Chronic obstructive pulmonary disease

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Fifty years ago, chronic obstructive pulmonary disease (COPD) was the ideal disease for physiologically oriented clinicians to study, for a number of reasons. First, it was becoming recognized as a major health problem. Second, it could only be diagnosed reliably by physiological testing; x-rays did not work. Third, it was associated with a lot of interesting pathophysiology, including cor pulmonale, alterations in the control of ventilation, and perhaps most interesting of all, abnormalities that were primarily related to the distributions of ventilation and/or perfusion as opposed to global inadequacy of either of them.

Thus, the study of COPD was part and parcel of the work of pioneers in Canadian respiratory medicine as indicated by Peter Macklem in the initial chapter of the present issue (pages 383-392). The emphasis was largely on pathophysiology and lung function. Thus, Christie (1) described the mechanical properties of the lung – reduced recoil and increased resistance – in emphysema before coming to Canada, as did Cherniack (2) somewhat later. Bates (3) developed a method for measuring diffusing capacity and showed that it was frequently reduced in emphysema, and infrequently reduced in asthma, an observation that has stood the test of time (4). Bates was the key author of three editions of *Respiratory Function in Disease* (3,5,6), an enormously influential text that emphasized the physiological approach to lung disease that had been established in the study of COPD. Bates and Christie recruited William 'Whitey' Thurlbeck, an American-trained South African pathologist, to McGill, in Quebec, and Thurlbeck soon afterwards established himself as the world's leading expert on the pathology of COPD (7). Structure-function correlation was one of his strengths. In the early years, he had obtained lung function studies in virtually all patients who were scheduled to undergo surgery for coronary artery disease. These were largely older men with smoking histories who had a substantial perioperative mortality. When mortality occurred, Whitey studied their lungs and developed a unique case series.

Peter Macklem's early research involved forced expiration, noting that this was often accompanied by collapse (or compression) of major airways in normal subjects, but especially in subjects with diseased airways. This was achieved by a heroic procedure called a 'pressure bronchogram', with colleagues serving as subjects. He worked several years in Boston with Dr Jere Mead, developing the 'equal pressure point' theory of expiratory flow limitation, an extremely rewarding analytical technique that established the elastic recoil of the lung as an important determinant of maximum expiratory flow. Probably more importantly, he developed a method of measuring 'peripheral' (less than 2 mm diameter) airway resistance, then returned to Montreal, where he collaborated with Thurlbeck and a new trainee named Jim Hogg in studying peripheral airways in disease. They established that the major site of increased airway resistance in COPD was in the peripheral airways (8); it was later shown that peripheral airway lesions were characteristic of smokers. Thus, it was established that the airflow limitation characteristic of COPD was due to emphysema, or loss of lung recoil and/or peripheral airways disease. Because peripheral airways normally did not contribute greatly to the overall resistance, peripheral disease had to be substantial before overall flow limitation occurred, possibly making peripheral disease more difficult to detect with ordinary lung function tests (9). There then followed an intense exploration of a variety of new tests led by the Montreal group. These tests chiefly involved using gas distribution, such as closing volume, and tests measuring changes in maximum expiratory flow with changes in gas density, because airflow in major airways was turbulent and density-dependent, but this was not the case in the periphery. In fairness, this work contributed greatly to physiological knowledge, but less so to the clinical problem of COPD.

The progress cited above brings us to (approximately) 1980. The pathology and pathophysiology of COPD were well understood, although its pathogenesis was not; for example, why did some smokers get the disease while others did not? We will return to these questions later.

The next 20 years were notable for clinical trials in COPD, in which Canadian centres played a major role. The first of these was the Nocturnal Oxygen Therapy Trial, a multicentre effort sponsored by the National Institutes of Health (NIH) of the United States. Winnipeg, Manitoba, was one of six participating centres, eligible for obscure reasons having to do with the trial being funded as a contract. It compared a round-the-clock (continuous) oxygen therapy with nocturnal-only oxygen in hypoxemic COPD patients. To the surprise of all concerned, there was nearly a twofold mortality benefit favouring the continuous treatment (10). A British study (11) simultaneously compared 15 h of oxygen a day with none, which also showed a substantial survival benefit with oxygen. The case was made. It is worth noting that the two studies involved a total of approximately 300 patients (200 in North America and 100 in the United Kingdom) and that the data acquired in these small cohorts have guided oxygen therapy ever since, something that sometimes confounds third-party payers.

The NIH then sponsored a trial of intermittent positive pressure breathing (IPPB) as treatment in COPD, and Winnipeg was one of five participating centres. IPPB was controversial at

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the time, and Reuben Cherniack was one of the people who were instrumental in laying the groundwork for the trial. It studied approximately 1000 patients over three years, and showed that IPPB did not work; in fact, it had no effect whatsoever on any reasonable end point (12). However, a wealth of useful data was generated. Whitey Thurlbeck productively studied the lungs of patients that died, and the evidence accumulated found that the overall mortality in COPD had declined over the preceding 20 years (13), something that has been borne out by subsequent studies.

As noted above, Winnipeg had participated in the IPPB study and had accumulated a substantial group of well-studied cooperative COPD patients. We re-recruited them and others, and performed a placebo-controlled trial of antibiotic therapy in outpatient COPD exacerbations. We showed that antibiotics (amoxicillin, doxycycline and trimethoprim-sulfamethoxazole) reduced the length and severity of such exacerbations, and that the effect was most prominent in patients who complained of dyspnea and increased sputum volume and purulence (14). The study contributed greatly in defining COPD exacerbations ('the Winnipeg criteria'). It has not to my knowledge been repeated, and is very widely cited.

In the 1980s, Peter Macklem began to study the respiratory muscles, noting that they were the only vital organs not studied in detail at autopsy. Respiratory muscle fatigue, or failure to maintain a given task, was an obvious threat to the organism, and it was established that in COPD the inspiratory muscles were inefficient. If 'chronic fatigue' occurred in COPD, then inspiratory muscle rest may improve quality of life and other things such as blood gases. This was tested in a single-centre Montreal trial using nocturnal negative pressure ventilation. The results showed that it was an extremely difficult intervention to apply, and that when applied, it was of no discernable benefit (15), implying that chronic fatigue may not occur in COPD.

Respiratory rehabilitation results in improvements in exercise capacity and in quality of life that clearly outstrip the effects of medications such as bronchodilators. Furthermore, the effects of such programs have been shown to be durable, in that they are maintained after the program ends. Canadians, notably Roger Goldstein, have been pioneers in this field, having published the best clinical trials and established the therapeutic approach (16,17). Most large Canadian centres now have pulmonary rehabilitation programs, and a trial is under way to examine the effects of home rehabilitation. Bourbeau et al (18) recently showed that rehabilitation, combined with a self-management program and careful follow-up, can reduce hospitalization in COPD. Their approach is now considered the state of the art.

In the late 1980s, the NIH launched the Lung Health Study (LHS), an ambitious study of smokers with mild-moderate airways obstruction, ie, early COPD. The initial objective was to determine whether a randomized trial of a smoking cessation intervention and inhaled bronchodilator impacted the course of the disease, as measured in terms of the decline of forced expiratory volume in 1 s. A total of nearly 6000 otherwise healthy smokers were recruited, approximately one-tenth of them from Winnipeg. The smoking intervention worked, in that people who received it had reduced rates of decline, and this overall effect was due to a striking benefit in those who actually succeeded in stopping (19). Participants were followed for a total of 14 years, past the turn of the century, and the differences were found to be maintained between treatment groups, again due to people who actually stopped smoking. Very few of these individuals developed clinical COPD, whereas this occurred in approximately 40% of those who did not stop (20). Finally, after 14 years, mortality was lower in the recipients of the smoking intervention than in those who did not receive it (21); the intervention was highly cost-effective.

The LHS was, and is, a vast accumulation of carefully acquired data on the course of COPD, allowing for examinations of risk factors for the disease other than smoking. For example, methacholine reactivity was important, in that reactive smokers did less well than those with low levels of reactivity; this is congruent with the 'Dutch hypothesis' of the pathogenesis of COPD. Smokers who had repeated airway infections did less well than those who did not, congruent with the 'British hypothesis' of the pathogenesis of the disease. Both respiratory infections and methacholine reactivity had little effect on people who stopped smoking.

Meanwhile, advances in the basic science of COPD continued, particularly in Vancouver. Jim Hogg became a world leader in structure-function relationships in COPD, collaborating with major clinical groups largely in the United States. He developed a novel hypothesis of the genesis of COPD, ascribing it to latent adenoviral infection combined with smoking (22), and has supported his hypothesis with numerous clinical and experimental studies. Peter Paré, a colleague of Hogg, is a leading figure in the genetics of COPD, having extensively studied genetic material from the LHS (23).

I believe the above brief summary clearly indicates that Canadians have contributed greatly to our current knowledge of COPD. Furthermore, current Canadian expertise in COPD is broad and deep. The Hogg-Paré group continues to be intensely productive. The work of Bourbeau (18), cited above, has made the most cogent argument for COPD self-management. Don Sin, a clinical epidemiologist, has almost single handedly ignited the controversy regarding the role of inhaled steroids in COPD, and he is one of their most compelling advocates, using both database studies and trial data (24). François Maltais is an international figure in the study of skeletal muscle function in COPD (25), pointing out that the disease is not necessarily confined to the lungs. Denis O'Donnell is renowned as a student of dyspnea in COPD, having established that this key symptom is closely related to compromise of inspiratory muscle function imposed by increases in lung volume (26). We Candaians continue to supply a disproportionate share of important new knowledge regarding the fascinating problem of COPD.

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