

VIEWS & REVIEWS

Setting research priorities: a layman's experience

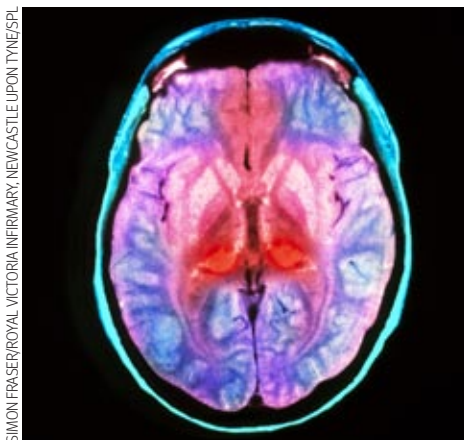
PERSONAL VIEW **Lester Firkins**

I am a 59 year old former banker. Seven years ago I lost my 25 year old son, Ellis, to new variant Creutzfeldt-Jakob disease (CJD). Until then I had no knowledge of or interest in clinical trials. It was because of my subsequent chairing of a CJD patients' charity that I became involved with the world of clinical trials. This involvement took several forms:

- Attending a "consumer workshop" on clinical trials for CJD run by the Department of Health and the Medical Research Council
- Co-chairing the steering committee for the prion-1 trial
- Co-chairing a "new therapies scrutiny group"
- Chairing monthly meetings of the two principal CJD research establishments in the United Kingdom, to try to ensure that they collaborated with each other, and
- Membership of the advisory group for a systematic review of treatments for prion disease.

Until I learnt otherwise I took the consumer workshop—a one day event at which families and carers were brought together and asked to help set research priorities—to be normal practice. A report was written that helped decide the way forward. I assumed that this was what always happened in planning clinical research; it seemed natural and made sense. I know now that the views of patients, their families, and even clinicians are rarely sought when research priorities are being decided.

CJD has been a high profile disease. (Within hours of being told of our son's diagnosis we were offered a strategy for coping with the media.) The Medical Research Council invited Iain Chalmers, founder of the Cochrane Collaboration, to chair the steering committee for the prion-1 trial. He agreed on two conditions, one of which was that he had the support of a lay person to co-chair the committee. I was approached to be the co-chairman and agreed. It seemed a normal and sensible thing to do: who else other than someone closely involved with the disease could help with some important elements in the design of the trial? Imagine my surprise



Who else other than someone closely involved with Creutzfeldt-Jakob disease could help with some important elements in the design of the prion-1 trial?

when I learnt that I was seen as an example of "cutting edge" involvement of lay people in clinical research. However, some of the researchers were deeply unhappy about my appointment, and much angst was to be experienced along the way. (My experience in banking helped to deal with this.)

In banking we try to research our customers' needs before we package a new product, so I was intrigued that we were embarking on a new clinical trial without any systematic review of existing evidence. Conducting such a review was the other condition on which Iain Chalmers had insisted. I accepted an invitation to join the advisory group for a systematic review. This review could have informed the design of the prion-1 trial, but it was eventually published four years after the trial began.

The new therapies scrutiny group was set up to take notice of emerging potential treatments for CJD so that new trials could be commissioned as necessary and to deal with any new discoveries that appeared on the front pages of the tabloid press. I was asked to co-chair the group alongside Michael Rawlins—like Iain Chalmers, another big hitter in medical research and currently chairman of the National Institute for Health and Clinical Excellence. This experience showed me that, if an emerging therapy does

not gain institutional favour, then it is easy for it—and the patients—to remain outside the establishment's embrace. Several children are receiving an alternative treatment (pentosan polysulfate) because their parents applied to the High Court for endorsement, but data on these children are still not being collected systematically under a standard protocol.

One of the key findings of the CJD clinical trials workshop was that, because of the very low numbers of cases of CJD, national collaboration was essential. To promote this collaboration it proved necessary to have a written agreement between the two leading UK institutions in CJD research. I chaired monthly meetings between them to try to nip potential conflicts in the bud and to protect patients' interests and care from the consequences of academic competition.

So what are my views as a result of these experiences? I'm wiser but sadder about what I have learnt. My views are inevitably biased and based on intimate knowledge of one orphan disease, albeit one with a high profile. Nevertheless, as an outsider—and a taxpayer—I have come to believe that:

- Involvement of patients and their professional and lay carers in shaping clinical research should be seen as normal and should be welcomed by researchers
- It is illogical to begin planning new research without first finding out systematically what can be known from existing research
- Unpleasant elements of competition among individuals are as present in the public world as they are in the grimy world of banking. Academic status and fiefdoms must take second place to patients' interests, particularly when funding for research is coming from the public purse, and there must be a totally open culture of sharing and publication, and
- Citizenship should encourage us all to know more about clinical trials and to participate in good trials, in the same way that we should all carry an organ donor card.

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A wise tour guide
to biology and
society,
p 117



REVIEW OF THE WEEK

The need for speed: the marketing of amphetamines

Amphetamines were for years a “drug looking for a disease.” **Allen Shaughnessy** considers a chronicle of their many uses in that time

Ask most doctors about methamphetamine and they will describe its ability to ruin many lives, causing a societal blight. Ask most doctors about methylphenidate and they will describe its valuable role in treating children and adults who can't focus. *On Speed* tracks “the many lives” of the amphetamines, from the discovery of amphetamine in 1929 to current use today as black market drugs of misuse and white market treatments for obesity and attention deficit hyperactivity disorder. Amphetamine started as a potent drug without a role—until one was created. The author characterises it as a “drug looking for a disease.” *On Speed* also traces the development of the market for amphetamines and the evolution of drug companies into the potent marketing machines they have become.

The first recorded use of amphetamine was by its developer, the biochemist Gordon Alles, who had a colleague inject him with 50 mg, five times more than what would become the usual dose. Concerned with its haemodynamic effect, Alles scrupulously recorded blood pressure readings for eight hours. In the margins he noted a “feeling of wellbeing.” In an addendum he noted, “Rather sleepless night. Mind seemed to run from one subject to another.”

Indeed. Such would become the hallmarks of amphetamine use. In the United States the effects of amphetamines were seen as “increasing pep” and making users more efficient. In Britain people admired its ability to make them feel confident, clever, and witty. Higher doses created aggressive soldiers in the battle theatre, unleashed creativity in the Beatnik generation, and served as a social lubricant for suburban parties.

Initial pursuit of a market for amphetamines considered all things neuropsychological, including alcoholism, schizophrenia, anxiety, bipolar disorder, dysmenorrhoea, Parkinson's disease, performance enhancement, and narcolepsy. After many misses amphetamine was marketed to treat depression, a diagnosis with only some similarity to its definition today. Early advertisements for the drug defined depression as heralded by a difficulty in thinking or acting, hypochondria, a “sensation of weakness,” and “apathy or discouragement,” allowing the drug to cut a wide swath through a doctor's day in the office.

At the same time amphetamine and methamphetamine gained a huge reputation as motivators of soldiers, a sanctioned role the drugs would play through to the end

of the Vietnam War. Used by both sides during the second world war, German troops consumed 35 million tablets of methamphetamine during the peak three months of the Blitzkrieg. The British military distributed 72 million tablets of amphetamine over the course of the war.

These “wakey wakeys” or “pepper uppers” were shown in many studies to be ineffective in improving work output and generally had a negative effect on judgment on the battlefield. However, amphetamines were prized by generals, who saw them increase morale and aggression, making men more determined to fight.

By the end of the war amphetamines enjoyed widespread use in many countries. Jazz artists would use high doses by opening plastic canisters of Benzedrine (amphetamine) inhalers sold without prescription for nasal congestion and eating the paper sections that contained 250 mg of the drug. The Beat generation fully embraced amphetamine use as an essential component of creativity. Legend has it that Jack Kerouac put a continuous roll of paper into his typewriter, went on an amphetamine bender, and pounded out *On the Road* in three weeks.

It wasn't until 1964 in Britain that possession of amphetamines without a prescription became a criminal offence. The eventual stiffer rules regarding the manufacture and sale of amphetamines did not decrease demand but simply set up different supply chains; with commonly available chemicals an amateur chemist can manufacture methamphetamine or its new cousins such as methylenedioxymphetamine (ecstasy).

The author also points out that licit makers of amphetamines had to find suitable commercial outlets, which they did by targeting overweight and underattentive people. The worldwide market in drugs to treat obesity is expected to expand to be worth some \$1.3bn by 2010 (*Nature Reviews Drug Discovery* 2002;1:257-8), a large part of it from the (legal) amphetamine sibutramine.

On Speed is a fascinating and thoroughly researched “biography” of a class of drugs for which markets had to be created. The history of amphetamines over the past 70 years shows the iron fisted grasp the drug industry has had and continues to have over the medical industry.

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On Speed: The Many Lives of Amphetamine

By Nicolas Rasmussen

New York University Press,
\$29.95, pp 352

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Rating: ★★★★★

The history of amphetamines over the past 70 years shows the iron fisted grasp the drug industry has had and continues to have over the medical industry

Medicine's living death

FROM THE
FRONTLINE
Des Spence



On Sunday afternoons we shuffle around Ikea's one way system with the identikit couples. Children whine and occasionally escape to bounce on a sofa. Eventually we find the various flat packs we need for the wardrobe. Then more queuing and the spontaneous purchase of lavender aromatherapy candles. At home we pore over the instructions and find that we need, seemingly, only a small allen key. Six angry hours later we beat the unrecognisable, pulverised plywood ball with a hammer, and decide that the only sensible option left is to burn the remains of the wardrobe in the back garden along with the aromatherapy candle. That's the problem with instructions—it depends who writes them and who reads them.

Medicine is full of written instruction. In the early 1990s I was grateful for some evidence pointers. Cochrane and the evidence based medicine teams did a fantastic job bringing order into the entirely archaic world of expert opinion. But this "evidence" left some discretion. Then, however, came the march of the guideline machines, and by 2000 things were getting out of hand. Getting three doctors together over a sponsored lunch gave rise to a new guideline, which lamentably would be laminated and circulated by tea time to all UK GPs. My own flow chart involved throwing them all straight into the waste paper bin

unread. Since then guidelines have become ever more restrictive and prescriptive.

But authors fail to understand or explain the severe limitation of the research, confounded by commissioning bias, publication bias, the stark lack of epidemiology, skewing of study groups. Evidence is treated like solid bricks rather than the shanty corrugated iron that it is. This is a slow garrotte of medical judgment. Doctors are under the constant spectre of litigation, haunted by the phrase "Did you follow the guideline, doctor?"

So discretion, once the keystone of the medical profession, is dead. It has been replaced by mass production medicine with lines of hunched shuffling patients, all treated the same with no thought to individual views or need. This is all in the name of quality assurance, governance, and driven by targets. No thought is given to the long term broader implications and there is no systematic process to evaluate the impact. I often want to ignore the guidelines, for they don't reflect the real world of work, but I simply can't. Our job is being reduced to a mere collection of algorithms to apply mindlessly in this NHS nanny health state. Where's that hammer?

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A real country herbalist

THE BEST
MEDICINE
Liam Farrell



My Auntie Mamie was a real countrywoman. A farmer's daughter, she married a farmer and spent her whole life milking cows, feeding pigs, growing vegetables, spreading manure (you can never have too much manure, she once told me), and smuggling petrol and cigarettes. We were a tactile family, and when she hugged you to her ample bosom both oxygen and light would be temporarily blocked out.

What she couldn't tell you about the earth didn't matter. She could identify every bird by its song, every creature by its footprint, every man by his bicycle. But it was no romantic idyll; the farm demanded hard and endless backbreaking graft, and her hands were stained with blood.

I'm probably the last generation to remember what it was like to kill what we eat. Every year a few days

were set aside for the slaughtering, and these days were very different from the others. The hay making and potato picking were sun filled days of laughter and stories and picnics and lemonade and ham sandwiches big enough to choke a horse and apple pies with pastry so thick you could have made shoes out of it, but on slaughtering days there was no laughter and no high spirits. They were sombre days; we paid our tribute to these creatures that we had raised, fed, and cared for by being sober and respectful. There was no room for sentimentality, but killing them as quietly and efficiently as possible was part of the unwritten contract.

Auntie Mamie was no invention of a Sunday magazine feature. She had the soil between her toes and underneath her nails (permanently). She had no affected nostalgia for the good old days; and

as soon as she could afford it she demolished her picturesque little thatched cottage (the thatch was always full of bugs, she said) and replaced it with a new bungalow, complete with aluminium windows. And when she or any member of her extended family (which ran into hundreds) was sick, she didn't go to the local wise woman, to the faith healer, to the new age shaman, to the kaftan wearing herbalist—she knew them for the blood sucking charlatans they were, and such middle class conceits had no meaning for her.

Instead she would go to her family doctor. The only use she ever had for herbs, she told me, was for stuffing a chicken to improve the taste.

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The neurotic heart

You can tell the age of an old book to within 20 or 30 years by such attributes as its font, the paper on which it is printed, and its cover. For example, there was a vogue at the end of the 19th century for covers of heavy boards with bevelled edges and coloured the deepest burgundy. They gave to the volume a weightiness that was not merely physical: read me and be serious, they seemed to say on behalf of the book within.

Medical works were often produced in this format, and I have a small collection of them. A surprising

proportion of them are inscribed "With the compliments of the author," suggesting either that they were more often given away by their authors than bought by strangers or that such an inscription was, and is, an aid to a volume's survival.

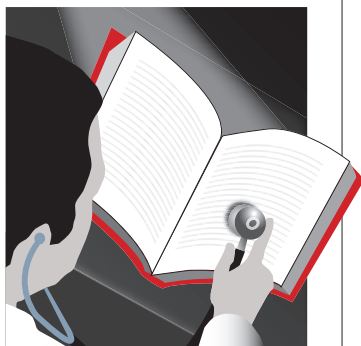
One such slender but weighty book is *Common Neuroses: Or the Neurotic Element in Disease and Its Rational Treatment*, by James Frederic Goodhart, published in 1894. It is a series of three lectures, on the subject of functional disorders, delivered to the Harveian Society in 1891 and reprinted from the *Lancet*.

The author was paediatrician to Guy's Hospital, later knighted for his services; but he dealt a great deal with adults in his private practice, and his book is mainly about them. My copy has clearly been read attentively by a medical practitioner, for the text is marked with pencil lines, and I can almost hear him sighing as he marks "Mrs. S" in the margin of this passage: "The next condition that requires mention is a very common one, and I can describe it no otherwise than as simple fatigue. 'I am always so tired,' say these men and women, but more often the latter than the former. 'I am tired when I get up in the morning and tired all day.'"

Having described phobic anxiety to open spaces and social situations, Dr

BETWEEN
THE LINES

Theodore Dalrymple



If the neuroscientists have their way, our successors may wonder a hundred years hence that the primitive concept of functional disease still existed in our time

Goodhart argues that pharmacotherapy is no good: "If we should have to do with a frightened horse that will not pass a certain spot, we do not send it to the veterinary surgeon that a bolus [of drugs] may be administered, but it is walked up and down before the object that disturbs it until its self-possession is regained."

And therefore, with humans: "The true method is to go and do all that comes to the hand to do, and thus to learn again that what had been thought impossible without a catastrophe is accomplished without ill result."

What is less reassuring about Dr Goodhart is that he ascribes the deafness that supervenes in Meniere's disease to neurosis. And at a time when comparatively little was known of heart disease he says: "No more common condition exists than the irregularity of the neurotic heart . . . it opens up a most interesting question: whether the irregularities of neurotic origin may not in the end lead to some failure of the muscle."

How does Dr Goodhart know that a young man whose "heart was tumbling around in a most extraordinary fashion" was neurotic? "It must suffice to say that the shape of his head, his whole bearing, and the previous history, showed conclusively that he was an extreme neurotic."

Just as Dr Goodhart did, we must practise according to the knowledge of our day. It is true that our science is infinitely more sophisticated than his, which was still fundamentally Baconian; but, if the neuroscientists have their way (as I hope and pray they do not), our successors may wonder a hundred years hence that the primitive concept of functional disease still existed in our time.

Theodore Dalrymple is a writer and retired doctor
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MEDICAL CLASSICS

The Lives of a Cell By Lewis Thomas

First published 1974

I decided to go to medical school towards the end of my college years in the United States and thus took only the absolute minimum number of premedical science courses. I worried about my lack of scientific preparation. In an attempt to remedy my deficiencies I took out a subscription to the *New England Journal of Medicine (NEJM)* when I began medical school in 1974. What a disappointment. I understood virtually nothing in the august journal, and what I did understand I found uninteresting. Lewis Thomas's *Notes of a Biology Watcher* column was the lone, wonderful, exception.

Thomas had begun writing his *NEJM* columns in 1971. A graduate of Princeton University and Harvard Medical School, he was a physician, immunology researcher, dean, poet, etymologist, and essayist. It is said that the journal's legendary editor, Franz Ingelfinger, offered him a monthly column for no pay but with the promise that he wouldn't be edited. Thomas accepted and wrote his monthly essays for 10 years.

I remember being enthralled by the columns. He seemed a wise tour guide with an encyclopaedic knowledge, who wrote clearly and beautifully about biology and society. I could understand everything he said, and he opened my eyes to subjects I never knew or cared about: obscure micro-organisms, organelles within cells, ants, termites. He connected microscopic particles and tiny animals to human biology and psychology. He was curious and speculative and seductively modest.

He gave me confidence that "basic" science was interesting and that medicine and basic science were actually connected—indeed, that society and medicine were linked and that it was important to understand both. Furthermore, it was great to realise that at least some doctors could write engagingly.

So it was with some trepidation that I began to reread *The Lives of a Cell*, the first book length compilation of Thomas's columns, after a gap of 30 years. I needn't have worried. The writing is still graceful, the perspective is intelligent, and the themes are, if anything, more relevant now than when they were written: the interdependence of different forms of life, the importance and universality of language, the process of scientific discovery. I was surprised at the modernity of some of his musings, about technology assessment, the difference between health care and medicine, and the important role of behaviour in health.

Thomas is endlessly quotable: "We might as well face up to it: there is a highly visible difference between the pace of basic science and the application of new knowledge to human problems." Or: "The great thing about human language is that it prevents us from sticking to the matter at hand." Thomas didn't invent the idea that the earth or human society can be seen as one huge cell, but he wrote with fascination and erudition about the interdependence of all living creatures.

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