

Respiratory medicine and research at McGill University: A historical perspective

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In 1801, an act of Quebec's Parliament established the Royal Institution for the Advancement of Learning in the province. The current downtown campus and an endowment of £10,000 were bequeathed by James McGill to the university that now bears his name. In 1821, a charter provided McGill College university powers. In 1819, the Montreal General Hospital was established and, in 1823, four of its physicians established a medical school entitled the "Montreal Medical Institution", which 10 years later was incorporated into McGill College as the first faculty of medicine in Canada. The Faculty grew in the 1800s and acquired a new medical building, the Royal Victoria Hospital in 1894 (reviewed by Dr RL Cruess at www.mcgill.ca/medicine/about/glance/history). The Royal Edward Institute, predecessor of today's Montreal Chest Institute, was established in 1909 as a tuberculosis dispensary. In the present article, we review the growth of respiratory medicine at these institutions and their affiliated research facilities, focusing on key individuals and their trainees.

THE BEGINNINGS OF ACADEMIC RESPIRATORY MEDICINE AT MCGILL

In the late 1800s, medicine in North America lagged behind the relatively advanced state of medicine in Europe, particularly in Germany where the scientific basis for medicine was already under intensive investigation. Medical education was purchased in private 'for-profit' schools in which entry criteria were less than stringent and exposure to patients was minimal. A scathing report on medical education in the United States (US) was prepared by Abraham Flexner for the Carnegie Foundation in 1910 (1) and, as a result, many schools in the US closed. Other schools associated with currently prestigious universities were strongly criticized. McGill and other Canadian medical schools were spared this criticism and none were recommended for closure. The University of Toronto (Toronto, Ontario) and McGill were singled out for particular praise. Flexner based his ideal on Johns Hopkins Medical School (Baltimore, Maryland, USA), an institution to which Sir William Osler – one of McGill's outstanding figures – contributed substantially.

Osler, a graduate of McGill, was appointed professor at McGill in 1874. He was recruited away to Philadelphia (Pennsylvania) in 1884 and subsequently to Johns Hopkins Hospital. He advised the appointment of a full-time chairman of the department of medicine at McGill. Sir Arthur Currie, McGill's Principal from 1920 to 1933, then raised funds to establish the University Clinic for Research in Internal Medicine at the Royal Victoria Hospital.

As a result, Dr Jonathan Meakins was recruited from Edinburgh (Scotland) to become the Physician-in-Chief at the Royal Victoria Hospital and the first full-time clinical professor at McGill (Figure 1). Dr Meakins was born in Ontario in 1882 and graduated in medicine from McGill in 1904. He studied at Johns Hopkins and the Presbyterian Hospital in New York (New York, USA), both notable institutions that were leading the charge in the development of medical science in North America. He was recruited to Edinburgh in 1919 but was recruited back



Figure 1) Dr Jonathan Meakins

to the Royal Victoria in 1924. It is likely that he was greatly influenced by the spirit of academic medicine created and fostered by William Welch at Johns Hopkins. His appointment was a signal event for respiratory medicine because Meakins was devoted to this domain and published many articles alone and with one of his most important recruits, Dr Ronald Christie. His interest in respiratory medicine led to the publication of his first book, *Respiratory Function in Disease* in 1925. Meakins removed clinical laboratories from the Department of Pathology and placed them within the hospital. As such, he was responsible for the development of hospital-based research, a tradition that persisted for several generations of clinician researchers (2).

THE EMERGENCE OF RESPIRATORY MEDICINE AND THORACIC SURGERY

Despite active research in respiratory physiology and pathophysiology, the specialty of respiratory medicine is relatively new in its current form. At the beginning of the past century, respiratory physicians occupied themselves with the treatment of tuberculosis, a specialty known as phthisiology. Tuberculosis was treated at the Royal Edward Institute, which opened on October 21, 1909, on the present-day site of Central Station in Montreal. It was established "For the study, prevention and cure of Tuberculosis" and was opened remotely by telegraphic signal from England by King Edward VII. In the 1920s and 1930s, increasing emphasis on resting the lung using collapse therapies led to the use of induced pneumothorax, the placement of foreign material in the pleural space, phrenic nerve crush and the deforming surgery, thoracoplasty. The latter treatment was introduced to North America by Dr E Archibald of McGill. The Royal Edward Institute

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moved to its current location on St Urbain in 1933 and, in 1941, all McGill tuberculosis-related thoracic surgery moved to the Royal Edward. In 1942, the Royal Edward Institute and Laurentian Sanatorium Association were merged to form the Royal Edward Laurentian Hospital.

One of the most notable surgeons practicing at the Royal Victoria Hospital and the Royal Edward Laurentian Hospital was Darrell ('Dag') Munro. In 1952, he joined the surgical staff of these hospitals and he acquired a vast experience of surgery for tuberculosis and, subsequently, for lung cancer. Dr Munro succeeded his mentor, Dr CA ('Sandy') MacIntosh, as Surgeon-in-Chief of the Montreal Chest Institute from 1964 to 1984. Dr Munro also introduced the first flexible fiberoptic bronchoscopy unit in Canada. In 1965, he led a team of surgeons at the Royal Victoria Hospital to perform Canada's first human lung transplantation, and the fifth in the world.

Meakins and Christie were forerunners of modern respiratory medicine as they performed important experiments in their exploration of respiratory physiology and the pathophysiology of common respiratory diseases such as emphysema (3,8). Dr Ronald Christie was recruited as a postdoctoral fellow by Jonathan Meakins in the early 1930s. Following a period of seven years at the Royal Victoria Hospital, he returned to St Bartholomew's Hospital in London (England), where he rose to the rank of full professor. He was enticed back as Chair of the Department of Medicine in 1955 and occupied the post for 10 years. He published extensively on the mechanical properties of the lung in common diseases, such as emphysema and heart failure, publishing many of his articles in the *Journal of Clinical Investigation*. His legacy was nothing short of extraordinary.

Dr David Bates was among Dr Christie's notable recruits; in turn, Bates recruited Drs Maurice McGregor, Margaret Becklake, William ('Whitey') Thurlbeck, Joseph Milic-Emili, Nicholas Anthonisen, Charles Bryan and Peter Macklem. Dr Bates published extensively in the area of respiratory physiology and he coauthored the book *Respiratory Function in Disease*, which integrated physiology into the analysis of disease. Dr Bates also occupied the position of Chair of the Department of Physiology at McGill. He later moved to the University of British Columbia and, in the latter days of his career, he focused his attention on the consequences of the environment for respiratory health. Dr Macklem has reviewed some of the contributions of McGill scientists to respiratory physiology and pathophysiology (7).

THE MID-TWENTIETH CENTURY

Dr JA Peter Paré joined the attending staff of the Royal Victoria Hospital and the Royal Edward Laurentian Hospital in 1949. A consummate clinician, he worked closely with Dr Robert Fraser, the chair and chief of radiology to write the reference text for respiratory disease, *Diagnosis of Diseases of the Chest*. This was a seminal contribution in its focus on radiographic findings as the basis for a systematic approach to diagnosis, and the correlation of these findings with pathological and clinical observations. He served as McGill Respiratory Division director from 1975 to 1983. With his colleague Dr B Rose, he was among the first in the world to use corticosteroids in the treatment of asthma (4). He and his colleagues were the first to describe pulmonary and retinal talcosis secondary to the intravenous injection of talc-containing drugs (9); they also provided the first comprehensive description of hereditary hypertrophic cardiomyopathy (10), and facilitated the discovery of a causative gene through the recruitment of an affected French-Canadian kindred (6). In addition, Dr Paré was a renowned teacher and role model for generations of clinicians across Canada, the US and beyond – so much so that the weekly case conferences are still known as 'Paré rounds', and the annual teaching award as the Paré award.

More generally, the synergy between clinical medicine, radiology, physiology and pathology ushered in a particularly productive era of investigation and teaching beginning in the early 1960s, which lasted >30 years. At the same time, the advent of antituberculous antibiotics in the 1940s, and their widespread use in the 1950s, led to a shift in

focus in clinical respiratory medicine – away from tuberculosis, and toward lung diseases of growing importance, notably asthma and chronic obstructive pulmonary disease (COPD). By 1960, the mandate of the Royal Edward had substantially broadened, such that it became and remains (as the Montreal Chest Institute) a centre of expertise in a variety of lung diseases. Tightly linked to this are the associated laboratory, clinical and epidemiology research programs, and also relevant technological innovations.

Dr Margaret Becklake immigrated to Montreal in 1957. Her impact was profound and, with other members of the McGill faculty, she worked on occupational lung disease, an interest she stimulated by her early medical career in South Africa. She established the now well-known respiratory epidemiology unit at McGill, which has graduated so many current Canadian leaders in respiratory medicine, including her former graduate students Drs Pierre Ernst, Dick Menzies and Jean Bourbeau. Dr Becklake is renowned for her insistence on the importance of a clearly stated, relevant research question and, more generally, for her clarity and insight. The unit she founded continues to emphasize respiratory research of direct relevance to patients and communities. Her husband, Dr Maurice McGregor, a cardiologist, was intimately acquainted with the lungs and the pulmonary circulation, and a key person in the 'cardiorespiratory service' of the time.

Another of David Bates' recruits was Dr William ('Whitey') Thurlbeck, born in Johannesburg, South Africa, and a graduate of the University of Cape Town in medicine. He immigrated to Boston (Massachusetts, USA) in 1955 to pursue his residency in pathology at the Massachusetts General Hospital. Subsequently, he spent a year of fellowship at the Brompton Hospital in London but returned to Boston as a research fellow to Harvard University from 1960 to 1961. David Bates arranged for his appointment as an assistant professor in the McGill Pathology Department in 1961. Thurlbeck had developed an interest in emphysema and chronic bronchitis and applied a structure-function approach in collaboration with Peter Macklem and other respirologists. As chief of the Royal Victoria Hospital autopsy service, he used pathological specimens to develop a semiquantitative grading system of gross emphysema severity based on thick (Gough) lung slices. He promoted the use of morphometry to quantify structural abnormalities (12). He also collaborated with Robert Fraser in radiologic-pathologic studies of pulmonary disease. Thurlbeck was instrumental in recruiting James Hogg to the pulmonary research laboratory in the Pathology Department, where they studied the contribution of small airways to lung resistance (5). Thurlbeck left McGill and the Royal Victoria Hospital in 1973 for Winnipeg (Manitoba) and subsequently moved to Vancouver, British Columbia.

Other pathologists who contributed to the respiratory field were Drs John Richardson, who performed important pharmacological experiments with airway smooth muscle (11), and Nai-San Wang who was a talented electron microscopist. The former trained Dr Meinhard Kneussl, professor of medicine in Vienna (Austria) and the latter trained Dr Dean Schraufnagel, later President of the American Thoracic Society.

Another signal event in the evolution of respiratory research at McGill was the construction of the Meakins-Christie Laboratories in 1972. This development was due largely to Paul Paré, the brother of Dr JA Peter Paré, who arranged financing for the project. Dr Peter Macklem, a trainee of Dr Becklake's, was the inaugural director of the laboratories and the initial focus was on respiratory mechanics, gas distribution within the lung and the contribution of airways of different sizes to overall mechanical behaviour of the lungs. The effects of cigarette smoking on lung dysfunction, mechanisms of loss of lung elastic recoil in asthma and control of bronchomotor tone were all additional areas of active investigation. Dr Macklem pioneered the study of the physiological consequences of small airway pathology, including an extensive exploration of tests of small airway function. Malcolm King was a PhD graduate in polymer chemistry at McGill and studied mucus rheology. Dr Richard Martin studied airway responsiveness and ventilation distribution and welcomed most

of the French-speaking fellows in respiratory disease to his laboratory, including prominent Quebec respiratory physicians such as Drs Robert Boileau and Robert Amyot.

An area that captured many investigators' attention in the 1980s was the notion of respiratory failure being a consequence of respiratory muscle fatigue. Drs Macklem and Charalambos ('Charis') Roussos made seminal contributions in this domain and, with Dr Michel Aubier, demonstrated the effects of theophylline on respiratory skeletal muscle (13). The concept of inspiratory muscle training was developed and demonstrated to be feasible. Although failure of the respiratory pump caused by skeletal muscle fatigue was difficult to demonstrate in chronic respiratory failure, these studies nonetheless triggered a long-lasting interest in rehabilitation and in noninvasive mechanical ventilation for acute and chronic respiratory failure. This fostered a more holistic approach to enhancing physical capacity in patients with respiratory disease.

Dr Milic-Emili, then chair of the Department of Physiology, succeeded Dr Macklem as director of the Meakins-Christie Laboratories in 1979. J Milic-Emili was already renowned for his work on ventilation distribution and the assessment of pleural pressure. With colleagues such as Drs David Pengelly, William Whitelaw, Magdi Younes, Jean-Philippe Derennes and Michael Grunstein, he developed convenient tools for the assessment of respiratory drive. He clarified the basis for carbon dioxide retention in patients with COPD placed on high inspired oxygen concentrations. His work also drew attention to the risks of volutrauma in severe noncardiogenic pulmonary edema and to the presence of flow limitation during tidal breathing in patients with COPD. His trainees were also many, and had a major influence in respiratory science at home and abroad. Dr Walter Zin has studied respiratory mechanics in a variety of models of human pathologies in Rio de Janeiro, Brazil. Dr Nicholas Siafakas has established a productive research group in Heraklion, Crete.

Dr Jacopo Mortola was recruited to the Department of Physiology in the late 1970s. An expert in respiratory system mechanics and the control of breathing, he established a program addressing neonatal respiratory physiology. His contributions to comparative respiratory physiology were many and strikingly original. He, in turn, launched the careers of other investigators including John Fisher who continued his interests in the control of breathing and bronchomotor tone and with another McGill graduate Dr Steven Iscoe formed a strong respiratory group at Queen's University, in Kingston, Ontario.

Another recruit of Milic-Emili's in the 1980s was Dr Jason Bates, who introduced digital technology. He revolutionized data acquisition and analysis, banishing forever the art of counting squares on large pieces of heat-sensitive paper on which outputs from transducers were registered. Jason Bates, in turn, trained a large number of students and fellows, among them Dr Michiaki Mishima who became professor of respiratory medicine at Kyoto University (Japan), contributing novel methods of quantifying emphysema on computerized tomographic images. Another of his trainees, Dr Anne-Marie Lauzon joined the faculty at the Meakins-Christie, bringing expertise in biophysics and smooth muscle physiology.

Dr Milic-Emili invited Dr Alex Grassino to join the Meakins Christie labs and he, in turn, studied the actions of the respiratory muscles and many of his trainees continued productive research careers elsewhere in Canada (Drs Paul Easton and Jeremy Roads) and in Europe.

Dr James Hogg studied the functional consequences of pathological processes for lung function during his PhD studies under the joint supervision of Drs Macklem and Thurlbeck. His contributions to understanding the basis for COPD are numerous and reflect the transdisciplinary knowledge from respiratory pathology and physiology that he possesses. His insights into the structural basis for functional impairment in COPD have been particularly noteworthy and have continued with the application of technologies such as microcomputerized tomographic imaging, morphometry and molecular biology to demonstrate the remarkable finding of the disappearance of airways within the diseased lung. He trained other outstanding investigators such as Peter

Paré Jr, with whom he founded the Pulmonary Research Laboratory in St Paul's Hospital in Vancouver (British Columbia) in 1977. Peter Paré Jr continued to explore his interests in airway smooth muscle and airway hyper-responsiveness, subjects that he initially addressed while at McGill, and advanced our understanding of the biomechanics of airway narrowing in asthma. Other prominent trainees from Dr Hogg's laboratory were Drs Marie-Claire Michoud and Richard ('Rick') Boucher. The former contributed to the field of asthma whereas the latter has made major contributions to the field of cystic fibrosis.

Dr Manuel Cosio built on earlier work with Macklem and Hogg in his development of key structure-function studies of COPD. He was instrumental in recruiting another generation of young investigators that included Drs Basil Petrof and John Kimoff, bringing excellence in sleep-disordered breathing and neuromuscular disease to McGill. He also trained Dr Marina Saetta, who made major contributions to the characterization of the airway inflammatory process in COPD and established a productive research unit at the University of Padova (Italy).

Dr Nicholas Anthonisen came to McGill in the 1960s from Dartmouth University (New Hampshire, USA). He made seminal contributions to the understanding of airway closure and gas distribution within the lungs while at McGill, but his more striking discoveries were made while he was at the University of Manitoba (Winnipeg, Manitoba) where he became Dean of the Faculty of Medicine. He performed the landmark trials of nocturnal oxygen therapy (1), intermittent positive pressure breathing and antibiotic use in COPD exacerbations (2), as well as leading the Lung Health Study (3). Another of Dr Macklem's trainees in the 1970s, Dr James Dosman pursued a career in Saskatchewan where he has addressed issues of rural health. His studies have examined asthma, sleep-disordered breathing and the consequences of various exposures on respiratory health. Dr Mara Ludwig was recruited by Dr Macklem in 1984 following a postdoctoral fellowship in Boston and the Harvard School of Public Health and contributed to our understanding of peripheral airway responsiveness and the importance of matrix proteins. She supervised, in turn, the work of Dr Takahide Nagase, now professor of medicine at Tokyo University in Japan.

Many other notable investigators received their training at the Meakins Christie Laboratories and contributed importantly to respiratory physiology and pathophysiology. Dr Ludwig Engel obtained his PhD under Peter Macklem and established himself in the area of ventilation distribution in health and in bronchoconstriction and the mechanics of breathing in asthma. After 10 years at McGill, he returned to Australia, where he continued to be highly productive in his study of the control of upper airway calibre. Ludwig trained a number of investigators including one of the authors Jim Martin, who succeeded Joseph Milic-Emili as director of the Meakins Christie Laboratories from 1993 to 2008. In turn, Jim Martin supervised Dr Stephanie Shore, who pursued a successful research career in the Harvard School of Public Health, and Dr David Eidelman who following a productive research career became Chair of Medicine and is currently Dean of the McGill Faculty of Medicine. He pioneered the development of small animal models for the study of the late allergic response in allergic asthma and of airway remodelling, with many talented clinicians (Drs Eidelman, Sapienza, Olivenstein, Watanabe, Suzuki, Hojo, Tamaoko and others). He expanded the faculty of the Meakins Christie Laboratories and recruited investigators from different disciplines, a strategy that may have contributed to the enduring success of the Laboratories.

Another prominent Australian, Dr Ann Woolcock, worked with Peter Macklem to study the control of bronchomotor tone and subsequently devoted her career to the study of asthma with a major focus on the clinical significance of bronchial hyper-responsiveness. She became president of the Asian Pacific Society of Respiriology. Dr Yoshinosuke Fukuchi, another of Dr Macklem's trainees, also held the position of president of the Asian Pacific Society of Respiriology, and provided invaluable leadership for respiratory diseases in Japan. Dr

Marc Decramer, a trainee of Drs Macklem and Milic-Emili made major contributions to the areas of respiratory skeletal muscle function and rehabilitation, continuing the interest in these domains in Europe, where he became president of the European Respiratory Society. Dr Andre De Troyer, a contemporary of Dr Decramer's and a co-author of studies together at McGill, has continued to be one of the world's experts on respiratory muscle actions. Dr Charles Irvin, currently a leading respiratory researcher at the University of Vermont (Vermont, USA), identified nonadrenergic noncholinergic inhibitory airway innervation in the cat with Dr Macklem. Dr Peter Calverley has had a stellar career in the United Kingdom in the pursuit of clinical studies related to the therapy of COPD.

The 1970s and 1980s also saw the emergence of a topnotch respiratory division at the Montreal General Hospital – initially under Drs Donald MacIntosh and JA Peter Paré and, in large part, under the leadership of Dr Neil Colman, who was later a lead author of the revised Fraser and Paré textbook. At the Montreal General, areas of particular clinical strength and investigation included asthma, occupational and immunological lung diseases. At the Jewish General Hospital, Dr Harold Frank led the Division and was the consummate clinician and as served as an important role model for other faculty members at that site.

THE LATE TWENTIETH CENTURY AND BEYOND

In 1989, the Meakins Christie Labs relocated to its current site on Rue St Urbain, adjacent to the Montreal Chest Institute. The research group now included Dr William S Powell, a renowned eicosanoid biochemist. Shortly thereafter, Dr Qutayba Hamid, then based at the Brompton Hospital, joined the Meakins-Christie Laboratories in 1994. In addition to an outstanding career in the area of the immunopathology of human asthma, he broadened the array of techniques routinely applied at the labs and has ably led the Meakins-Christie

Labs from 2008 to the present. Other recruits to the new site were Drs Elizabeth Fixman, Bruce Mazer, Christina Haston, Simon Rousseau, Carolyn Baglolle and Christine McCusker, expanding the range of experimentation and scientific interest.

The late 1990s and the early 21st century also witnessed the flourishing of the Respiratory Epidemiology Unit, under the leadership of Drs Pierre Ernst, Dick Menzies and, most recently, Jean Bourbeau. It moved from McGill University to the Montreal Chest Institute in 2004. This paved the way for expanded clinical and translational research programs in COPD, tuberculosis, asthma, sleep disorders and other pulmonary diseases – often in collaboration with colleagues from the adjacent Meakins-Christie Laboratories. It now leads large scale, multicentre studies in COPD and tuberculosis, with trainees from around the world and faculty recruits in other areas (eg, sleep disorders, lung cancer, critical care). It houses PhD scientists with expertise in epidemiological methods and biostatistics, as well as respiratory clinician researchers.

CONCLUSION

Respiratory physiology and medicine at McGill benefitted from a strong start through the influence of Meakins and Christie. The subsequent recruitment of talented and creative faculty members with absolute dedication to academic medicine continued their legacy. In reviewing the evolution of the strength in respiratory medicine at McGill, it is clear that, no matter how significant the scientific contributions of the individuals themselves, their most important impact resulted from the training of a large cohort of other gifted physicians and scientists. The authors consider themselves incredibly fortunate to have benefited accordingly, and apologize that not all McGill respiratory researchers and trainees could be listed individually in the present review.

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