Pulmonary Oxygen Toxicity: Investigation and Mentoring

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**Medical History**

**Pulmonary Oxygen Toxicity: Investigation and Mentoring**

John Hedley-Whyte

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**SUMMARY**

At sea level oxygen is toxic to man when breathed for more than twenty-four hours at a percentage greater than about forty percent. Pulmonary pathology is the first manifestation in subjects with previously normal lungs. In patients with pre-existing lung disease the results are often additive. There is, however, great variation in response from subject to subject and between patients. Queen’s Belfast and Harvard University Medical School have been the sites of seminal investigations. Mentoring at both universities is due to training at the University of Copenhagen.

**Key words:** Pulmonary Oxygen Toxicity

**INTRODUCTION**

Prescribing the correct dose of oxygen remains a serious concern with still unresolved quandaries in patient management. The descriptions and investigative work of James Lorrain Smith on oxygen toxicity, while at Queen’s College, Belfast at the turn of the nineteenth and twentieth centuries has stood the test of many further investigations1-4 (Fig. 1).

James Lorrain Smith was born in 1862 to a talented family where his father, Walter, was a Free Church of Scotland minister in Half Morton just north of Gretna Green1,5. An elder sister, Annie, became so distinguished that in 1888 she was employed, sub rosa, at the British Museum, paid from special funds5. James went to Edinburgh University graduating in medicine in 1889, and immediately went to work with Sir John Scott Burdon Sanderson’s Regius Professorial Unit at Oxford. There he joined John Scott Haldane who had graduated in medicine at Edinburgh University in 1884. Haldane was the Regius’s maternal nephew6.

Lorrain Smith became Walker Student in Pathology at Cambridge and later Demonstrator under Professor Charles Roy, who sent him to von Recklinghausen’s laboratory at Strasburg to study histology and to Christian Bohr’s laboratory at Copenhagen1. In 1892 and 1893 Lorrain Smith and Haldane carried out “some research in the laboratory under Bohr’s direction”. “Far more important was getting into personal touch with Bohr himself”, wrote Haldane subsequently7. In 1894 Lorrain Smith was appointed Lecturer in Pathology at Queen’s College, Belfast, where he remained until 1904; in 1901 he was promoted to Professor1. During this decade working in Belfast, Lorrain Smith and Haldane laid the foundations of the eminence of British respiratory physiology1,8-14.

Lorrain Smith was exactly correct in writing in 1897, “We may in the study of oxygen tension in various pathophysiological conditions not only find the explanation of various phenomena of respiratory disease but also obtain data for estimating the clinical significance of disturbance to the respiratory functions in these conditions10”. By 1899 Lorrain Smith had demonstrated that oxygen at up to 41 percent of an atmosphere is well tolerated. At seventy to eighty percent inspired oxygen, fifty percent of mice are dead at the end of the week12. “Mice have a remarkable power of recovering from the effects of high inspired oxygen. The same is probably true of man,” wrote Lorrain Smith.

**FALSE TRACK**

In their investigations of the transport of oxygen from the airways into blood, Bohr, Haldane and Lorrain Smith erroneously espoused active oxygen secretion into the blood.
generally finding arterial oxygen tension to be higher than alveolar. The causes were the lack of reliable methods of measuring oxygen tension in blood. Maybe the purity of the oxygen was a problem. Cylinders were supplied by the Scottish and Irish Oxygen Company. "The gas was manufactured by the peroxide of barium method and contained no impurity except nitrogen." Almost pure oxygen produced by rectification for welding was not available.

**THE KROGHS’ RESPONSE**

It was not until 1910 that Marie Krogh, the wife of Christian Bohr’s successor August Krogh, proved that oxygen diffuses across the alveolar capillary membrane. They wrote different dissertations in proving diffusion to be the only method of alveolar-capillary transit. In the last of the seven theses, August Krogh wrote “I shall be obliged in the following pages to combat the views of my teacher Professor Bohr...Real progress, made during the last twenty years in the knowledge of the processes in the lungs, is mainly due to his labours and to the refinement of methods which he has introduced.”

**HALDANE AND OXFORD**

Why did JS Haldane in his uncle’s department as Lecturer in Physiology, University of Oxford, Grocers’ Company Research Scholar, do his research work in Professor Edmund Albert Letts’ Chemical Laboratory of Queen’s College, Belfast? Were the facilities better in Belfast as in Copenhagen? Letts was Professor at Queen’s from 1879 to 1917. Probably it was at least in part due to Lorrain Smith’s return in 1894 to Belfast from Oxford and Cambridge and Continental Europe. But there is another possible cause, dissatisfaction with the Oxford scientific milieu.

In 1903 Haldane’s uncle’s intention to resign became known. Sanderson and his colleagues, chiefly Francis Gotch, Haldane and Arthur Thomson were desirous that one of their own group should continue Sanderson’s tradition. The London graduates expressed themselves in favour of a clinician, preferably an Oxonian: they met in London on January 5, 1904 and stated in *The Times*: “The Regius Professor of Medicine should be held by a physician who is representative of Medicine in its widest sense”—a statement inimical to the prospects of candidates: Reader, James Ritchie, a pathologist of Medicine in its widest sense—a statement inimical to the prospects of candidates: Reader, James Ritchie, a pathologist in Sanderson’s group or Haldane. Pamphleteering began, London versus Oxford.

**HARVARD**

At this time, Mr. Charles W Eliot, President of Harvard University, tried to get William Osler to come to Harvard. Osler gave the Ingersoll Lecture on Science and Mortality. Mr Eliot after the lecture “Expressed himself as greatly disappointed.” Osler’s wife and mother-in-law, a Bostonian, also were disapproving. “Willie should not rub the calf of his leg with his other foot to stir up ideas”; said his wife at Eliot’s informal reception after the lecture. The Osler’s future was settled by Arthur J Balfour who as Prime Minister nominated Osler to King Edward VII, as Regius Professor. Oxford, presumably with Osler’s connivance, made Haldane a Reader in 1907, a decade after his FRS. Haldane removed his research work to a structure in his North Oxford garden after Lorrain Smith left Belfast.

Osler in July 1906 visited Professor Lorrain Smith now translated to Victoria University, Manchester. Lorrain Smith had founded the ‘new’ Pathological Society of Great Britain and Ireland and was chief host at the Society’s inaugural meeting.

In 1913, Francis Gotch, having been made a Waynflete Professor of Physiology in 1905, died. Osler was the Chairman of the Board of Electors for the succession. They chose Charles S Sherrington. Haldane was most disappointed, but remained a Fellow of New College.

**PERSONAL INTERACTIONS WITH THE CONSEQUENCES OF THE WORK OF BOHR, HALDANE AND LORRAIN SMITH**

In 1931 as a senior Harvard Medical student, Henry K Beecher won the Warren Triennial Prize of the Massachusetts General Hospital for two papers on the effect of surgery on gas exchange in man. He subsequently received a Moseley Travelling Fellowship to work in the laboratory of Augustus Krogh who had won his Nobel Prize in 1920. After joining Beecher’s Anesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital in 1960, we continued work initiated a lifetime before by Lorrain Smith. Our values, validating the principles of Bohr are in more recent fabrication of polarographic oxygen and carbon dioxide electrodes employing semi-permeable membranes. Incidentally, US patent requests were denied to the developers because of prior use of the methodology by John R Pappenheimer, Higginson Professor of Physiology, Harvard University.

We investigated the effect of intrapulmonary shunting as described by Sackur in 1897 and Christian Bohr’s 1905 values for oxygen solubility in solutions: values which had been superseded. We found Bohr’s measurements and principles superior to those quoted in the Handbook of Chemistry and Physics. We used a Haldane apparatus, a successor technique to those Haldane and Lorrain Smith had developed in Belfast in 1895 and 1896. Our values, validating the principles of Bohr are in more recent handbooks. Aage Bohr wrote to us in 1964 to welcome validation of his grandfather’s work. In 1967 we were asked to review and update Lorrain Smith and Haldane’s work on the effects of oxygen.

Further work on the effects of inspired oxygen over 42 percent needs to be done on patients with very large right to left intrapulmonary shunts (fig. 2), on patients with altered cholesterol metabolism and in patients with intracranial pathology. The genetic basis of the variability of pulmonary pathologic response to oxygen needs to be explored.

**END OF AN ERA**

John S Haldane died in March 1936, a Companion of Honour, as was his sister Elizabeth. His brother Richard, twice Lord Chancellor, was a Viscount with an Order of Merit. JS Haldane wrote James Lorrain Smith’s 1931 obituary. James’s sister Annie was, in 1904, among the first women elected to
During respiratory failure in a patient with ARDS and pneumonia despite minute ventilation ($V_E$) of more than 20 liters per minute provided on the thirtieth hospital day by a constant volume ventilator, effective ventilation (alveolar ventilation $VA$) was only 2.5 liters per minute. Ineffective ventilation (dead space ventilation) is shown in blue. The ratio of dead space to tidal volume ($VD/VT$) is a measure of lung inefficiency (and consolidation in this patient). For two weeks this man had to be ventilated with 100 percent oxygen and mercury. The 60 percent intrapulmonary shunt, venous to arterial immediately diminished as the patient recovered. Six months later the patient was in excellent health with no exercise limitation (Reproduced by permission from the New England Journal of Medicine). Adapted from Hedley-Whyte J. Control of the uptake of oxygen. New Engl J Med 1968;279(21):1152-8.

**Figure 2.** Increase in ventilation and inspired oxygen tension requirements in respiratory failure due to pneumonia and ARDS.

Henry K Beecher subsequently recruited University of Copenhagen graduates Henrik H Bendixen (graduated 1951) and Henning Pontoppidan (graduated 1952), to the Harvard Anaesthesia Laboratories of the Massachusetts General Hospital. This Copenhagen-trained trio illuminated, in the laboratories and at parties, with wit and anecdote, stories of Lorrain Smith and JS Haldane, the Bohrs and the Kroghs.

We have twice previously reported Queen’s support of the endeavours of Harvard Medical School: first during World War II, secondly during the 1950’s and 60’s. In this third example, the influence was inherited from John S Haldane and James Lorrain Smith’s work at Queen’s Belfast between 1894 and 1904.

The author has no conflict of interest

**REFERENCES**


* My father told me that Lorrain Smith had been Musgrave Professor. The Musgrave Chair in Pathology at Queen’s College Belfast was founded by James Musgrave (1826-1904) a native of Lisburn, County Antrim who had established a firm of patent stove-makers and ironmongers in Belfast. In 1901 Lorrain Smith was appointed the first Musgrave Professor of Pathology.


