

Oxygen therapy, then and now

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Dr Warren (pages 81-85) has written a delightful history about the pioneers in oxygen therapy and the two Canadian heroes of medicine who had different views about the topic. Osler and Meakins sound like the voices of two schools of medical thinking that go back as far as we can see in history. The story of oxygen therapy is part of the history of evidence-based medicine.

Ancient Greek physicians were divided into rival schools. Most, like the pneumatists and dogmatists, had elaborate theories about health and disease from which they confidently derived recommendations for treatment. Opposing them were the empiricists, who were unconvinced by explanations involving elements, humours, pneuma, seasons, climate, complexions and diet. They rejected the theories of pneumatists and dogmatists and insisted that treatments be based purely on experience. Dogmatists and pneumatists in turn scorned the validity of conclusions drawn from experience. Modern physicians would agree with both critiques. We now see the ancient theories as worthless, and the empiricists' evidence cannot have been better than level 4.

Both our theory and our ability to draw correct conclusions from experience have advanced somewhat since the time of Galen, but it is still true that there are few clinical situations where we understand the biology so well that we can give a novel treatment with the confident expectation that it will prove safe or effective, and few situations where we have outcome data that are so good that we can be sure a given patient will benefit from the treatment. As a result, the old discussion between schools of thought is still going on. Nowadays, the empiricists have turned into evidence-based medicine doctors while the pneumatists and dogmatists have turned into scientists (physiologists, biochemists, cellular and molecular biologists and pharmacologists). Most of us are now trained in both evaluation of clinical outcome data and biological science, but we are all either empiricists or scientists at heart. When neither theory nor outcome give clear guidance, the empiricists among us are tempted to try treatments for which outcomes data are only 'suggestive', whereas scientists are tempted to try treatments that current biology theory predicts will work. (There are also the skeptics, who fall back on the *primum non nocere* principle.)

In the oxygen therapy story, Meakins sounds like a scientist. He was impressed by data showing that oxygen saturation went up with oxygen therapy. Osler, on the other hand, sounds like an empiricist. He had heard about oxygen toxicity and worried

that oxygen might do more harm than good. He was waiting to see evidence of benefit – not proof of a change in oxygen saturation, but proof that death rates go down. If they had lived another 80 years, Osler would be a hard-headed supporter of clinical trials, rather like the current editor of this *Journal*, while Meakins would continue to produce physiological data that give very good reasons to perform new clinical trials.

The early studies of oxygen therapy make a catalogue of pitfalls in clinical investigation. Joseph Priestly, who isolated oxygen for the first time and knew some of its biological effects, inhaled some himself and noted an agreeable glow and lightness of the chest. Beddoes, a chemist, took oxygen and noted that his fingertips turned carmine in color. It is possible that he had severe, chronic respiratory disease with cyanosis and his observation was valid, but it is more likely that, given what we know now about 'central and peripheral' cyanosis and the difficulty of perceiving cyanosis, he either imagined the colour change or his excitement caused blood flow in his fingers to increase. Both scientists illustrate the fallacy of trusting physiological observations reported by subjects who are themselves theorists. JS Haldane and colleagues, having discovered the principle of negative feedback homeostatic control of carbon dioxide in the blood, performed on themselves the experiment of hyperventilating and then watching their own relaxed breathing to see if they went apneic. They did, as expected. This is a reproducible experiment. I performed it on myself as a first year medical student during the respiratory physiology course. Subsequent research showed that posthyperventilation apnea occurs only in stroke patients and physiologists who believe the simple theory of feedback control of ventilation by chemoreceptors. Similarly, Davy found that oxygen eased all types of breathlessness, whereas most properly controlled modern experiments have shown little effect of oxygen on dyspnea in lung disease. Dr Kellogg's claim about the "wonderful vitalizing and invigorating influence of oxygen" can be trusted about as much as his conviction that oxygen enemas were good for liver disease. He may have been a quack, but his evidence was as valid as that of Davy and Beddoes. He might have been quoting them.

These early modern scientists, and others like them, had such confidence in their theories about oxygen that they felt no need to ask questions about clinical outcomes. Their authoritative pronouncements were probably very important in establishing the myth of oxygen (ie, a strong and widespread belief that oxygen can both treat disease and improve health in

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ways that go far beyond any evidence base) that prevails today. The oxygen myth is the foundation of industries that sell oxygen-enriched air in 'oxygen bars', oxygen from tanks to revive tired football players on the bench, hyperbaric chambers for all kinds of illnesses, and oxygenated water as an invigorating drink. On my desk is a recently manufactured bottle of antiphlogistic tablets, proof of the living influence of Joseph Priestly, who called his oxygen dephlogisticated air. Fortunately for the vulnerable public, antioxidant tablets are also sold in abundance.

The first reports on the use of oxygen in patients from the 1895 British Medical Association meeting described in Dr Warren's article are more in keeping with expectations based on modern experience. Oxygen was given to patients with cardiac or cardiorespiratory disease, but only in desperate cases with cyanosis. It had only a palliative effect, reducing symptoms, but only "maintaining life a little longer". Patients with pneumonia or heart failure severe enough to cause cyanosis are expected to show improvement in cerebral function, change in colour and reduction of pulse rate with oxygen. The next step might have been to study the biology of oxygen treatment or to assess its clinical effectiveness more thoroughly.

Meakins concentrated his attention on measurements of oxygen, first showing that cyanosis in severe lung disease was not due to methemoglobin but, in fact, to low oxygen. Studying the treatment, he showed that oxygen administration could correct saturation in patients with low oxygen. His admirable preoccupation was with measurable physiological variables. Having seen oxygen levels rise with oxygen treatment he was certain that oxygen treatment was important. He lived in the era before modern empiricists gave their school the new evidence-based medicine name and made it commonplace to ask the 'so what' question that Osler was interested in. In the paper reporting 10 cases of pneumonia with moderate

desaturation, of whom only three had improvements in symptoms with oxygen, Meakins concluded that oxygen "is absolutely indicated to relieve or remove the ill effects of a very dangerous condition". Although one of the first large-scale comparative outcome studies in medicine was performed on pneumonia patients in Paris by PCA Louis in the 1820s to assess the value of bloodletting, such studies were never done for oxygen in acute disease. Barach's paper promoted oxygen therapy for pneumonia because it made the patients feel better but five of his 16 patients died and he thought oxygen had no effect on prognosis, because that was about the death rate he was used to seeing without oxygen. At the end of the story, as Dr Warren points out, oxygen became accepted treatment for pneumonia and various other acute respiratory diseases without benefit of any convincing systematic evidence of effectiveness. It also became accepted treatment for acute coronary syndromes with normal oxygen and cancer palliation, where the myth of oxygen makes it a powerful placebo.

Where are we now? For chronic respiratory disease we have good evidence from long-term oxygen trials for the use of oxygen treatment in stable, hypoxemic, chronic obstructive pulmonary disease patients. But an unplanned spin-off of those trials has had a huge influence on oxygen treatment in all kinds of patients. The 85% oxygen saturation value, the cutoff value chosen for entry into those trials, has somehow become a magic number, the saturation criterion for prescribing oxygen in any acute or chronic case. Patients, families, and health care professionals of all kinds have concerns about the hour-to-hour safety of any patient with 84% or less oxygen saturation. The number drives discharge dates, short-term oxygen needs and patient anxiety. We thus prescribe oxygen for our chronic obstructive pulmonary disease patients according to the principles of empiricists, but rely on arguments by analogy and the principles of scientists for the rest of our patients.