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<b>Citation</b>	Hedley-Whyte, John. 2008. Pulmonary Oxygen Toxicity: Investigation and Mentoring. The Ulster Medical Journal 77(1): 39-42.
<b>Published Version</b>	<a href="http://www.ums.ac.uk/umj077/077(1)039.pdf">www.ums.ac.uk/umj077/077(1)039.pdf</a>
<b>Accessed</b>	February 19, 2015 3:58:31 AM EST
<b>Citable Link</b>	<a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:4825927">http://nrs.harvard.edu/urn-3:HUL.InstRepos:4825927</a>
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## Pulmonary Oxygen Toxicity: Investigation and Mentoring

John Hedley-Whyte

Accepted 31 July 2007

### 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 investigations<sup>1-4</sup>(Fig. 1).

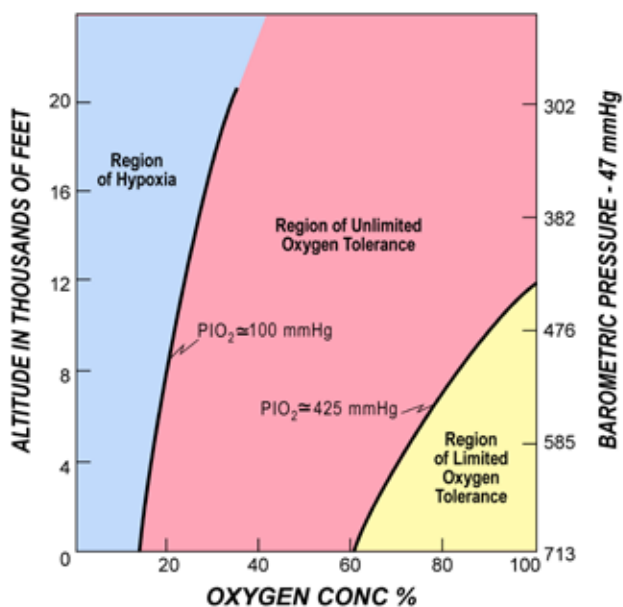


Figure 1. The inspired oxygen tension rather than the inspired oxygen concentration determines pulmonary oxygen toxicity (Modified from Becker-Freyseng H, Clamman HG. Zur Frage der Sauerstoffvergiftung. *Klin Wehnschr* 1939;**18**:1382-5<sup>42</sup> and Hedley-Whyte J, Winter PM. Oxygen therapy. *Clin Pharmacol Ther* 1967;**8**(5):696-737<sup>4</sup>).

### LORRAIN SMITH AND JS HALDANE

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 Green<sup>1,5</sup>. An elder sister, Annie, became so distinguished that in 1888 she was employed, sub rosa, at the British Museum, paid from special funds<sup>5</sup>. 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 nephew<sup>6</sup>.

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 Copenhagen<sup>1</sup>. 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 subsequently<sup>7</sup>. 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 Professor<sup>1</sup>. During this decade working in Belfast, Lorrain Smith and Haldane laid the foundations of the eminence of British respiratory physiology<sup>1,8-14</sup>.

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 conditions"<sup>10</sup>. 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 week<sup>12</sup>. "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,

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generally finding arterial oxygen tension to be higher than alveolar. The causes were the lack of reliable methods of measuring oxygen tension in blood<sup>9</sup>. 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<sup>9,10</sup>." 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<sup>15,16</sup>. The Kroghs wrote seven 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"<sup>17</sup>.

### 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<sup>18</sup>. 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<sup>19</sup>.

In 1903 Haldane's uncle's intention to resign became known. Sanderson and his colleagues, chiefly Francis Gotch, Haldane and Arthur Thomson<sup>20</sup> 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 in Sanderson's group or Haldane. Pamphleteering began, London versus Oxford<sup>20-21</sup>.

### HARVARD

At this time, Mr. Charles W Eliot, President of Harvard University, tried to get William Osler to come to Harvard<sup>19</sup>. Osler gave the Ingersoll Lecture on Science and Mortality. Mr Eliot after the lecture "Expressed himself as greatly disappointed<sup>19</sup>." 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<sup>19</sup>. The Oslers' future was settled by Arthur J Balfour who as Prime Minister nominated Osler to King Edward VII, as Regius Professor<sup>19</sup>. 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<sup>1,22</sup>. Lorrain Smith had founded the 'new' Pathological Society of Great Britain and Ireland and was chief host at the Society's inaugural meeting<sup>22</sup>.

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<sup>23</sup>. 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<sup>24,25</sup>. He subsequently received a Moseley Travelling Fellowship to work in the laboratory of Augustus Krogh who had won his Nobel Prize in 1920<sup>26</sup>. After joining Beecher's Anaesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital in 1960, we continued work initiated a lifetime before by Lorrain Smith<sup>2-4,27-29</sup>(fig.1). This continuation was enormously helped by recent fabrication of polarographic oxygen<sup>30,31</sup> and carbon dioxide electrodes employing semi-permeable membranes<sup>32-34</sup>. 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<sup>33</sup>.

We investigated the effect of intrapulmonary shunting as described by Sackur in 1897\*<sup>1,35</sup> and Christian Bohr's 1905 values for oxygen solubility in solutions: values which had been superseded<sup>36</sup>. We found Bohr's measurements and principles superior to those quoted in the Handbook of Chemistry and Physics<sup>37</sup>. We used a Haldane apparatus, a successor technique to those Haldane and Lorrain Smith had developed in Belfast in 1895 and 1896<sup>8,9</sup>. Our values, validating the principles of Bohr are in more recent handbooks<sup>38,39</sup>. Aage Bohr wrote to us in 1964 to welcome validation of his grandfather's work<sup>40</sup>. In 1967 we were asked to review and update Lorrain Smith and Haldane's work on the effects of oxygen<sup>29,41</sup>.

Further work on the effects of inspired oxygen over 42 percent<sup>42</sup> needs to be done on patients with very large right to left intrapulmonary shunts (fig. 2)<sup>3</sup>, on patients with altered cholesterol metabolism<sup>43</sup> and in patients with intracranial pathology<sup>44</sup>. 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<sup>6</sup>. JS Haldane wrote James Lorrain Smith's 1931 obituary<sup>1</sup>. James's sister Annie was, in 1904, among the first women elected to

\* P. Sackur was a member of the Pharmacology Institute of the University of Breslau (now Wroclaw, Poland). The university library was totally burned by the Red Army on May 10, 1945.

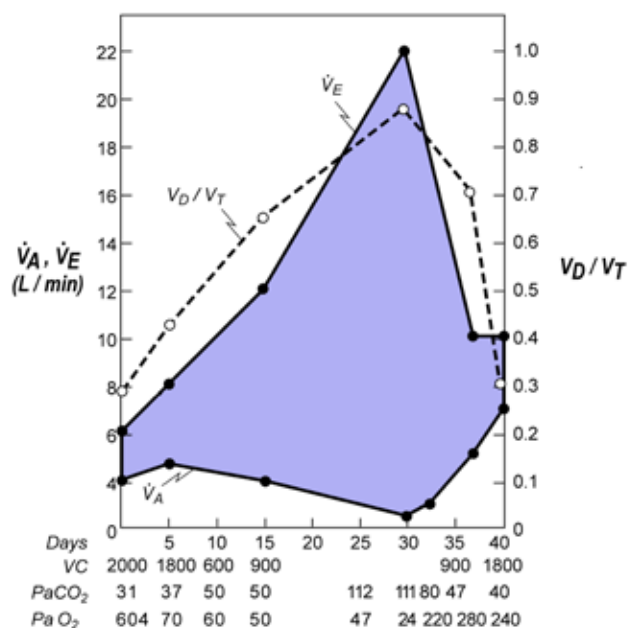


Figure 2. Increase in ventilation and inspired oxygen tension requirements in respiratory failure due to pneumonia and ARDS.

During respiratory failure in a patient with ARDS and pneumonia despite minute ventilation ( $\dot{V}_E$ ) of more than 20 liters per minute provided on the thirtieth hospital day by a constant volume ventilator, effective ventilation (alveolar ventilation  $\dot{V}_A$ ) was only 2.5 liters per minute. Ineffective ventilation (dead space ventilation) is shown in blue. The ratio of dead space to tidal volume ( $V_D/V_T$ ) 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 heavily sedated to decrease oxygen consumption, and even so his arterial oxygen tension ( $P_aO_2$ ) was consistently under 50 mm of mercury. The 60 percent intrapulmonary shunt, venous to arterial 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<sup>3</sup>).

the Linnaean Society. She became an OBE in 1934<sup>5</sup>. Christian Bohr died in 1911. Subsequently his son Niels (1922) and grandson Aage (1976) won Nobel Prizes for physics.

Marie Krogh died under German occupation, in 1943. In 1946 August Krogh visited Harvard University. He lectured both at the College and Medical School. His daughter, Bodil Schmidt-Nielsen, has written that he was very pleased with this visit to Cambridge and Boston. He was entertained, in turn, by the five Harvard University Professors and Department Heads whom he and Marie had trained: James Howard Means, Jackson Professor of Clinical Medicine from 1923; Cecil K Drinker, Professor of Physiology from 1923 and Dean of the School of Public Health Science from 1935; Edward D. Churchill, John Homans Professor of Surgery from 1931; Henry K Beecher, Henry Isaiah Dorr Professor of Research in Anaesthesia from 1941; and Eugene Landis, George Higginson Professor of Physiology, who had succeeded Walter B Cannon in 1943<sup>45</sup>. August Krogh died in 1949<sup>46</sup>.

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<sup>27,47</sup>. 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<sup>48\*</sup>, secondly during the 1950's and 60's<sup>51</sup>. 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

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\* My father<sup>48</sup> 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<sup>49</sup>. In 1901 Lorrain Smith was appointed the first Musgrave Professor of Pathology<sup>50</sup>.

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