VIEWS & REVIEWS

Why is Exubera being withdrawn?

PERSONAL VIEW **Clifford J Bailey, Anthony H Barnett**

On 18 October Pfizer announced that it would withdraw the first inhaled insulin, Exubera, from the market, as sales were too low. In January 2006 Pfizer bought the worldwide rights to Exubera from Sanofi-Aventis for \$1.3bn (£0.6bn; €0.9bn), and in August 2006 the product was introduced in Britain. In the first nine months of 2007, worldwide sales of Exubera amounted to \$12m, rather short of its projected \$2bn blockbuster status. Instead it will cost Pfizer an estimated \$2.8bn to “write it off.”

So why were sales of Exubera so far below expectations? Was it that labelling and national guidance were too restrictive? Did Pfizer not persist long enough for the market to open up? Was the cost too high? Was the inhalation device less convenient than anticipated? Was the dose equivalence confusing or inaccurate? Were there doubts over its long term safety? Was it because temporary cough can be irritating? Was it none, some, or all of the above?

Exubera's withdrawal has implications for the companies that make the insulin and the inhalers, as well as Nektar Therapeutics, which developed the inhaler. Nektar has yet to announce how it will proceed. Several other companies have inhaled insulin products in development, including Eli Lilly, Novo Nordisk, and the MannKind Corporation, and it is not yet clear how the withdrawal will affect these programmes, although the companies have said they intend to continue.

In principle the lungs offer several opportunities for the delivery of peptides. Their large surface area aids rapid absorption, administration is painless, and trial participants who use Exubera have reported a high level of satisfaction and acceptability. After careful evaluation, the US Food and Drug Administration and the European Medicines Agency were sufficiently satisfied about the product's safety to grant a licence, although with some important exclusions (such as cigarette smokers, people with major pulmonary disease, and children) and a

requirement for pulmonary function testing before patients started Exubera and then at intervals afterwards.

We believe this to be the first time that a licensed product for managing a common chronic disease has been withdrawn from the market so quickly for what would seem to be purely economic reasons. Despite any criticisms that might be levelled at Pfizer's marketing strategy, and practical difficulties with the device itself, it seems that restrictive guidelines may have contributed to the poor sales. In its preliminary consultation document the UK National Institute for Health and Clinical Excellence (NICE) did not recommend the use of Exubera at all, saying that cost effectiveness had not been shown. After comments from groups such as Diabetes UK, the Association of British Clinical Diabetologists, and various nurses' organisations, NICE softened its attitude and recommended use of Exubera, but only in patients with a true needle phobia or where there were major needle site problems (www.nice.org.uk/TA113quickrefguide).

The conclusions of NICE and similar bodies recommending Exubera only in restricted cases should send a warning to drug companies that their development programmes should look beyond what is needed to gain a licence: their studies may have to demonstrate cost effectiveness of the product and use in “real life” clinical practice situations. This may not be easy in the case of drugs for chronic diseases, given that hard data on outcomes are unlikely to be available by the time of the launch, so that surrogate

end points may still be needed to demonstrate cost utility.

NICE guidance and labelling restrictions made it almost impossible for clinicians to prescribe Exubera to many UK patients who might have benefited from this new technology, including people with poorly controlled type 2 diabetes who refused to start insulin treatment because they did not want to inject (rather than those with true needle phobia) and those with type 1 or type 2 diabetes who needed to intensify insulin treatment to improve control but would not do so because it would mean more injections.

What do we do about our patients who already take inhaled insulin? One of us (AHB) runs an inhaled insulin clinic for patients who fulfil the NICE criteria. The response among those who have been prescribed Exubera has been almost universally positive. What are we to tell them? The lifeline that they have been offered and have taken up has now been cruelly removed, and they will have to wait at least two years for alternative products to appear. We also have several patients who have been promised access to this new technology and who now have to be told that it is no longer available.

Perhaps more worrying, however—if the decision on Exubera is indeed solely economic (as seems to be the case)—is that drug companies may now be less inclined to speculate on the development of new products unless there is greater assurance over reimbursement. As a result the industry may reduce its commitment to research and development of novel compounds and concentrate in other areas, such as “me too” products. The appetite to invent and develop novel treatments may be suppressed. This is in nobody's interest, least of all our patients'. Clifford J Bailey (c.j.bailey@aston.ac.uk) is head of diabetes research, School of Life and Health Sciences, Aston University, Birmingham. Anthony H Barnett is clinical director of diabetes and endocrinology, University of Birmingham, Department of Medicine Undergraduate Centre, Heart of England NHS Foundation Trust, Birmingham.

[A longer version of this article with references is on *bmj.com*](#)

FRANK RUMPFENHORST/DPA/PA

A licensed product for managing a common chronic disease has been withdrawn from the market for what would seem to be purely economic reasons

The story of
English outbreaks
of the sweating
sickness, p 1159

REVIEW OF THE WEEK

A funny thing happened on the way to the lab

W F Bynum is impressed by a book about the role of chance in medical innovations

**Happy Accidents:
Serendipity in Modern
Medical Breakthroughs**

Morton A Meyers

Arcade Publishing, \$29.95,
pp 408

ISBN 978 1 55970 819 7

Rating: ★★☆☆

It is no news that science is messy. Louis Pasteur said it most famously: "Chance favours the prepared mind." His compatriot the physiologist Claude Bernard chipped in with: "Experimental ideas are often born by chance." The Nobel prize winner Peter Medawar probably argued it most subtly, when he wrote a paper, cheeky but serious, announcing that the scientific paper is a fraud. Medawar wasn't a whistleblower; he merely analysed, in his inimitable style, the fact that scientific papers routinely present the route to their results through a series of logical experiments, correct deductions, and obvious conclusions. In practice, things rarely go as expected. Abortive experiments are abandoned, and results are tidied up to be presented in their strongest form. This is normal experimental practice, although it took someone of Medawar's stature to make it public quite so blatantly.

It is significant that Morton Meyers draws his examples from major medical innovations and can usually draw on the authors of those discoveries to confess that something went wrong or that they found results they were not looking for. It is easy to confess that things were not all that neat when the result has won the researcher fame (and, often, fortune).

The phenomenon of serendipity in science and medicine is well known, but Meyers has collected a particularly well populated group of such discoveries and presented them in a chatty, readable fashion. In four sections he exposes the role of chance in the discovery of antibiotics, anticancer drugs, cardiovascular innovations, and psychopharmacology. The familiar examples are all here: Flem-

ing's exposed petri dish leading ultimately to penicillin; Waksman's work with soil bacteria that turned up streptomycin; the road from nitrogen mustard gas to cancer chemotherapy or from spoiled clover to coumarin.

Meyers has also scoured the literature and uncovered some less well known examples. Nearly all of the physical treatments in psychiatry seem to have been stumbled on. Short chapters detail the centrality of chance in the introduction of fever therapy for treating general paralysis of the insane, chemically and electrically induced shock, lobotomy, lithium, chlorpromazine, mephenesin, monoamine-oxidase inhibitors, tricyclic antidepressants, fluoxetine, chlordiazepoxide, diazepam, disulfiram, and LSD. In each case someone noticed something unexpected in the laboratory or clinic and was able to develop the observation further—or at least publish the paper that allowed others to do so.

Meyers has an eye for detail and anecdote, and the book is an excellent read. To his credit he unfolds his story within a reasonably sophisticated philosophy of discovery. We are treated to the role of "normal" and "revolutionary" science, as developed by Thomas Kuhn. One gets the impression that Meyers is no fan of the medical paper with 50 or more authors. Creativity, not teamwork, is the hero of this monograph.

Occasionally Meyers exaggerates the role of serendipity. For instance, Julius Wagner-Jauregg, who won a Nobel prize for his work on malaria infection as treatment for general paralysis of the insane, knew, as did many psychiatrists of the 1910s, about reports of psychotic patients improving after a bout of fever. His creativity, such as it

was, lay in devising a controlled way of giving patients a high temperature with vivax malaria, which could then be treated with quinine.

The messiness of modern drug discovery and marketing gets fairly short shrift in this account. Meyers is more likely to tell us how many Americans are taking anticoagulants, antidepressants, or tranquillisers, or what the first billion dollar cancer drug was than about side effects, inappropriate prescribing, or dubious claims by drug companies. When we do get such information it is presented in the blandest of terms, quite unlike the tone when Meyers describes original observations.

His cosy blandness is partially redeemed in his last chapter, when he castigates the pernicious lobbying and direct advertising strategies of modern drug companies in the United States. Even here Meyers blames but two of the three guilty parties: companies, for their direct advertising to the general public of expensive add-on drugs that have no benefit; and patients, for responding to such advertising and demanding the drugs from their doctors. But doctors, too, have a responsibility, notwithstanding Meyers' cogent criticisms of the US style medical marketplace.

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May the force be with you

FROM THE
FRONTLINE
Des Spence

"Use the force, Luke. Let go!" He turned off his targeting computer—certain folly! But the torpedoes went down the ventilation shaft and Death Star, the most advanced weapon to threaten the universe, exploded. The whole cinema whooped. My brother and I spent the next few years imaging we were duffle coated Jedi knights, following the code and saving the universe, and mimicking the noises and voices of *Stars Wars*. I am not sure whether I still believe in the force, but I do believe in something even more unlikely: clinical intuition.

It is hard to explain the ancient power of clinical intuition to the young "padawan" of the i-generation, whose only faith is the binary code of the microchip. But a few of us still believe. You can spot them: in general practice their garb is brown corduroys or tweed skirts and jackets with leather patches. In the hospital their trousers are too short and they wear the same shirt every day, but it is their footwear—comfortable brown Clark's shoes—that marks them apart. Understated and seemingly invisible, they quietly get on with clinical commitment in all the unfashionable corners of the NHS. Their colleagues, especially the young ones, shackled by evidence based

medicine, smirk at their mumbled ancient incantations, such as, "That just doesn't fit with the story," and, "There's something else going on."

But over many thousands of clinical contacts some vividly stand out where clinical intuition saved the day. Intuition is hard to put into words but is a sense that something somehow is just "not right." It is a change in the smooth and regular wave forms that radiate from patients—perhaps a change in the tone, pitch, or pace of their voice or a change in posture. But really intuition is just a feeling, a disturbance in the clinical force. These odd experiences are shared by many of us but are spoken of only in hushed voices, for fear of being overheard.

Clinical intuition is stronger in some people but is present in all of us. It is just a question of tuning in, letting go, and trusting. But this is medical heresy in these days of the randomised controlled trial and systematic review, in this evil empire of technological medicine. However, I will try to instruct students in the old ways for as long as I can, before the Empire's stormtroopers close in and I face banishment to the desolate planet of Protocol.

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Homoeopathy and the star that fell

PAST CARING
Wendy Moore

COLIN CRISFORD

Some are born great, some achieve greatness, and some tragically squander greatness in a hopelessly misguided obsession, launching centuries of self delusion.

Take Samuel Hahnemann. Born in Meissen in 1755, he displayed early brilliance in languages before opting to study medicine, graduating in 1779. Rapidly disillusioned by the barbaric practices of the day, Hahnemann condemned his peers' ignorant reliance on copious bloodletting, toxic purges, and caustic enemas. By contrast Hahnemann advocated the healing effects of a sensible diet, fresh air, plentiful exercise, and routine hygiene as "the preliminary conditions of wellbeing." His proposals for preventing epidemics in prisons urged well ventilated cells and regular washing of inmates, their clothes, and bedding.

Hahnemann devoted as much time to studying chemistry as medicine. And as one contemporary noted, he "would have made a great chemist"—or indeed a pioneering

public health doctor, enlightened psychiatrist, or champion of evidence based medicine—"had he not turned out a great quack."

Sadly his stellar trajectory faltered when he turned to investigating certain treatments by testing them on himself, in time honoured medical tradition, and alighted on cinchona, one of the few effective treatments of the time. Discovering that it produced symptoms similar to those of the ailment it treated—malaria—he vaulted to the conclusion that all effective medicines must show similar symptoms to the disease they cured.

So the principle of treating "like with like" was born and the enduring industry of homoeopathy emerged. Hahnemann expounded his doctrine in his *Organon der rationellen Heilkunde* (*Organon of Rational Healing*) in 1810. His views excited vociferous opposition and widespread support from the start.

Students attended his lectures in Leipzig only to mock, while the city authorities banned him from

practising in 1820. Yet Prince Karl of Schwarzenberg travelled expressly to the area so that Hahnemann could treat him after a stroke. The prince's death from a second stroke a few months later did nothing to deter continuing patronage from royalty over the ensuing centuries, which helped popularise homoeopathy throughout Europe and especially in England.

Given the fact that homoeopathic remedies were just as likely to work, and much less likely to harm, as the dangerous treatments offered by conventional physicians in Hahnemann's day, early 19th century patients might be excused their enthusiasm. Later advocates might like to consider Hahnemann's own creed: "One should proceed as rationally as possible by experiments of the medicines on the human body. Only by these means can the true nature, the real effect, of the medicinal substance be discovered."

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A longer version of this article giving sources is available on bmj.com

Grumpy old men

It is generally admitted, wrote R R Madden MD at the beginning of his book *The Infirmities of Genius Illustrated by Referring the Anomalies in the Literary Character to the Constitutional Peculiarities of Men of Genius*, published in 1833, that literary men are an irritable race, subject to many infirmities, both in mind and body. Worldly prosperity and domestic happiness are not often the result of their pursuits.

Fame and frailty, he says, are inseparable companions. This, he continues, is just as well; for it renders those of humbler capacities contented with their lot. Let us “thank God [we] are not like the . . . poor children of genius, frail in health, feeble in resolution, in small matters improvident, and unfortunate in most things.”

Madden was an Irish doctor who served in the tropics, wrote a book of his travels in Turkey and a history of the United Irishmen, and translated *Poems by a Slave in the Island of Cuba, Recently Liberated*, as well as *The History of the Early Life of the Negro Poet, Written by Himself*, published in 1840, when slavery had many years still to run in Cuba.

To what did Dr Madden attribute the irritability of literary men? Unfortunately, like many medical writers of the time, he was not clear or precise in his hypothesising. Most of his examples—Pope, Johnson, Burns, for example—had what he called “dyspepsia,” a protean disorder that accounted for palpitations of the heart, depression of the spirits, and nervous pains in the head. Sometimes this dyspepsia preceded, and sometimes followed, literary endeavours.

At any rate, the dyspepsia disturbed “the functions of the brain” and “ultimately debilitated that organ, and left it no longer able to resist the effects of the constant exercise of the mental faculties.”

BETWEEN THE LINES

Theodore Dalrymple

Most of Madden's examples had what he called “dyspepsia,” a protean disorder that accounted for palpitations of the heart, depression of the spirits, and nervous pains in the head

This led to “alteration in the structure, softening of its substance, or effusion serous or sanguineous.”

We believe something different now: that mental activity preserves the faculties. Where we say, “Use it or lose it,” they said, “Use it and lose it.”

Sixty-one years after Madden published his book about the infirmities of literary men, a scion of the famous Tuke family, J Batty Tuke, delivered the Morison Lectures in Edinburgh entitled “The Insanity of Over-Exertion of the Brain.” (Is it not

strange how men with the names Madden and Batty should have been interested in insanity, while Henry Head and Russell Brain became neurologists?)

According to Tuke, over-exertion of the frontal lobes and exhaustion of the neurones by chronic emotion led to Wallerian degeneration. Thus, in treatment, “the first object to be obtained is REST for the brain.” The madman must be put to bed.

Dr Tuke continues, “I need not tell you that the physician is most powerful in the sick-room or hospital, and that he strengthens his position when he orders the patient to bed. Even in cases which at first resent the order, as soon as it is obeyed no difficulty arises in maintaining it. A good nurse, or even two may be necessary.”

We may smile pityingly: but will not our descendants smile at us? Besides, many of my patients asked for help to stop thinking, not any thoughts in particular, but all thoughts whatsoever. They are tired of thought and its responsibilities. I suppose this is one of the reasons that meditation is so popular.

Theodore Dalrymple is a writer and retired doctor

MEDICAL CLASSICS

A Boke or Counsell against the Disease Commonly Called the Sweate or the Sweating Sickness By John Caius

First published 1552

Sweating sickness was a disease of unknown cause and very high mortality that first appeared in England in 1485. John Caius's book is our main source of knowledge about the disease, outbreaks of which recurred until 1578.

John Caius was born in Norwich in 1510. He entered Gonville Hall in Cambridge in 1529 and then moved to Padua to study under Vesalius. He refounded his former college as Gonville and Caius College and became its master. In the first part of his book Caius describes the disease as “not a sweat onely (as it is thought or called) but a fever.” It lasted 24 hours, with pain in the arms, legs, back, and shoulders, followed by a “marvellous heaviness, and a desire to sleepe.”

Dengue fever (“break bone fever”) seems the most likely candidate, although it usually lasts more than 24 hours and is often accompanied by a rash, which the book doesn't mention. At a time when conditions in England were favourable to the ague (malaria), it is plausible that dengue fever, another mosquito-borne disease, would also be prevalent.

Caius then deals with the causes of the condition: “infection” and “impure spirites in bodies corrupt by repletion [overeating].” Infection is due to “evil mistes and exhalations drawn out of the grounde.” Repletion,

from eating too much meat, bad meat, or rotten fruit, causes an “excess of humores” to develop.

He then discusses “preservacion” (prevention). He recommends a long list of meat, fish, and fruit to eat. In his view people have become effete: “But we are nowe a daies so unwisely fine, and

Caius: Galenical teaching womanly delicate, that we may in no wise touch a fische. The olde manly hardnes, stoute courage, & painefulnes of Englande is utterly driven awaye, in the stede whereof, men now a daies receive womanlines & become nice, not able to withstande a blaste of wynde, or resiste a poore fische.”

Caius then goes on to describe “the cure or remedy.” The most important thing is to let out the poison by sweating, he says. He recommends numerous herbs, such as “wilde tansy, mogwort [common wormwood] or feverfew.” Sweating should be provoked by gentle rubbing and warm drinks. The patient's nose and ears should be pulled to prevent sleep. After 24 hours have passed the patient may get up and put on warm clothes but not go out for two days. Finally, Caius says, “If other causes ther be supernatural, theim I leve to the divines to serche, and the diseases thereof to cure, as a matter with out the compasse of my facultie.”

Although Vesalius was beginning to discard Galenical medicine, Caius clearly still clung to Galen's teaching. Despite sweating being an important symptom of the disease, it is curious that Caius lays great emphasis on the induction of sweating as part of the cure.

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