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The Deadly Business of an Unregulated Global Stem Cell Industry

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Abstract

In 2016, the Office of the State Coroner of New South Wales released its report into the death of an Australian woman, Sheila Drysdale, who had died from complications of an autologous stem cell procedure at a Sydney clinic. In this report, we argue not only that Mrs Drysdale's death was avoidable, but that it was the result of a pernicious global problem of an industry exploiting regulatory systems in order to sell unproven and unjustified stem cell interventions.

Keywords: Stem cells, clinical innovation, medical law, professionalism, health product regulation

The Death of Sheila Drysdale

In December 2013, the private Sydney clinic of cosmetic surgeon, Dr Ralph Bright, admitted 75-year old Sheila Drysdale for a liposuction procedure. Dr Bright did not perform this procedure for cosmetic reasons, but rather to 'treat' her advanced dementia with adipose-derived stem cells. Tragically, Mrs Drysdale died within ten hours of the procedure.

According to the NSW Deputy Coroners' Report,(1) Dr Bright had removed approximately 500ml of fat from Mrs Drysdale's flanks and buttocks on the day of the intervention. This tissue was then "processed" in the clinic's laboratory to derive "1.5 billion stem cells" for subsequent intravenous administration later that day. In the immediate post-operative period, Mrs Drysdale was noted to be drowsy and hypotensive. Even though Mrs Drysdale was being monitored and administered medications to assist in her recovery, she continued to deteriorate and died at her nursing home less than three hours after being discharged.

The Deputy Coroner found that the cause of Mrs Drysdale's death was hypovolemic shock due to uncontrolled blood loss following the liposuction procedure. He attributed the blood loss to Dr Bright's failure to ensure that the patient had ceased her anti-platelet medication prior to the surgery. The Deputy Coroner was also critical of Dr Bright for failing to recognise or appropriately respond to clinical signs indicating post-operative blood loss; discharging Mrs Drysdale prematurely and, when it became clear that her condition had deteriorated, failing to recommend that she be taken to hospital for immediate treatment.

Mrs Drysdale's death, while unfortunate, resulted from a well-recognised complication of liposuction: the likelihood of death following liposuction is estimated to be between 3-100 per 100,000 procedures.(2) What makes her death so profoundly tragic, however, is that it occurred as a complication of an intervention for which there is no scientific support. While there is some pre-clinical data and (weak) evidence from clinical trials to suggest that autologous adipose-derived mesenchymal stem cells may have some benefit for the treatment of arthritis and other joint or muscular injuries,(3) there is *no* published scientific research that indicates *any* benefit for patients with dementia.(4, 5)

This fact was not lost on the Deputy Coroner, who stated that the use of stem cells for dementia was "highly questionable" and that it displayed "some of the hallmarks of 'quack' medicine: desperate patients, pseudo-science and large amounts of money being charged for unproven therapies" (1). Consequently, the Coroner recommended an investigation into Dr Bright's conduct and called for the relevant agencies to develop guidelines to regulate more rigorously "experimental" or "innovative" medical or surgical procedures in Australia.

Questionable ethics and regulatory failures

This case raises serious ethical and legal issues concerning the professional conduct of medical practitioners and their duty of care towards patients, the regulation of innovative therapies, and the global emergence of businesses marketing stem cells directly to consumers. Practitioners have ethical, professional, and legal duties to act in their patient's best interests and in ways that provide benefit (beneficence). These obligations can conflict with the commercial imperatives and financial interests of private clinics and businesses that market stem cells.

Importantly, this duty of care is in no way diminished by the provision of information to patients, or demands from consumers for the freedom to access innovative therapies, even if they are risky and are unlikely to be beneficial.(6) This means that novel medical interventions administered outside

the context of clinical trials should have, at least, some likelihood of benefit to justify the potential risks of harm. From a legal perspective, one can only consent to a serious bodily medical intervention when that intervention is clinically justified by, for example, there being a tangible therapeutic benefit. The implication is that if a medical intervention has no therapeutic benefit, it cannot be consented to, and any 'informed consent' will be vitiated. Such 'treatments' are regarded in the common law as assault and/or batteries.(7)

This issue of informed consent was raised in the Drysdale case, with the Deputy Coroner contending that Dr Bright might not have fully-informed Mrs Drysdale's husband (who was her surrogate decision-maker and who had himself been 'treated' by Dr Bright for osteoarthritis) about the lack of scientific evidence and justification for the intervention. Yet, even if this were not the case and Mr Drysdale had been fully informed of both the risks of harm from the liposuction procedure and the unlikelihood that the treatment would be effective for his wife's dementia, the intervention would still have been clinically unjustified, morally inexcusable and legally suspect. The act of providing information does not, *ipso facto*, validate the choices of patients, nor does it remove a doctor's duty of care.

Mrs Drysdale's death was not the first to occur in the context of unjustified and dangerous stem cell procedures. In 2008, an 18-month old child with cerebral palsy died in Germany following complications of a procedure in which autologous bone marrow-derived stem cells were injected into the brain.(8) In 2009, a 27-year British patient died in Ecuador of intracranial hypertension following an unspecified stem cell procedure for his spinal injury.(9) In 2010, a 73-year old Korean patient died in Japan from a pulmonary embolism and another died in China following a procedure with autologous adipose-derived stem cells for arthritis.(10) And two patients died in Florida after being administered stem cells at the same clinic.(11) The first patient died in 2010 from a cerebellar infarct after having bone marrow-derived autologous stem cells injected into the arterial circulation of her brain for the 'treatment' of peripheral neuropathy. The other patient died in 2012 after being injected intravenously with autologous adipose derived stem cells for the treatment of pulmonary hypertension and fibrosis; he died at the clinic suffering a cardiac arrest.

These troubling incidents are indicative of the invasive procedures that are frequently used in stem cell clinics, which includes intrathecal injection and intravenous infusions that are associated with non-trivial risks. Recent reports have identified hundreds of businesses offering such procedures in countries with diverse economies and infrastructure for regulating the claims and conduct of medical professionals. This includes the United States,(12) Japan,(13) Australia,(14) as well as China, Mexico, India and many more.(15-17) These clinics often form loose collaborative networks to exploit weaknesses and loopholes in regulations across different geographic jurisdictions,(18) and wilfully misinterpret imprecise definitions and vagaries in laws that regulate the manufacturing and marketing of human cells for medical purposes.(19) In Australia, for example, a regulatory 'loophole' that explicitly excludes autologous cellular therapies from regulation as biological drugs (14) helped to create the context in which Mrs Drysdale's death occurred.

In addition to taking advantage of regulatory loopholes, it appears that doctors offering autologous stem cells outside the context of clinical trials may also be deliberately misconstruing laws that distinguish medical practice from clinical research and innovation.(19) Although porous distinctions between clinical practice and research may offer a degree of regulatory flexibility and potentially promote worthwhile innovation, they also provide opportunities for doctors to administer unproven and unjustified interventions to highly vulnerable patients under the guise of 'innovation' without any of the oversight provisions given to participants in formal clinical research.

Conclusion: weak regulation, pseudo-science and bad medicine

While innovation is an important and desirable goal in the clinical sector, it is clear that weakly regulated innovation has pernicious consequences. Unprincipled practitioners can readily evoke the language of innovation and a patient's 'right to choose', and interpret poorly framed and weakly enforced regulation tendentiously in a bid to avoid oversight from within the domains of either clinical care or human subject research. This lack of oversight has resulted in a range of avoidable harms, ranging from the financial and psychological burden of failed treatments, to physical harm, illness and even death (20, 21).

While patients bear the greatest risks of weak regulation, the emergence of this predatory sector also harms legitimate stem cell innovation. Stem cell research has always been a controversial field, and extensive community consultation and parliamentary debate has been required to establish legitimate forms of research and research oversight.(22) Avoidable deaths from what are marketed as stem cell treatments risks a withdrawal of public trust from the entire sector, with potentially serious consequences for research funding and regulatory initiatives that might otherwise help promote innovative stem cell therapies.

The values of *Responsible Research and Innovation* (RRI) that form the centrepiece of the European Commission's Science Research funding system can be evoked in this context. RRI approaches advocate social deliberation and careful risk-benefit assessment to underpin the 'ethical acceptability, sustainability and societal desirability of the innovation process and its marketable products'.(23) Such an approach is essential if true stem cell innovation is to result in safe, beneficent treatments. Clinicians and regulators should recognise Mrs Drysdale's death, and others that preceded it, as a tipping point towards best practice, and ethical and responsible innovation. If not, we can expect that Sheila Drysdale's entirely preventable death will not be the last such tragedy.

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Conflicts of Interest Declaration

We have read and understood JME's policy on declaration of interests and declare the following interests: Ian Kerridge is a bone marrow transplant physician, Chair of New South Wales Bone Marrow Transplant Network Long Term Follow-Up Working Group, Board member New South Wales Stem Cell Network and Member of the National Health and Medical Research Council's Xenotransplantation Committee. No other authors have any conflicts to declare.

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