

## In memoriam: Frederick E Hargreave (1938–2011)



A wonderful clinical scientist, great friend and mentor to many in the field of respiratory medicine, Frederick E Hargreave (known to everyone as Freddy), died suddenly on 15 June 2011. Freddy was born in Hong Kong

and completed his medical school training at the University of Leeds. After completing his initial clinical training, Freddy moved to London to work as a house officer in respiratory medicine with Dr EJ Moran Campbell at the Hammersmith Hospital. A short while later, Moran Campbell accepted the position as the founding chair of the Department of Medicine at the Faculty of Health Sciences at McMaster University in Hamilton, Ontario, a move that was to change Freddy's life both personally and professionally. Subsequently, Freddy began his research training with Professor Jack Pepys at the Brompton Hospital. During this time, Freddy described a new clinical entity, bird fancier's lung disease, a type of allergic alveolitis caused by the inhalation of bird antigens.<sup>1</sup>

In 1969, Freddy Hargreave joined the Department of Medicine at McMaster University, at the behest of Moran Campbell and Norman Jones (who was the first division director for respiratory medicine at McMaster). Shortly after arriving in Hamilton, he started what was to become a lifelong collaboration and close friendship with Dr Jerry Dolovich and their focus turned to understanding the mechanisms and treatment of asthma. Within 10 years, the studies led by Freddy Hargreave had changed the way that asthma was diagnosed and had paved the way to future studies that have revolutionised its treatment. In particular, Dr Don Cockcroft (who was Freddy's first clinical fellow), who described the methodology for the measurement of airway hyper-responsiveness in asthma,<sup>2</sup> had demonstrated that

this was a crucial component of the disease and present in all patients with current symptoms and determined that the degree of airway hyper-responsiveness was related to the amount of treatment needed to manage asthma.<sup>3</sup> The paper describing this methodology<sup>4</sup> is a citation classic, having been cited almost 1800 times.

Other studies conducted in his laboratory, during this time, described a method for allergen inhalation challenge<sup>4</sup> (cited almost 900 times), which remains widely used still to examine mechanisms of allergen-induced airway responses. Also, his studies demonstrated that allergen inhalation could change airway responsiveness for up to several weeks and that this was particularly obvious in subjects who developed allergen-induced early and late phase responses.<sup>5</sup> The changes in airway responsiveness were also seen in patients with occupational asthma.<sup>6</sup>

In the early 1980s, the importance of persistent airway inflammation in the pathogenesis of asthma became apparent. The type of inflammatory response differed from patient to patient and was difficult to measure because it required fiberoptic bronchoscopy<sup>7</sup> and could not be done routinely. The brilliance of Freddy Hargreave's research was that it was always focused at directly solving patient-related issues. He recognised that the non-invasive measurement of airway inflammation was a critical step in the evaluation and treatment of patients with difficult-to-treat asthma. This resulted in the development of the methodology for sputum induction and measurement of inflammatory cells in sputum.<sup>8</sup> Almost immediately, this resulted in the identification of a new syndrome—persistent eosinophilic airway inflammation in the absence of asthma<sup>9</sup>—that accounts for about 10% of patient referrals with chronic persistent cough to respiratory clinics.<sup>10</sup>

In his research, Freddy did not aspire to be the very first with a discovery, but he passionately strived to provide the most accurate data. The standardised methods that Freddy's laboratory developed for sputum induction and processing<sup>11</sup> are now considered the gold standard and used as a research tool in all laboratories that conduct clinical research in asthma; however, from extensive experience in measuring sputum inflammatory cells in the clinical setting, Freddy was convinced of its added value in the everyday management of difficult-to-control asthma. Clinical trials comparing standard guideline directed management of asthma with a management scheme, which added the routine measurement of induced sputum, showed a dramatic advantage of adding the sputum method in reducing the risks of severe asthma exacerbations and also in determining the appropriate doses of inhaled and/or oral corticosteroids to manage these patients.<sup>12</sup> In addition, using induced sputum allowed the identification of a group of patients (about half of those with difficult-to-treat asthma) who greatly benefit from the use of a monoclonal antibody directed against interleukin 5.<sup>13</sup> Some, but not all, tertiary level asthma clinics worldwide have embraced this methodology; based on this evidence and a driving ambition until his untimely death, he wanted to extend the use of this method to benefit patients. His contribution to asthma care worldwide has been recognised by several honorary lectureships and an honorary degree from the University of Modena in 2010.

His research inquisitiveness was complemented by his extraordinary qualities as a caring physician. He showed deep

empathy and a genuine concern for all his patients. He listened intently to their problems and demonstrated extraordinary patience and skill in eliciting a history particularly in patients with occupational lung diseases. He would also show extreme tenacity to get to the root of problems and getting investigations done to establish accurate diagnosis. In the current era of technology-driven medical practice, watching Freddy elicit a careful history and establishing a diagnosis with minimal investigation after a thorough physical examination, was a real treat for his fellows.

Freddy Hargreave's brilliance as a clinical scientist was only eclipsed by his skills as a mentor. He embodied every quality expected of a mentor. He provided his trainees with extraordinary supervision, unselfish love and affection and trained them with the expectation that they would be not just as good as he was, but to be better than him. Many of the research leaders in asthma in Canada have trained at his laboratory at the Firestone Institute and his previous fellows are research leaders in more than 20 countries. Freddy was also genuinely interested in international research developments and was among the first North American respiratory scientists who actively and consistently participated in the European Respiratory Society. His openness to colleagues around the world made him highly respected, beloved and led to an unprecedented acceleration of the research field. Freddy's implicit confidence in his long list of trainees made them flourish. The nicest aspect was that he hardly realised that any of this was exceptional.

His honesty, integrity and precision in research were legendary and he tried to impart these qualities to his trainees. He had the skill of real listening. His supervision extended beyond clinical and research training. He paid particular attention to ensure that his fellows were trained in literary skills, writing skills, grammar and semantics, often insisting that manuscripts be drafted time and time again to ensure perfection. He was singularly insistent on the use of nominalism to define diseases such as asthma and argued that essentialist definitions did not have a place in scientific discussions.<sup>14</sup> In addition to making landmark advancements in the diagnosis and treatment of asthma and other obstructive airway diseases, he mentored his trainees to be caring physicians first, researchers and scientists second. His research was driven entirely by the clinical needs of his patients and epitomised translational research. Every observation directly led to improved health of his patients. He rejoiced, not from his over 300 publications in high impact journals or his h-index of 68, but from the recognition of his grateful patients and successes of his trainees.

McMaster University, the city of Hamilton, the Canadian respiratory community and the international scientific community have lost an extraordinary physician, humanitarian and clinician scientist. His untimely demise has deprived physicians and scientists across the world of a trusted colleague, friend and mentor. His wife, Alix, his children Clare, Erica and

Peter and his grandchildren have lost a devoted husband, a loving and caring father and an affectionate grandfather. Despite his world-class accomplishments, he did not care for titles, accolades or his own advancement. To his patients, he was not Dr Hargreave, but Freddy—the doctor and friend who wore shorts, sandals and knee high socks, even in the depth of winter. There never has been and probably never will be a physician whose phone and home were always open to anyone in need. He cared genuinely, and in everything he did, he brought a level of decency that many overlook.

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