the authors describe Haffkine's attempts at curing plague in patients by experimenting with various doses of his "serum". There is a description of a prison experiment where Haffkine tested his vaccine on 154 healthy prison inmates without obtaining a proper informed consent. This would be totally unacceptable by today's standards of research ethics. Invasion into the privacy of people's homes, forcing people to undergo compulsory inspections in railways stations and ports, forced segregation of the sick and the healthy, forced quarantine are all seriously contentious issues in public health ethics. Ethical dilemmas are highlighted when the *Sarkar* (British Raj) wants to contain the disease by all possible means and the people show a lack of trust in the methods of the oppressive *Sarkar*.

A compendium of medical humanities

This book is an excellent compendium of the history of medicine, the history of public health, illness narratives, social determinants of health, medical, research, and public health ethics. For a person from a health sciences background the 500 pages of the book may seem too many, which is probably its only downside. Medical and public health students should read this book and discuss the various dimensions of the plague outbreak of Bombay in 1896. Important excerpts from the book can serve as resource materials for courses on public health, medical and public health ethics. In summary, *Room 000* is a grand drama of medicine with lessons on various aspects of healthcare for several types of health professionals!

Peeling the onion from the inside out

JOHN NOBLE JR

Margaret Whitstock, *Reducing adverse events in older patients taking newly released drugs.* Saarbrücken, Germany: Verlag/Scholar's Press, 2015, 197 pages, US $ 54.00, ISBN 978-3-639-76797-1

For those looking for a primer on how the Vioxx® debacle came about, Margaret T Whitstock's new book, *Reducing adverse events in older patients taking newly released drugs*, is a must-read (1). Reading the plain-talk narrative is like peeling away an onion's layers but from the inside out. Like a prosecuting attorney, the author meticulously presents the heap of forensic evidence showing how in the course of time the coordinated actions of industry, government, and the biomedical research community have degraded the basic rules of empirical science to produce a foreseeable and preventable tragedy.

Its chilling conclusion is that there are more such tragedies awaiting us unless patients and their physicians take steps to confront the research community and its political leadership about the privileged use of flawed and manipulated randomised controlled trials (RCT) to guide evidence-based medicine (EBM). The forensic evidence demonstrates how EBM guidelines depending on RCTs as now conducted lead physicians to make treatment decisions that increase the morbidity and mortality of older patients who have been systematically excluded from RCT participation because of their comorbidities and use of multiple medications.

Most damning is Dr Whitstock's indictment of the current US Food and Drug Administration* (FDA) approach and policy for assessing the generalisability of the RCTs on which it depended for approving the effectiveness and safety of new drugs. That policy in effect makes the older patient population guinea-pigs in the uncontrolled experiment, sometimes referred to as "pharmacovigilance," that depends on the voluntary reporting by physicians of perceived adverse effects in patients for whom they have prescribed FDA vetted and approved drugs on the assumption of their effectiveness and safety. As she points out, "drug manufacturers would prefer that risks associated with a newly approved medication are established by patients' experiences of adverse events, as this occurs at no cost to the manufacturer" (1: p 172).

Dr Whitstock's book of six chapters and 197 pages, including figures, tables and three appendices, starts out with the essentials about older patients as consumers of new drugs, as participants in RCTs of new drugs, and safety concerns when prescribed new drugs that have been approved on the basis of the RCTs from which older patients with comorbidities and poly-drug use have been systematically excluded for the sake of internal validity.

Chapter 2 covers the genesis and development of the randomised controlled trial and its epistemological foundation in epidemiology with its focused search for a pathogenic cause-and-effect relationship—an agent and a disease. The root source of confusion in the interpretation of RCTs is the "frequentist" approach to statistical inference that emphasises ritualised $p<0.05$ stochastic significance rather than the quantitative judgement of the significance of single-agent interventions from a clinical perspective.The use of surrogate end-points in the assessment of statistical significance adds to the confusion.

Chapter 3 addresses the privileging of the RCT as the "gold standard" of scientific medical evidence and underpinning of

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EBM. Adopting the average effect of an RCT on often surrogate end-points constrains choice of which interventions can be investigated for clinical decision-making.The tradeoff often involves design, analytic, and cost-efficacy at the RCT level at the expense of gaining knowledge about how well an intervention works in the clinical context. There is an inherent conflict in values insofar as EBM levels of evidence tables put clinician opinion at the lowest level of scientific rigour and confidence. Dr Whitstock points out that the privileging of the RCT as providing objective and neutral scientific evidence is specious every step of the way because the "selection and definition of the problem, the variables to be evaluated, the participating subjects, the procedures and measuring techniques, the nomination of what will be considered as an outcome, the statistical analyses to be performed, and the interpretation of those analyses . . . are made from a position of pre-specified interests" (1: p 71). In effect, the EBM stance seemingly sacrifices the very interests of the clinicians and their patients it purports to serve.

Chapter 4 documents the external pressures from pharmaceutical regulation that reinforce and enhance the privileging of RCT evidence—especially those resulting from the political process and economic and regulatory domination by the USA. In my view, Dr Whitstock's concise history of the "political capture" of the FDA by the pharmaceutical industry is among the best narratives about the FDA as an "inherently political actor." FDA regulatory decisions extend well beyond US borders with significant impacts on the lives and well-being of the citizens of the world. The Prescription Drug User Fee Act (PDUFA) of 1992 completed the political capture of the FDA by industry with attendant erosion of safety standards and corruption of internal decision-making, as reported by FDA whistleblowers and an external survey of FDA scientists by the Union of Concerned Scientists (UCS). The truth of the German proverb, "Whose bread I eat, his song I sing!" rings no truer than from the mouths of one in five FDA scientists reporting that they "have been asked explicitly by FDA decision-makers to provide incomplete, inaccurate or misleading information to the public, regulated industry, media, or elected/senior government officials." In addition, more than a quarter (26%) feel that FDA decision-makers implicitly expect them to "provide incomplete, inaccurate, or misleading information" (2: p 2).

Chapter 5, titled "Where the truth lies: managing the RCT to mislead," provides a carefully-researched airing of what is known about the Merck clinical trials of the COX-2 selective NSAID rofecoxib (Vioxx®) to demonstrate how to manipulate an RCT to produce desired results. Had I written the chapter, I would have titled it, "A primer for knaves to mislead fools." Why? It took sophistication to figure out how to create composite end-points in the RCTs of Vioxx® to mask end-points that might have caused concern. The discrepancy between what was known by the FDA and what was published about the VIGOR RCT in the *New England Journal of Medicine* (*NEJM*) is troublesome and raises doubt about the knowledge and sophistication of high-impact medical journal peer-reviewers. Dr Whitstock's conclusion is that the efficacy and safety of a new drug depends not on the presence or absence of an RCT study design but the "competing pressures of internal and external validity" that played out in the Vioxx® RCTs. Clearly, these RCTs could say nothing that had internal or external validity about excluded older patients with comorbidities and poly-drug use.

Chapter 6 reports the results of a Western Australian use of clinical trial data linked to administrative health data to prospectively identify patient groups at potential risk for an adverse drug reaction. The benefit–cost ratio of preventing avoidable adverse drug reactions would always be positive from a societal perspective. The direct costs incurred by government and private insurers to pay for treatment of new short- and long-term morbidities arising from drug reactions are large. The indirect costs of the burden of suffering and foregone opportunities that these new morbidities impose on individual patients and families are still larger. Dr Whitstock envisions improvements in accessing information about clinical trials, such as implementation of Section 801 of the US Food and Drug Administration Amendments Act of 2007 that mandates registration via ClinicalTrials.gov of all RCTs submitted in support of FDA marketing approval, as empowering development of early warning systems like the one developed for Western Australia.

The Western Australian endeavour demonstrates the feasibility of designing and implementing early warning systems for patients who have been excluded from RCTs because of comorbidities and poly-drug use. In my view, it will be a steep uphill climb to overcome resistance from the pharmaceutical industry and government and private sector sponsors of research as well as biomedical research opinion leaders and the researchers themselves. Paying attention to the requirements of external validity comes at some cost (3). There will be need to anticipate and include rather than exclude clinically relevant populations within larger sample size RCTs. Alternatively, there will be need to design and implement separate RCTs to directly establish the efficacy and safety of new drugs on these excluded populations before granting regulatory approval. Hopefully, the EBM leadership will strike a balance between pursuing improvements in the design, implementation, and reporting of internally valid RCTs and promoting their external validity. The Oxford Centre for Evidence-Based Medicine is uniquely qualified and capable of taking on the challenge (4).

The importance of Dr Whitstock's recommendation that EBM develop early warning systems to protect at-risk patients is reflected in Abramson and Starfield's observation: "Among even the highest quality clinical research (included in Cochrane reviews) the odds are 5.3 times greater that commercially funded studies will support their sponsors' products than non-commercially funded studies. …. [The] primary purpose of commercially funded clinical research is to maximise financial return on investment, not health" (5: pp 414, 416).

Note

* *This was corrected on June 23, 2016, in the online version of this review.*

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Making life and death meaningful

GITA RAMASWAMY

Paul Kalanithi, *When breath becomes air*, Foreword by Abraham Verghese. USA: Random House, 2016, 256 pages US $ 25.00, ISBN-13: 978-0812988406

Thirty-five years ago, when my father died of a massive heart attack at the age of 61 after lingering for three days in a hospital, the family suffered no guilt – was he diagnosed early enough? Was good treatment provided? The answers were in the affirmative, given the quality of healthcare provided to a middle-class citizen in India at that time. Our (read middle-class) attitude to death, when we face it, is now complicated. As in the West, we prolong life even when its quality has decreased dramatically, we medicalise situations like pregnancy, scoffing at centuries of women's wisdom, and we refuse to allow dignity in death. We now watch our dear ones as they linger for days in the intensive care unit (ICU); sometimes, the hospital does not declare death for a couple of days, but claims payment, unwilling to keep an unoccupied bed. We watch 90-year-olds living their last days in the terrible confines of the ICU instead of within the warm walls of their own homes, surrounded by their loved ones. We watch lives being prolonged by the intubator and other invasive devices even when there is no hope of recovery and when the patient is clearly suffering.

This is a grotesque charade like much else in India where lakhs of rupees are spent on maintaining breath in a dying body. I suggest that we look at death and dying in different ways today. Helping us do this are four major literary interventions in health – all made by Indians in the West. In 1994, Abraham Verghese wrote, *My own country: a doctor's story of a town and its people in the age of AIDS* – a compassionate doctor's account of the early days of AIDS. Not much later in 2010, came Siddharth Mukherjee's *The emperor of all maladies*, a magnificent laying out of the history, diagnosis and treatment of cancer, and more importantly, presenting the physician's dilemma in treating cancers. In 2014, Atul Gawande wrote *Being mortal and what matters in the end*, questioning allopathy's vision of healthcare of the elderly and the issue of quality of life. Now in 2016 comes *When breath becomes air*, by Paul Kalanithi, which asks what a dying man can do in the face of near-certain death. There have been other Indian doctor-writers in the West too – Sandeep Jauhar for instance (*Intern: a doctor's initiation*, 2009), making us wonder at the proliferation, in the last two decades, of the Indian doctor-writers who are laying bare issues of the healthcare system in the West. Is it that raised in one culture, transported to another head-on, has given them the capacity to see life and death with fresh eyes?

As I write this, Paul Kalanithi's book continues in the *New York Times* bestseller lists, despite being a dark memoir. A literature student-turned-neurosurgeon, Kalanithi grew up in an Arizona desert town. His father a Christian, his mother a Hindu, condemned on both sides for their love, the couple fled to the USA. While his father was a cardiologist, his mother a physiologist, and both his brothers doctors, Kalanithi chose literature, but turned to medicine when literature did not satisfy his urge to explore the relationship between meaning, life and death. Kalanithi sees medicine as "the heroic spirit of responsibility amid blood and failure".

Confronting death in the form of lung cancer, Paul Kalanithi wrote the book in the last year of his life. He and his wife Lucy – also a doctor, chose to have a child at this time. The baby and Kalanithi's parents and brothers lightened his last days. Kalanithi remained fully alive. Despite physical collapse, he remained full of hope, not for an unlikely cure, but for days that were full of purpose and meaning. Probably much of this was due to his Indian family that surrounded him closely. His parents came down to stay in his town, taking a house on rent close by, so that they were not a burden on their son's nuclear family, but were available for all help. Despite the great love surrounding him, Kalanithi's account shows how difficult it is

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