy, literature and music. He revelled in fine dining, especially in Paris. But, at heart, he was also a man of simple pleasures, enjoying nothing more than stimulating conversation over breakfast with his friends at his local coffee house in Crickhowell.

Susan A. Ward (Human Bio-Energetics Research Centre, Crickhowell, UK)

David C Poole (Department of Anatomy and Physiology, Kansas State University, Manhattan, Kansas, USA), a former PhD student, continues:

Professor Brian Whipp was a mentor like no other. In UCLA's Medical School physiology class, Brian (*Y Ddraig Goch* - The Red Dragon) captivated the students en masse. His powerful, crisp and erudite delivery, spiced with medical anecdotes and Shakespearean segues, sparkled with intensity. Should Shakespeare's Richard III really be given credit for the discovery of pulmonary surfactant? Born prematurely and consequently physically disadvantaged, Richard's opening soliloquy laments "Deformed, unfinished, sent before my time. Into this breathing world, scarce half made up…" To *Whippian* thinking this was perhaps(!) evidence for Shakespeare acknowledging the presence and importance of pulmonary surfactant – over four hundred years before its official discovery (by R.E. Pattle in 1955). In his graduate class, Brian demanded that equations and their derivation be mastered; all bluff was exposed and the limits of their understanding publicly dissected. This was how Brian prosecuted his science: attacking and riposting his scientific peers with penetrating logic and a superb command of the literature. I was among an enthralled audience at the *ACSM*'s 1984 Congress in San Diego when Brian engaged George Brooks of the University of California at Berkley in a scintillating debate over the mechanistic bases of the "anaerobic threshold." It was then that I knew I wanted to be a scientist. Subsequently, as one of his doctoral students, I would present data and allude to mechanisms, whereupon Brian would fix me with those pale rapturous blue eyes. In short order, he would remove all conjecture and woolly thinking from my thesis leaving only stark fact. In this I have never met Brian's equal.

Brian was a superb athlete who held an international ranking in squash well into his 50's. He was fond of commenting that squash was "a sport where age and deceit won out over youth and enthusiasm." He played squash as he lived science and life: Thinking three moves ahead of his opponent, precise positioning of each strike and ending the point with a devastating kill shot. As his many vanquished opponents will recall, Brian was gracious to a fault. Their 'good' shots would be acknowledged with an "AAAAverage" from Brian; with the length of the "AAAs" proportional to his opinion of their prowess. Whether in the scientific arena or walking the hills and vales of his beloved Wales, one could not talk to Brian without learning something extraordinary. He was a gentleman and a scholar *par excellence*. To this day when faced with a seemingly intractable problem, I often find myself asking "What would Brian do?" It is by standing on this Welsh giant's shoulders that Brian helped so many scientists to see further. Our Doctor Mirabilis endures.

Harry B Rossiter (Rehabilitation Clinical Trials Center, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, USA), a former PhD student and postdoctoral fellow, continues:

In 1992 Brian returned to the UK to chair the Department of Physiology at St George's Hospital Medical School. In addition to serially beating the entire Medical School 1st team at squash at the age of 64, he continued to inspire and enthrall a new generation of clinicians and researchers. Brian's engaging and formidable performances at the lectern are legendary, but his generosity towards his students sets him aside as a truly exceptional teacher. "I wish upon you a student such as yourself" would be the words to greet you on entering his office – a *Whippian* way of encouraging scientific inquiry at which, as students, we would blush with a mixture of embarrassment and pride. But despite the stern demeanor, he was always liberal with his time. He would not only answer whatever misguided question the student had arrived with, but took the time to ensure that he or she left with a clear understanding of the justification for the explanation. A tutorial with Brian was a lesson in rigor, veracity and scientific scrutiny. He would guide you on an adventure of challenging assumptions and identifying flaws of logic while, on the way, reminding you that "words matter": He placed a strong emphasis on the great benefit of a correctly phrased question. One always left Brian's office having learnt something new, whether it be of physiology, philosophy, music or rugby (as long as it was Welsh rugby!). He was a Professor defining the term.

Brian was a proud pupil of science, tireless in his pursuit of evidence and knowledge. It is perhaps fitting then, that his academic lineage (his PhD supervisor's supervisor… and so on) traces back 15 generations to Father of Science, Galileo Galilei. Although, it is perhaps a shame that this genealogy could not be traced quite as far as the Greek philosophers, Brian's scholarly command of their writings was demonstrated in his 2010 *ACSM* 'D.B. Dill lecture', where he reminded the packed auditorium that the ancient parameters of scientific enquiry transcend the ages and disciplines.

On his 'retirement' in 2001, Brian said that he felt sufficiently equipped to "complete a really good post-doc" - and he did not disappoint. Unhindered by retirement, he continued his inquiry and influence. He published over 50 papers following this watershed (including some of his most cited contributions), delivered some of his most memorable presentations (his 2010 *ERS* 'Yernault Lecture' was one for the ages), and inspired clinicians and physiologists through contributions to cardiopulmonary exercise testing courses the world over.

Brian had the correct phrase for every occasion; able to cut to the essence of the moment with a careful molding of just of few words. When especially harried he would turn to Samuel Beckett: "I can't go on… I'll go on". He will be sorely missed, but he will 'go on' through his many fundamental contributions to physiology, his engaging orations and inspirational teachings.

Brian Whipp died on October 20th, 2011 at the University of Wales Hospital Cardiff, after a short illness. He leaves his children from his first marriage, Laura and Brian, and his wife, Sue.

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