Institution:	**UNIVERSITY OF CAMBRIDGE**
Unit of Assessment:	**B13** Electrical and Electronic Engineering, **Metallurgy and Materials**
Title of case study:	**Topical oxygen therapy for wound healing**

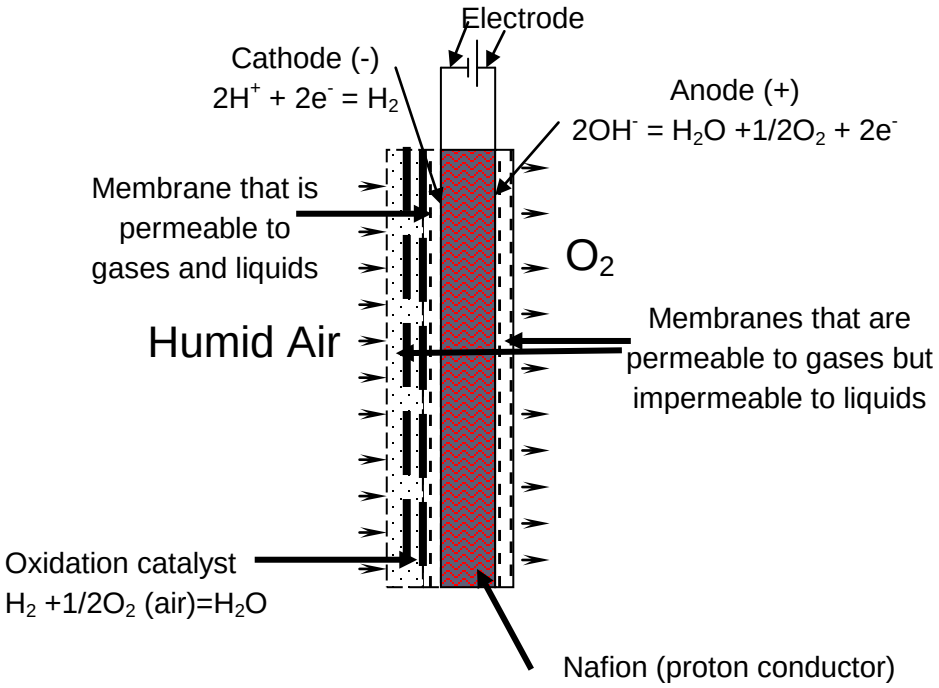
1. Summary of the impact

A small, battery-powered device for oxygen generation and distribution (*Natrox*™), has been developed that, with air as input, can supply humidified oxygen evenly to wounds, such as ulcers, surgical wounds and burns, allowing the patient to be treated in a discrete efficient way without interfering with their lifestyle. With conventional approaches, oxygen can be supplied to hospital patients with ulcers only via gas bottles or piped oxygen, with the limb or body being enclosed in a plastic bag. Many successful trials of the *Natrox*™ device have been performed, initiating considerable interest, leading to the manufacturing and distribution of the device by *InotecAMD Ltd*, a University of Cambridge spin-out.

2. Underpinning research

The Materials Chemistry Group, Dept of Materials Science & Metallurgy, University of Cambridge has been very active, for many years, in aqueous electrochemistry. In particular, *Nafion* membranes, which are proton conductors under humid conditions, were used to create hydrogen sensors [1] and membranes for electrowinning cells [2,3]. Furthermore, in work initiated in 1993, hydrophobic porous membranes were used to create fine bubbles (*sparging*) in electrowinning cells [2,3]. Critical lessons (on the benefits of smaller gas bubbles and how they can be achieved) from this hydrometallurgy work were directly applicable in developing the *Natrox*™ device for oxygen generation.

An earlier oxygen-generating device had been developed by others in the US, but this device had several disadvantages, including: failure of the cell due to drying out of the electrolyte; formation of hydrogen peroxide which is a known carcinogen; and, lastly, oxygen was fed by a small-diameter tube (*cannula*) to the wound (a method not favoured by UK clinicians).



DJ Fray & V Kotzeva, 'Oxygen Apparatus and Method', USP 2009008261 (filed 2005)

Figure 1. Diagram of *Natrox*™ oxygen generator showing, on the right, the electrochemical cell that produces the oxygen from water in the membrane and the oxidation catalyst, on the left, where the hydrogen is reacted with oxygen from the air, to produce water that is returned to the membrane.

Building upon previous research, described in the first paragraph, **Derek Fray** (Professor of Materials Chemistry 2001–2007, Director of Research and Emeritus Professor of Materials Chemistry 2007–) concluded that it was feasible to create a device that overcame all of these problems. Together with Dr Vega Kotzeva, (Post Doctoral Research Associate 2005–2006), a small cell was built, based on a design that had been previously used for a hydrogen sensor [1], which used a *Nafion* membrane surrounded by a small reservoir of water.

This successfully demonstrated that, by applying a small voltage (1.5 V) across the membrane, a flow of oxygen was created which would satisfy the needs of an average ulcer (15 ml/h) with a weekly consumption of water of 1 ml. It was thought desirable to oxidize the hydrogen (a by-product of the electrolysis process) by placing a catalyst layer a short distance from the cathode, allowing the hydrogen to react with air to form water which then returns to the membrane [4,5]. Rather surprisingly, it was found that with a combination of hydrophobic and hydrophilic membranes it was possible to operate the device indefinitely, producing humidified oxygen without the need for a water reservoir, provided the batteries were kept charged. A diagram of the cell is shown in Figure 1. The distribution pad for the oxygen was, again, created using the discoveries in the hydrometallurgical studies of *sparging*. This previous research showed that, by applying a modest gas pressure, a porous hydrophobic membrane allowed the creation of a uniform supply of bubbles [2,3]. This is ideal for supply of oxygen to a wound but, in order for the exudate to escape, it is necessary to also have very much larger holes in the membrane. The end result is a pad that allows oxygen bubbles to be created at the wound and the exudate successfully removed (Figure 2 [6]). Furthermore, unlike the cannula approach, the hydrophobic pad does not stick to the wound which makes the removal of the pad from the wound easy and painless. The combination of the oxygen generator and oxygen-delivery system has been trademarked as *Natrox*™.

3. References to the research

1*****. FWH Dean & DJ Fray: A low temperature hydrogen in steel potentiometric sensor, *Solid State Ionics*, **70–71** (1994) 584; DOI: 10.1016/0167-2738(94)90377-8

2*****. F Tailoka & DJ Fray: Enhancement of mass-transfer using microporous sparger materials, *Trans Inst Mining Metal* **102** (1993) C1.

3. F Tailoka & DJ Fray: Electrowinning of copper from chloride solutions in presence of gas sparging, *Trans Inst Mining Metal* **102** (1993) C7.

4*****. DJ Fray & VP Kotzeva, 'Oxygen Apparatus and Method'. Filed 3/03/2005. Published patents: US2009008261, WO2006092612, GB2431668*, EP1856307, CN2068001317*

5. MF Vinton & DJ Fray, 'Oxygen Concentrator and Method'. Filed 13/09/2010. Published patents: WO2102035298, GB248520*

6. MF Vinton, A Hurst & DJ Fray, 'Hyperbaric Dressing'. Patent filed 1/04/2005. Published patents: US2008269658,WO2005094744, GB2412589*, EP1755510, CN200580017913*

*****references best indicating the quality of the underpinning research.

The three patents [4–6 above] have been published and are either under examination or granted. The distinction of Professor Fray's research in electrochemistry has been widely recognised. During the REF assessment period he was elected to Fellowship of the Royal Society, and he was the first person to receive the Federation of European Materials Societies' *Innovation Award*. In 2011, an International Conference (with some 450 delegates) was held in his honour in Cancun, Mexico.

4. Details of the impact

Professor Fray first had the ideas for exploiting the hydrometallurgical results and adapting them for oxygen generation in 2001 (ie before the assessment period for research in the REF). It wasn't until 2003, when in discussion with Melvin Vinton, it was decided to form a company, *InotecAMD Ltd* [i] (references in Section 5), to initially design an oxygen-distribution system, funded by a Smart Award. In 2005, the Dept of Materials Science & Metallurgy at UCAM funded a one-year research project (£100k) to develop the oxygen-generation system. This device was a success and was patented by the University in 2005 and, subsequently, licensed to *InotecAMD Ltd* on 27 July 2009, with an effective date of 1 January 2008. From 1 January 2008 to 31 July 2013, [text removed for publication]

. This allowed the oxygen-generation system to be industrialized and the oxygen-distribution system to be perfected.

***Natrox*™ is the first device that can successfully deliver oxygen, almost indefinitely if the batteries are kept recharged, to patients without interfering with their lifestyle.**

Over 200 *Natrox*™ units have been made with many being used for **random controlled trials** at three hospitals in Prague. The remainder have been used for trials in the UK and sent to agents/distributors in the UK, USA, France, Singapore, Malaysia, Turkey and Dubai.

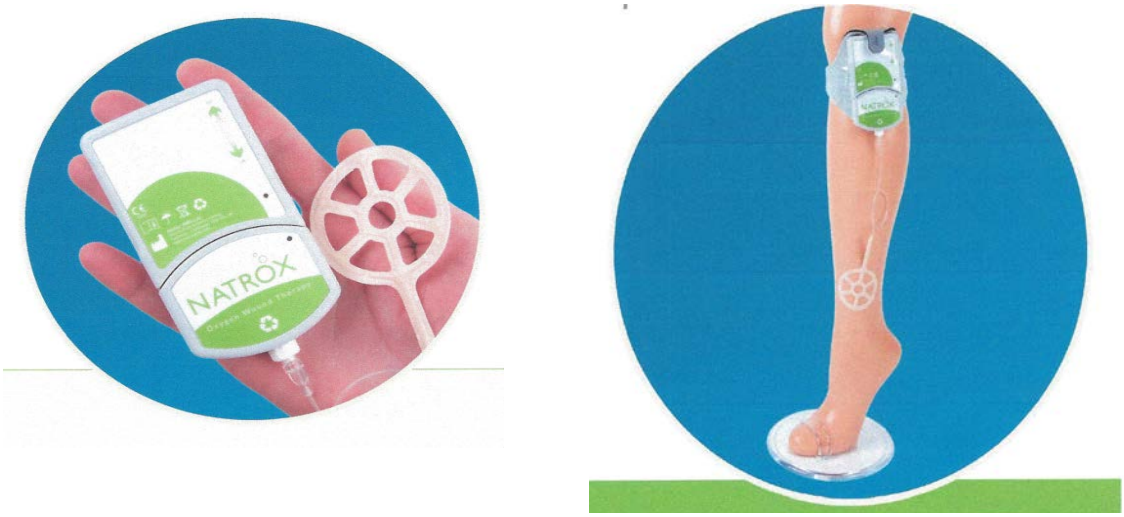


Figure 2. The oxygen generator and circular pad in close-up (on the left), and positioned on the leg of a mannequin (right). The oxygen is evenly distributed over the wound by the pad and the large spaces in the pad allow the escape of exudate.

Health impacts

To check the viability of the *Natrox*™ device, trials were performed at the end of 2009 at a Tissue Viability Clinic in Eastbourne, which dramatically showed the efficacy of such a device with 10 patients who had been referred to the clinic by the NHS as not treatable; 8 showed considerable improvement after six weeks treatment [iv]. A bonus not originally considered was that the pain, experienced by the patients, also decreased considerably when oxygen was fed to their wounds [iv]. Further successful trials have been carried out at Doncaster Royal Infirmary on hard-to-heal wounds as the result of surgery. An evaluation of oxygen therapy was undertaken on a range of complex surgical wounds, which included post-mastectomy wounds which had dehisced (ie opened) following surgery. It was found that, after about six weeks treatment with oxygen, the wounds improved dramatically and conventional treatment could then be applied to procure a complete recovery. It was concluded that this therapy was successful, both in promoting healing and improving the quality of life in a group of anxious patients [v]. In early 2012, the *Natrox*™ system was subjected to a safety study at the FNKV Hospital in Prague on ten patients with non-healing leg ulcers and all patients showed considerable shrinkage of their ulcers.

In June 2012, *InotecAMD Ltd* received a CE mark for the oxygen-delivery system giving all the regulatory approvals for sales in the EU. In July 2012, the US FDA awarded the 510(k) approval for the *Natrox*™ system meaning that *Natrox*™ can be sold in the US [vi].

At present, a random controlled trial is being performed in Prague on ~60 patients so that the treatment can be sold to the NHS. In November 2013, Doncaster & Bassetlaw hospitals will embark on a 12-month trial studying non-healing surgical wounds and breast reconstruction [v].

Overall, about 80 patients have been successfully treated, ie healed, with a considerable decrease in their suffering, coupled with an increase in their general wellbeing.

Impacts on public policy and services

About 2 million patients in the European Union suffer from non-healing ulcers, and the annual cost of treating these is estimated to be 10 billion Euros. The clinical trials provide hard evidence that the use of *Natrox*™ would decrease the number of patients and shorten treatment times. *Natrox*™

has opened up possibilities for more cost-effective healthcare, with better outcomes. Secondly, the rationale for the trials at Doncaster & Bassetlaw hospitals is to study oxygen as an anti-microbial treatment, as many patients have increased resistance to antibiotics [v]. The use of oxygen instead of antibiotics for treating infected wounds would again improve both outcomes and the cost-effectiveness of the service.

Economic impacts

As well as cost savings to national budgets, the manufacture and supply of *Natrox*™ devices will generate employment and income for the UK. In 2013, the company employed a part-time CEO, a full-time Chief Technical Officer and three other part-time staff. In addition, much of the equipment, circuitry, oxygen-distribution pad and units are manufactured, under subcontract, in the UK. The random controlled trial is being organized by UK-based SME *Wound Market Consulting* (www.woundmarketconsulting.com). Sales of *Natrox*™ devices have commenced in the Far East, and distributors in UK and France are organizing trials, prior to sales. Virtually all the investment of [text removed for publication]

to increase the rate of production, to investigate a wider range of applications for the device such as treatment of other types of ulcers, burns and surgical wounds, and to employ more technical and sales personnel.

5. Sources to corroborate the impact

[i] *InotecAMD Ltd* (Chairman, Chief Executive Officer, Chief Technical Officer) (www.inotecAMD.com) — for corroboration of all information on the development of the *Natrox*™ device, current tests, approvals, marketing, orders, etc.

[ii] 2005 http://www.angelnews.co.uk/article.jsf?articleId=1158

[iii] 2009 http://www.praxisunico.org.uk/news/member-detail.asp?ItemID=254

[iv] R Mani: Topical oxygen therapy for chronic wounds: a report on the potential of Inotec® a new device for delivering enriched oxygen to chronic wounds, *J. Wound Technology*, **no. 9** (July 2010) 1–4.

[v] Doncaster and Bassetlaw Hospitals NHS Foundation Trust: (Sister, Wound Care Service) — for corroboration of effectiveness of the *Natrox*™ device for wound care, particularly after mastectomy.

[vi] 2012 FDA approval of *Natrox*™ — http://www.accessdata.fda.gov/cdrh_docs/pdf11/K112634.pdf