Respiratory medicine at McMaster University, Hamilton, Ontario: 1968 to 2013

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The medical school at McMaster University (Hamilton, Ontario) was conceived in 1965 and admitted the first class in 1969. John Evans became the founding Dean and he invited Moran Campbell to be the first Chairman of the Department of Medicine. Moran Campbell, already a world figure in respiratory medicine and physiology, arrived at McMaster in September 1968, and he invited Norman Jones to be Coordinator of the Respiratory Programme.

At that time, Hamilton had a population of 300,000, with two full-time respirologists, Robert Cornett at the Hamilton General Hospital and Michael Newhouse at St Joseph's Hospital. From the clinical perspective, the aim of the Respiratory Programme was to develop a network approach to clinical problems among the five hospitals in the Hamilton region, with St Joseph's Hospital serving as a regional referral centre, and each hospital developing its own focus: intensive care and burns units at the Hamilton General Hospital; cancer at the Henderson (later Juravinski) Hospital; tuberculosis and rehabilitation at the Chedoke Hospital; pediatrics and neonatal intensive care at the McMaster University Medical Centre; and community care at the Joseph Brant Hospital in Burlington (Ontario). The network provided an ideal base for a specialty residency program. There was also the need to establish viable research.

These objectives were achieved through collaboration, support of hospital administration, and recruitment of clinicians and faculty, mainly from our own trainees and research fellows. By the mid-1970s the respiratory group numbered more than 25; outpatient clinic visits and research had grown beyond our initial expectations. The international impact of the group became reflected in the clinical and basic research endeavours.

ASTHMA: Freddy Hargreave and Jerry Dolovich established methods to measure airway responsiveness to histamine and methacholine. Allergen inhalation was shown to increase airway responsiveness for several weeks, and the late response was shown to be an immunoglobulin E-mediated phenomenon. Paul O'Byrne and Gail Gauvreau showed that the prolonged allergen-induced responses were due to eosinophilic and basophilic airway inflammation and, with Judah Denburg, revealed upregulation of eosinophil/basophil progenitor production in bone marrow and airways. The Firestone Institute became the centre of studies identifying the inflammatory phenotype of patients with difficult-to-control asthma. Freddy Hargreave and others developed methods for sputum induction to identify persisting eosinophilic airway inflammation and documented its presence in the absence of asthma and in patients with persistent cough. Parameswaran Nair has applied these techniques to the management of asthma in routine

clinical practice. The Asthma Quality of Life Questionnaire and the Asthma Control Tests were developed by Drs Liz Juniper and Gordon Guyatt. The first Canadian evidence-based clinical guidelines for asthma management in 1989 were coordinated by Freddy Hargreave, Jerry Dolovich and Michael Newhouse.

DISTRIBUTION OF INHALED PARTICLES: Michael Newhouse and Myrna Dolovich used inhaled radiolabelled aerosols to study the distribution of inhaled particles and their clearance in normal subjects, smokers and patients with chronic obstructive pulmonary disease. They developed the aerochamber, and were the first to radiolabel therapeutic aerosols to distinguish the effects of peripheral versus central deposition. Particle deposition and clearance were shown to be impaired in ciliary dyskinesia and cystic fibrosis.

DYSPNEA: Moran Campbell and Kieran Killian measured psychophysical estimates of the sense of effort in breathing in studies of loaded breathing and exercise to show that dyspnea increased as a power function of both duration and intensity of respiratory muscle contraction, and in relation to reductions in respiratory muscle strength. These principles also applied to dyspnea in cardiorespiratory disorders.

EXERCISE CAPACITY: Norman Jones and Moran Campbell developed a system for noninvasive cardiopulmonary exercise testing using an incremental exercise test, and more complex studies with measurement of mixed venous PCO₂ by rebreathing. The 6 min walk test was validated by Gordon Guyatt. Kieran Killian and Norman Jones introduced routine muscle strength measurements in clinical testing and symptom assessment in exercise testing. Muscle strength training improved exercise capacity in older subjects and patients with chronic obstructive pulmonary disease.

METABOLISM AND ACID-BASE CONTROL IN EXERCISE: After showing that imposed acidosis reduced, and alkalosis improved performance, Norman Jones, John Sutton and George Heigenhauser investigated the interactions between acid-base status and metabolism in exercise.

HIGH-ALTITUDE MEDICINE: John Sutton and Peter Powles participated in high-altitude research on Mount Logan (Yukon), demonstrating sleep hypoxemia in acute mountain sickness and its reversal by acetazolamide, and participated in Operation Everest II.

EPIDEMIOLOGY: David Pengelly and Tony Kerrigan followed children living in areas with differing air quality to show that lung development was adversely affected by pollution and maternal smoking. Malcolm Sears and Neil Johnstone showed that the 'return to school' asthma exacerbation epidemic was due mainly to rhinoviruses. David Muir investigated the effects of silica exposure in hard-rock miners, and mortality in the nickel industry.

SUMMARY: The Respiratory Division has grown to more than 50 physicians and PhD scientists, and currently provides the busiest outpatient clinic in Hamilton, and has successful training and research programs.

There were plans for a medical school at McMaster University (Hamilton, Ontario) as early as the 1940s; however, nothing came of them until 20 years later when the University's Chancellor, Dr Harry Thode, made a strong case to the Ontario government. By this time, Dr Thode, a nuclear physicist, had established strong science faculties in the university, and a department of medical research to investigate the medical use of radioisotopes produced by the nuclear reactor he had acquired for the university. McMaster's medical school was born in 1965, with the goal of admitting the first class in 1968, with plans to graduate its first class in 1971. After a lengthy search, Dr Thode invited Dr John Evans, a junior member of the University of

Toronto's (Toronto, Ontario) medical faculty to become the founding Dean of the medical school in 1967. A priority for Dr Evans was the appointment of a Chairman for the key Department of Medicine, but his search remained unsuccessful despite visits from at least 25 candidates. Then, in 1968, he wrote to Dr Moran Campbell in London, England, asking whether he may "be prepared to do a bit of work in the colonies" and, a little later, he hosted a recruitment party at the Hammersmith Hospital (London, England) at which a famous promotional film presenting the attraction of Ontario as 'a place to grow' was shown. The result was not only the recruitment of Dr Campbell, but also of several other faculty and support staff.

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THE BEGINNINGS: 1968–1972

Dr Campbell arrived at McMaster University in September 1968, followed shortly after by Dr Norman Jones as coordinator of the Respiratory Programme. They had worked together for six years in the respiratory division of the Royal Postgraduate Medical School at the Hammersmith Hospital, headed by Dr Charles Fletcher. Dr Campbell was already a world figure in respiratory medicine and physiology, with a reputation largely built on his two books, *The Respiratory Muscles and Clinical Physiology*, and the prestigious *Amberson Lecture to the American Thoracic Society* in 1967, a brilliant contribution to our understanding of respiratory failure in chronic obstructive pulmonary disease (COPD). He became a powerful magnet in attracting well-qualified trainees and fellows from across Canada, but especially from abroad.

Student enrollment to the new medical school was delayed for a year, to 1969, with the intention of the first year of 20 students graduating in 1972, the year of completion of the McMaster University Medical Centre (MUMC). This innovative building, designed by the same architects who designed Ontario Place on the lakefront of Toronto, was situated on the university campus. Perhaps more importantly for the local community, it was built on what had been a centrepiece 'sunken garden' of the Royal Botanical Gardens, an action that early faculty members were not allowed to forget! Because of this time gap in the completion of the medical school, student teaching was located at the Chedoke Hospital, the site of the Mountain Sanatorium, once famous as the "largest TB sanatorium in the British Empire". Here, teaching resources were developed to meet the requirements implicit in the vision of Dr Evans – a three-year course featuring integrated, clinically based learning in small-group tutorials and using a problem-based approach. In short, a very radical teaching system that was derided by many outside academics but embraced by the local faculty who did not want to repeat the mistakes inherent in their own, classical medical education.

For the fledgling Respiratory Programme, the initial emphasis was placed on undergraduate education and the needs of the community for excellent clinical care. At the time, Hamilton had a population of 300,000, with a comparable figure in its 'catchment area'. Serving this large clinical base were two full-time respirologists, Dr RW Cornett at the Hamilton General Hospital, and Dr MT Newhouse, who had been recruited by Dr WM Goldberg to St Joseph's Hospital following completion of his training at McGill University (Montreal, Quebec). From the clinical perspective, the aim was to develop a network approach to clinical problems among the five general hospitals in the Hamilton region, under the aegis of the District Health Council. In this network, St Joseph's Hospital served as a regional referral centre (Figure 1), with comprehensive facilities for the investigation of respiratory problems including bronchoscopy, radiology, thoracic surgery and pathology. Finally, there was recognition that research momentum needed to be built as soon as possible, requiring application for research funding and recruitment of faculty and support staff.

All of the initial aims were challenging; the fact that they were, in large part, successfully achieved is testament to great cooperation and goodwill, in addition to the support of the hospital administration as well as several individuals who came to Hamilton, often at an early stage in their careers. Notable among these were trainees and research fellows who came from other parts of the commonwealth, particularly Australia, with some staying for several years and making significant contributions to education and research.

From the educational standpoint, our aims required the design of suitable clinical problems that allowed students to explore all aspects of respiratory physiology, anatomy and pathological processes. This was accomplished by boxes containing a clinical story, radiographs and the results of investigations, together with slide/audio presentations on specific topics and anatomical preparations. Dr John Dickinson, co-author of *Clinical Physiology* and on leave from St Bartholomew's Hospital in London, masterminded the development of computer models of respiration (McPuf) and the cardiovascular system (McMan) (1). Many individuals contributed to all of these resources or became involved as tutors (mentors, advisors and facilitators) to the small

Figure 1 The Respiratory Unit at St Joseph's Hospital (Hamilton, Ontario) in 1969. **Back row:** J Kane, Moran Campbell, M Newhouse, –, D Robertson, R Taylor, J Gibson, –, –, –, J Sanchis, D Levy, –. **Middle row:** J Lane, R Fautley, J Mehta, R Hannah, –, F Hargreave, N Jones. **Front row:** S Skpmarowski, L Head, –, –, P Willan, R Chalmers, M Morris, Sister Michael, J Thomas

student tutorial groups. The clinical network, including intensive care units, outpatient clinics and pulmonary function laboratories, provide a wide experience for trainees, supplemented by weekly teaching events.

Recruitment to clinical staff positions was initially from the residency training program, with Dr Stu Pugsley and Dr John Morse joining St Joseph's, Dr Anthony Kerrigan and Dr Clive Davis going to the Hamilton General Hospital, Dr Serge Puksa and Dr Alan McLennan to the Henderson Hospital, Dr Roger Haddon to the Joseph Brant Hospital and Dr Jack Mehta to the Chedoke Hospital. Dr Leo Kahana came from Montreal to head the regional tuberculosis service. By the mid-1970s, there were 25 full-time respirologists in Hamilton.

Research studies were soon underway in several areas. Dr Jones was able to establish an exercise laboratory with the help of Medical Research Council grants, Dr DG Robertson as a research fellow, and the technical expertise of Jim Kane, Ann Hart and Monte Smith. Dr Newhouse was able to take advantage of an Anger scintillation camera in the nuclear medicine department headed by Dr Ken Ingham, and radioisotopes produced by the reactor at McMaster for imaging of the lung. He was joined by Myrna Dolovich, who managed the Aerosol Laboratory and began studies investigating regional lung deposition. Dr Campbell was able to commandeer space at the medical centre, then less than 10% completed, to continue studies of loaded breathing with David Pengelly, who came from McGill, on the recommendation of Dr David Bates.

In 1969, Dr Freddy Hargreave joined the group at St Joseph's, following completion of studies for his MD thesis on bird fancier's lung under the supervision of Dr Jack Pepys at the Brompton Hospital (London, England). Around the same time, Dr Jerry Dolovich was appointed to the Division of Clinical Immunology and Department of Pediatrics, and the two struck up an immediate friendship. Thus began an extraordinary collaboration that was to last almost 30 years until Dr Dolovich's death in 1997. They established an Allergy and Asthma Clinic at St Joseph's Hospital, and commenced joint research projects, which eventually culminated in international recognition and lifetime achievement awards. Through the years, many research fellows and trainees joined Dr Hargreave, beginning with Dr Don Cockcroft; their subsequent successful careers attest to his mentoring skills and the welcoming environment that he provided. In fact, many of the pre-eminent asthma clinical scientists across Canada and overseas were mentored by Freddy Hargreave, including Drs Louis-Philippe Boulet, Andre Cartier, Don Cockcroft, Mark FitzGerald, Peter Gibson, Margaret Kelly, Richard Leigh, Catherine Lemièrre, Andrew McIvor, Parameswaran Nair, Paul O'Byrne, Ian Pavord, Malcolm Sears, Peter Sterk, Susan Tarlo and Neil Thompson.

Figure 2) Airway responsiveness to inhaled histamine, expressed as the provocative concentration causing a 20% fall in forced expiratory volume in 1 s (PC₂₀) in normal and asthmatic subjects. The asthmatic subjects are divided into seasonal asymptomatic, those requiring as-needed (prn) and regular bronchodilator treatment, and those requiring inhaled corticosteroids. Reproduced with permission from reference 2

Early in the program, a weekly morning was devoted to academic activities in three sessions: a clinical presentation, a research-in-progress session and a business meeting. The first two became a highlight of the week and have continued, more or less, unchanged since then; the third became less necessary as the group enlarged.

THE OPENING OF MUMC

Opening in early 1972, MUMC provided a large increase in ideal space for educational, clinical and research endeavours. Dr Jones left St Joseph's Hospital to direct the Ambrose Cardiorespiratory Unit. In 1977, Dr David Muir was recruited to head an occupational medicine program; in addition to initiating many epidemiological research studies, the group developed an innovative diploma course in occupational health and a referral clinic for occupational lung problems. Dr Pengelly set up an air-pollution laboratory and embarked on a long-term epidemiology study on the effects of pollutants on lung development.

Several commonwealth postgraduates, including John Alpers, Jack Cade, Steve Leeder, Tony Rebuck, John Rigg, Nick Saunders, John Sutton and John Wicks from Australia and Peter Powles from New Zealand, contributed to the development of the educational, clinical and research efforts in the early 1970s. Many stayed for a year or two and returned home, but Dr Sutton and Dr Powles remained for many years and collaborated in high-altitude studies. MUMC was situated on the university campus, and collaboration soon developed with Dr Neil Oldridge and other members of the Kinesiology Department. These efforts resulted in several studies of the effects of training and the Ontario Collaborative Study of exercise rehabilitation in postmyocardial infarction patients.

At St Joseph's Hospital, there was a steady increase in clinical work, accommodated in the Firestone Regional Chest and Allergy Unit, named for Morgan Firestone, a generous supporter of St Joseph's over many years. The ambulatory unit and pulmonary function laboratory were housed in a refurbished Salvation Army home attached to the hospital; it housed the Allergy and Asthma Clinic, and a clinic devoted to COPD, led by Dr Pugsley and one of the first nurse-practitioners, Mrs Lee Robinson. Outpatient visits increased from 2000 in 1972 to 6000 in 1976. The unit also became the centre of the residency training program, which went from strength to strength under the leadership of Dr Morse, and later Dr Lori Whitehead. In 1990, Dr Malcolm Sears was appointed head of service, having previously spent a year on sabbatical leave from his position in New Zealand, where he had earned international recognition for a large prospective study of asthma in childhood, and

critical studies of short-acting bronchodilators. Dr Michael Kay joined the Department of Pathology in 1977 to provide an exemplary service for lung histology, thereby also making a notable contribution to the specialty training program.

Chedoke Hospital became the regional centre for a respiratory rehabilitation program, where patients with severe lung disease could be admitted at the start of a comprehensive program of education, physiotherapy and exercise. Initiated by Dr Jack Mehta and Dr Roger Haddon, this program continued under Dr Les Berman and Dr David Stubbing.

Dr Paul O'Byrne was appointed division director of Respiratory Medicine in 1990, followed by Dr Gerard Cox in 2002. The current division director is Dr Martin Kolb.

THE FIRESTONE INSTITUTE FOR RESPIRATORY HEALTH (1999)

In 1967, Dean Evans sought the advice of two consultants regarding the development of a strong academic program in respiratory medicine; they proposed that an institute be established at St Joseph's Hospital. Some 30 years later, the Firestone Institute for Respiratory Health (FIRH) was commissioned and built with the financial backing of the Canadian Foundation for Innovation, the Ontario Ministry of Health and several charitable organizations. The Institute furnished office and clinic space both for respiratory medicine and for thoracic surgery, laboratories, lecture theatres and a library. At around the same time, plans were developed to turn MUMC into a children's hospital, eventually eliminating most adult services.

Research

Driven by clinician-scientists, initial research efforts had a clear clinical focus, leading later to a greater emphasis on underlying biological mechanisms.

Asthma

Drs Hargreave, Dolovich and Cockcroft investigated measurements of airway responsiveness to histamine and methacholine, and established the methods for inhalation challenge, now used worldwide (2) (Figure 2). They also developed an allergen provocation test, and demonstrated conclusively that allergen inhalation had prolonged effects, increasing airway hyper-responsiveness for days or weeks after challenge (3). Dr Jerry Dolovich proved that the allergen-induced late response was an immunoglobulin E-mediated phenomenon (4). Subsequently, Drs Paul O'Byrne and Gail Gauvreau showed that the prolonged allergen-induced responses were caused by eosinophilic and basophilic airway inflammation (5) and, in collaboration with Dr Judah Denburg, a marked upregulation of eosinophil/basophil progenitor production in both the bone marrow and the airways. Allergen inhalation challenge also became a useful way to evaluate drug efficacy in asthma. Other studies conducted with Dr Ellinor Adelroth identified the importance of other inflammatory mediators, particularly the cysteinyl leukotrienes (6) in both allergen- and exercise-induced bronchoconstriction (7). This group also conducted the initial studies identifying persistence of eosinophilic airway inflammation, even in mild asthma (8). Other seminal studies that came from this laboratory included the identification of the benefit of inhaled corticosteroids in milder asthma (9) and the development of the Asthma Quality of Life Questionnaire and the Asthma Control Tests by Elizabeth Juniper and Dr Gordon Guyatt (10).

In 1999, several scientists moved into the newly built FIRH from MUMC and began studies investigating the more basic mechanisms of asthma and airway smooth muscle function. These included Dr Mark Inman, who developed murine models of allergic airway inflammation and measurements of lung function; Dr Luke Janssen, whose studies focused on the molecular mechanisms of airway smooth muscle and calcium handling in myocytes; and Dr Roma Sehmi, who examined the mechanisms of bone marrow progenitor development and trafficking in asthma. Subsequently, Dr Mark Larché was recruited from

Imperial College, to lead studies on the immunological mechanisms of allergic airway responses and inflammation and Dr Kjetil Ask, whose studies examined protein misfolding and endoplasmic reticulum stress.

The FIRH also became the centre of studies to identify the inflammatory phenotype of patients with difficult-to-control asthma. With Drs Peter Gibson, Marcia and Emilio Pizzichini, Isabel Pin and others, Freddy Hargreave developed methods for sputum induction and automated differential cell counting (11) (Figure 3), enabling distinction of these conditions and examining the cellular responses to treatment (12). They identified the importance of recognizing persisting eosinophilic airway inflammation in making treatment decisions for these patients, and described a newly recognized clinical entity, eosinophilic airway inflammation without asthma (13), which is present in 20% of patients with persistent, troublesome cough. Drs Lata Javaram and Parameswaran Nair have applied these techniques to the management of asthma in routine clinical practice, and to identify patients with severe asthma and persisting airway eosinophilia, in whom new treatments directed against airway eosinophilia show promise (14). In addition, the development of the first Canadian evidence-based clinical guidelines for asthma management in 1989 owed much to the initiative of Drs Hargreave, Dolovich and Newhouse (15). More recently, Drs Gerard Cox and John Miller have led a trial of bronchial thermoplasty for difficult-to-control asthma, which has shown significant benefit (16).

Distribution of inhaled particles

Inhaled radiolabelled aerosols were shown by Dr Newhouse, working initially with Myrna Dolovich, Dr Joachim Sanchis and Carol Rossman, to be unevenly distributed in the lungs of smokers and patients with COPD (17). Much of the inhaled load did not reach below the oropharynx, the distribution being, in part, dependent on the method of aerosol administration. With Denis Corr, they found that lung deposition was improved with the use of a chamber between the aerosol generator and the mouth (18); an ideal chamber volume was found, and the device became known as the 'AeroChamber' (Trudell Medical International, Canada), now in use worldwide, in both its original form and adapted for special applications such as in infants. This group, which included Dr Richard Ruffin and Dr Fritz Oldenburg Jr, were the first to radiolabel therapeutic aerosols to quantify aerosol deposition in the respiratory tract and the pharmacological effects of peripheral versus central deposition (19,20). Studies that followed demonstrated the location of cholinergic receptors in proximal airways, contrasting with the more widespread distribution of adrenergic receptors throughout the respiratory tree. Particle clearance was studied by Carol Rossman in what came to be known as 'ciliary dyskinesia syndrome', after her observation that movement of cilia in what had been termed 'immotile cilia syndrome' was present but uncoordinated (21). Dr Joachim Sanchis showed that impaired ciliary function played an important role in cystic fibrosis (22).

Dyspnea

Dr Campbell's interests in the ability to detect imposed resistive and elastic loads to breathing began in the 1960s and led to the concept of 'length-tension inappropriateness' as a major factor in the sense of dyspnea. Kieran Killian followed these early studies of load detection by quantifying the sense of effort using psychophysical estimates. The sense of effort in breathing was related to power functions of the imposed loads and could be expressed numerically using the psychophysical scale described by Gunnar Borg. Quantitatively, dyspnea represented the imbalance between the demand for breathing and the ability to achieve the demand in the face of the respiratory system's impedances, resistive and elastic. The Borg scale has been especially useful in assessing dyspnea in exercise. Drs Killian and Clive Kearon showed in normal subjects, during endurance as well as progressive incremental exercise, that dyspnea increased as a power function of both duration and intensity to reach the maximum effort that could be tolerated (23). In a series of studies involving normal subjects with

Figure 3) Identity plots of the percentages of eosinophils in sputum for two plugs of the same specimen (left panel) for specimens collected on two consecutive days (right panel). Reproduced with permission from reference 11

loaded breathing at rest and during exercise, Graham Jones, Mark Inman, Pierre Leblanc and Ali El-Manshawly showed that dyspnea increased in relation to reductions in respiratory muscle strength – whether static or dynamic – when weakened by a shortened length (ie, at high lung volume) or by increases in contraction velocity (shortened time for inspiration at high breathing frequencies). The quantitative interaction between these factors was demonstrated by Drs Pierre Leblanc and Denis Bowie in patients with a variety of cardiorespiratory disorders (24).

Exercise capacity

Initial objectives were to establish a progressive incremental exercise test to maximum capacity with measures of metabolism and the associated respiratory and cardiac responses ('stage 1'), suitable for the clinical evaluation of patients with exercise-related symptoms. A noninvasive measurement of cardiac output and respiratory gas exchange allowed more complex assessment of these factors (stages 2, 3 and 4) (25). The key measurement was a rebreathing estimate of mixed venous PCO_2 ; algorithms were developed and validated that have become incorporated into metabolic carts worldwide. The 6 min walk test was developed and validated by Guyatt et al (26). The importance of muscle strength in determining exercise capacity was recognized early on, and led to the inclusion of strength measurements in clinical testing. Killian's work with the Borg scale led to its routine inclusion during stage 1 tests; it may appear obvious that voluntary exercise is limited by the intensity of dyspnea and skeletal muscle effort; however, this was the first time that symptom assessment was shown to be valuable in exercise testing (Figure 4). A study by Lydia Makrides clarified the effects of sex, age and stature on exercise capacity, and identified the important role of skeletal muscle strength (27). Studies of resistance (muscle strengthening) training improved exercise capacity in older subjects (28) and patients with COPD (29).

The application of computer storage of test results, early on by Monte Smith and later by George Obminski, resulted in huge amounts of data (now from over 40,000 tests) being available for analysis of limiting factors in many conditions. Exercise capacity is not a linear additive function of such factors as age and stature but is better expressed in terms of interactive power functions (30).

Metabolism and acid-base control in exercise

In 1969, Robert Taylor, an MSc student, wanted to understand why high-intensity exercise appeared to be less fatiguing following sodium bicarbonate administration. His study showed that endurance was doubled following bicarbonate (alkalosis), and halved following ammonium chloride (acidosis) administration; also, alkalosis was accompanied by higher blood lactate concentrations than either acidosis or control conditions (31) (Figure 5). The discrepancy between performance and changes in plasma lactate concentration brought into question the established dogma of increases in lactate,

Figure 4 Intensity of leg effort and dyspnea during progressive exercise (as a percentage of predicted maximal power), in patients with varying severity of chronic obstructive pulmonary disease. Intensity of dyspnea is matched by increased leg muscle effort. CAL Chronic airflow limitation; PR Predicted

indicating a deficit in oxygen delivery, and led to studies to clarify the mechanisms of lactate production and the interplay between acid-base control and skeletal muscle metabolism. These studies had, as an initial objective, the investigation of factors influencing CO_2 production and clearance, and are reviewed elsewhere (32). Briefly, they followed the precepts of Peter Stewart in a quantitative physicochemical approach to acid-base physiology, and of Eric Newsholme in metabolic regulation through the activity of rate-limiting enzymes. Dr Jones was joined by Dr George Heigenhauser, Dr Neil Toews and Dr John Sutton working with a succession of graduate students: Rolf Ehram, Melanie Hollidge-Horvat, John Kowalchuk, Larry Lands, Paul Leblanc, Michael Lindinger, Neil McCartney, Robert McKelvie, Michael McKenna, Michelle Parolin, Sandra Peters, Ted Putnam, Lawrence Spriet and Graham Ward. The group was the first in North America to apply needle muscle biopsy and microbiological techniques under the tutelage of Dr Eric Hultman of the Karolinska Institute (Solna, Sweden). Control of muscle lactate production, and the factors influencing choice between fat and carbohydrate sources of fuel, depends on a complex interaction between rate-limiting muscle enzymes, hormones and intramuscular pH to account for differences in the responses to high exercise intensity (33), hypoxia (34), diet (35) and training (36). Removal of CO_2 , and movements of strong ions and water between the working muscle and plasma, across the red blood cell membrane, and into less active muscle are all important in the maintenance of function.

Figure 5 Effect of alkalosis (top curve) and acidosis (lowest curve) compared with control in healthy subjects at three levels of exercise (30%, 60% and 95% of maximum), showing higher plasma lactate concentration and longer endurance at 95% in alkalosis. Reproduced with permission from reference 38

High-altitude medicine

John Sutton joined the group in 1973, intending to stay for a year, but remained for 17. During this time, he was an influential figure in high-altitude research on Mount Logan (Yukon) with the High Altitude Physiology Group of the Arctic Institute, headed by Dr Charles Houston. These studies were performed in mid-summer for several years, becoming notorious for the disappearance of a large amount of equipment and staff for four to six weeks. With their colleagues from other institutions, Drs Sutton and Powles established the role of sleep hypoxemia in acute mountain sickness and its reversal by acetazolamide (37). The incidence of retinal hemorrhages was studied using fluorescein retinal angiography. They and others participated in Operation Everest II in the hypobaric facility at the United States Army Research Institute for Environmental Medicine, an ambitious study that, over a six-week period, simulated an Everest expedition to establish all of the physiological changes that occur (38) (Figure 6).

Epidemiology

David Pengelly recognized that Hamilton was an ideal city to study the effects of air quality on lung function and development. The concentration of heavy industry in the east end of the city caused a large variation in pollutant concentrations. Three thousand children residing in areas with widely differing air quality were evaluated yearly for several years and, finally, at 30 years after enrollment. Children's lung development was adversely affected by pollution and maternal smoking, with additional effects of low income and crowded housing (39). However, long-term follow-up indicated that exposure to pollution did not predict adult respiratory symptoms or impairment. Other studies investigating the effects of air pollution included those of David Levy, performed while an undergraduate student, on the link between indexes of pollution on hospital admissions for asthma and COPD, and of Dr Ron Wolff on the effects on exercise of limit values of sulphur and nitrogen oxides and particulates.

Dr Malcolm Sears and Neil Johnston examined the epidemiology of childhood asthma and identified the 'return to school' epidemic of severe asthma exacerbations, which was a consistent occurrence seven to 10 days after children return to school in September, after summer vacation. This finding has been replicated in many other countries and their work identified that this epidemic is caused by the sharing of upper respiratory tract infections, mainly caused by rhinoviruses (40). Dr Sears also leads the Canadian Healthy Infant Longitudinal Development (CHILD) study, which has enrolled

Figure 6 Maximal exercise oxygen consumption as a function of partial pressure of inspired oxygen (P_{iO_2}) in Operation Everest II. $\dot{V}O_{2\max}$ Maximal oxygen uptake. Reproduced with permission from reference 28

>3500 newborn infants and their families across Canada, together with collaborators in Toronto, Winnipeg (Manitoba), Edmonton (Alberta) and Vancouver (British Columbia). This study will examine the genetic and environmental underpinning of asthma and allergic diseases.

Dr David Muir and his group investigated the effects of silica exposure in hard-rock miners (41), and mortality among various occupations in the nickel industry (42).

Interstitial pulmonary fibrosis

This research program is based on two decades of basic science that was initially performed at MUMC, led by Dr Jack Gaudie and Dr Manel Jordana, and later also in the laboratories of Dr Martin Kolb at St Joseph's Healthcare. The published work has helped to identify novel mechanisms of interstitial pulmonary fibrosis (IPF) and

promising treatment targets, several of them now in clinical development. The IPF activities at FIRH include translational research on biomarkers and also a large clinical trial program coordinated by Drs Cox and Kolb with novel compounds.

SUMMARY

The Respiriology Division has grown from two physicians in 1969 to more than 50 physicians and PhD scientists currently. FIRH is now the busiest outpatient clinic in Hamilton, with >50,000 visits per year. The Division has a very successful fellowship training program and its research output has changed the understanding of many aspects of respiratory medicine, including exercise physiology and metabolism, acid-base balance, dyspnea, asthma diagnosis and treatment, particle deposition in the lungs, and IPF. Numerous graduate students, fellows and visiting faculty from other institutions have made significant contributions and are now in faculty positions throughout Canada and elsewhere.

DEDICATION: The authors dedicate this article to the memory of many colleagues who contributed to the Respiratory Programme at McMaster, but who, sadly, are no longer with us: John Alpers, Les Berman, Moran Campbell, Bob Cornett, Jerry Dolovich, Freddy Hargreave, Joe Jacobs, Leo Kahana, Al McLennan, David Pengelly, David Stubbing, John Sutton and Neil Toews. They also acknowledge their debt to Dr Moran Campbell, an inspiring leader as first Chair of Medicine at McMaster. No one who met him could fail to be overawed by his intellect and humour, and the way he developed and guided the department. As he described in his memoir *Not Always on the Level*, his mood swings became a trial to himself and his colleagues, eventually limiting his influence outside McMaster, but never diminishing his reputation as one of the giants of respiratory physiology and clinical science.

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REFERENCES

- Dickinson CJ. A Computer Model of Human Respiration. Lancaster: Medical and Technical Publishing, 1977.
- Cockcroft DW, Killian DN, Mellon JJ, Hargreave FE. Bronchial reactivity to inhaled histamine: A method and clinical survey. *Clin Allergy* 1977;7:235-43.
- Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen-induced increase in non-allergic bronchial reactivity. *Clin Allergy* 1977;7:503-13.
- Kirby JG, Robertson DG, Hargreave FE, Dolovich J. Asthmatic responses to inhalation of anti-human IgE. *Clin Allergy* 1986;16:191-94.
- Gauvreau GM, Watson RM, O'Byrne PM. Kinetics of allergen-induced airway eosinophilic cytokine production and airway inflammation. *Am J Respir Crit Care Med* 1999;160:640-7.
- Adelroth E, Morris MM, Hargreave FE, O'Byrne PM. Airway responsiveness to leukotrienes C4 and D4 and to methacholine in patients with asthma and normal controls. *N Engl J Med* 1986;315:480-4.
- Manning PJ, Watson RM, Margolskee DJ, Williams VC, Schwartz JI, O'Byrne PM. Inhibition of exercise-induced bronchoconstriction by MK-571, a potent leukotriene D4-receptor antagonist. *N Engl J Med* 1990;323:1736-39.
- Kirby JG, Hargreave FE, Gleich GJ, O'Byrne PM. Bronchoalveolar cell profiles of asthmatic and nonasthmatic subjects. *Am Rev Respir Dis* 1987;136:379-83.
- Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990;142:832-36.
- Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
- Gibson PG, Girgis-Gabardo A, Morris MM, et al. Cellular characteristics of sputum from patients with asthma and chronic bronchitis. *Thorax* 1989;44:693-9.
- Pizzichini MM, Popov TA, Efthimiadis A, et al. Spontaneous and induced sputum to measure indices of airway inflammation in asthma. *Am J Respir Crit Care Med* 1996;154:866-9.
- Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough: Eosinophilic bronchitis without asthma. *Lancet* 1989;1:1346-8.
- Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.
- Hargreave FE, Dolovich J, Newhouse MT. The assessment and treatment of asthma: A conference report. *J Allergy Clin Immunol* 1990;85:1098-111.
- Cox G, Thomson NC, Rubin AS, et al. Asthma control during the year after bronchial thermoplasty. *N Engl J Med* 2007;356:1327-37.
- Sanchis J, Dolovich M, Rossman C, Newhouse M. Lung clearance in patients with airways obstruction. *Bull Physio-Path Respir* 1973;9:325-35.
- Dolovich M, Ruffin R, Corr D, Newhouse M. Clinical evaluation of the Aerochamber: A simple demand inhalation MDI aerosol delivery device. *Chest* 1983;84:36-41.
- Dolovich M, Sanchis J, Rossman C, Newhouse M. Aerosol penetrance: A sensitive index of peripheral airways obstruction. *J Appl Physiol* 1976;40:468-71.
- Newhouse MT, Ruffin RE. Deposition and fate of aerosolized drugs. *Chest* 1978;73:936-43.
- Rossman CM, Lee RM, Forrest JB, Newhouse MT. Nasal ciliary ultrastructure and function in patients with primary ciliary dyskinesia compared with that in normal subjects and in subjects with various respiratory diseases. *Am Rev Respir Dis* 1984;129:161-7.

22. Sanchis J, Dolovich M, Rossman C, Wilson W, Newhouse M. Pulmonary mucociliary clearance in cystic fibrosis. *N Engl J Med* 1973;288:651-4.
23. Kearon MC, Summers E, Jones NL, Campbell EJ, Killian KJ. Effort and dyspnoea during work of varying intensity and duration. *Eur Respir J* 1991;4:917-25.
24. Leblanc P, Bowie DM, Summers E, Jones NL, Killian KJ. Breathlessness and exercise in patients with cardiorespiratory disease. *Am Rev Respir Dis* 1986;133:21-5.
25. Jones NL. *Clinical Exercise Testing*. Philadelphia: WB Sanders Co, 1997.
26. Guyatt GH, Thompson PJ, Berman LB, et al. How should we measure function in patients with chronic heart and lung disease? *J Chronic Dis* 1985;38:517-24.
27. Makrides L, Heigenhauser GJ, McCartney N, Jones NL. Maximal short-term exercise capacity in healthy subjects aged 15-70 years. *Clin Sci* 1985; 69:197-205.
28. Makrides L, Heigenhauser GJ, Jones NL. High-intensity endurance training in 20- to 30- and 60- to 70-yr-old healthy men. *J Appl Physiol* (1985) 1990;69:1792-8.
29. Simpson K, Killian K, McCartney N, Stubbing DG, Jones NL. Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. *Thorax* 1992;47:70-5.
30. Jones NL, Summers E, Killian KJ. Influence of age and stature on exercise capacity during incremental cycle ergometry in men and women. *Am Rev Respir Dis* 1989;140:1373-80.
31. Jones NL, Sutton JR, Taylor R, Toews CJ. Effect of pH on cardiorespiratory and metabolic responses to exercise. *J Appl Physiol Respir Environ Exerc Physiol* 1977;43:959-64.
32. Jones NL. Research in exercise physiology and dyspnea at McMaster University. *Can Resp J* 2007;14:399-406.
33. Jones NL, Heigenhauser GJ, Kuksis A, Matsos CG, Sutton JR, Toews CJ. Fat metabolism in heavy exercise. *Clin Sci (Lond)* 1980;59:469-78.
34. Parolin ML, Spriet LL, Hultman E, Hollidge-Horvat MG, Jones NL, Heigenhauser GJ. Regulation of glycogen phosphorylase and PDH during exercise in human skeletal muscle during hypoxia. *Am J Physiol Endocrinol Metab* 2000;278:E522-E534.
35. Putman CT, Spriet LL, Hultman E, et al. Pyruvate dehydrogenase activity and acetyl group accumulation during exercise after different diets. *Am J Physiol* 1993;265:E752-E760.
36. Putman CT, Spriet LL, Hultman E, Dyck DJ, Heigenhauser GJ. Skeletal muscle pyruvate dehydrogenase activity during acetate infusion in humans. *Am J Physiol* 1995;268:E1007-E1017.
37. Sutton JR, Houston CS, Mansell AL, et al. Effect of acetazolamide on hypoxemia during sleep at high altitude. *N Engl J Med* 1979;301:1329-31.
38. Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol* (1985) 1988;64:1309-21.
39. Poulou T, Kanaroglou PS, Elliott SJ, Pengelly LD. Assessing the health impacts of air pollution: A re-analysis of the Hamilton children's cohort data using a spatial analytic approach. *Int J Environ Health Res* 2008;18:17-35.
40. Johnston NW, Johnston SL, Norman GR, Dai J, Sears MR. The September epidemic of asthma hospitalization: School children as disease vectors. *J Allergy Clin Immunol* 2006;117:557-62.
41. Muir DC, Julian JA, Shannon HS, Verma DK, Sebestyen A, Bernholz CD. Silica exposure and silicosis among Ontario hardrock miners: III. Analysis and risk estimates. *Am J Ind Med* 1989;16:29-43.
42. Roberts RS, Julian JA, Muir DC, Shannon HS. A study of mortality in workers engaged in the mining, smelting, and refining of nickel. II: Mortality from cancer of the respiratory tract and kidney. *Toxicol Ind Health* 1989;5:975-93.