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EDITORIAL

Inhaled insulin: gone with the wind?

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Rainbow's end

Yesterday it was going to sweep the world; today it is gone. Exubera is no more: there was no money in it. As for the patients who volunteered to test the new therapy, and those to whom it has offered a new lease of life: tough luck. Pfizer took a look at the bottom line and decided to quit. Their statement on 18 October 2007 [1], announcing the withdrawal of Exubera, contained no apologies, expressed no regrets, and offered no special provision for the patients who have come to depend on this heavily promoted therapy. 'Despite best efforts,' it said, 'Exubera has failed to gain the acceptance of patients and physicians.' We didn't totally misjudge the market, the statement implied, the market let us down. So, what have the rest of us lost, what have we learned, and where do we go from here?

Dangerous safety

There have always been two sides to diabetes: safety and danger. As Thomas Watson [2] said long ago, 'It is better to keep a man on the edge of a precipice, if you cannot pluck him away from it, than to let him fall over. And many diabetic patients are kept in this predicament of dangerous safety.' Chris Feudtner developed this idea in a book called *Bittersweet,* which chronicles the experience of patients attending the Joslin Clinic in the early days of insulin therapy [3]. For them, insulin held out the sweetness of life; the bitterness lay in the fact that insulin brings dangers of its own, and symbolises a lifetime of discomfort and denial. The natural history of diabetes, as Feudtner points out, means something different for patient and physician. The physician perceives it in terms of complications, but the patient perceives it in terms of a tedious and unending routine. To this day, when the physician says 'diabetes' to a newly diagnosed patient, the patient hears only 'insulin'.

The need for injections, with all their pain and discomfort, together with the problem of allergic reactions, dominated the early years of the insulin era. People have always wanted an alternative. The first paper on inhalation came out in 1924 [4], and other routes, such as transdermal, oral, nasal, intestinal and rectal were actively explored [5, 6]. The conclusion was that insulin can cross any mucosal surface, but that most of it gets lost in the process. Injections, as was learned 80 years ago, are the most reliable and effective means of insulin administration (Fig. 1).

Happily for our patients, the technology of diabetes care has improved beyond measure over the same interval. Needles are shorter, sharper and silicone tipped, and pen injectors have transformed a messy ritual into an unobtrusive manoeuvre that can be performed in a crowded restaurant. Injections still hurt, but they have become more acceptable. Repeated surveys show that they remain the leading cause of anxiety for newly diagnosed patients, but drop rapidly down the league table of concerns over the months that follow, compared with the other tasks and restrictions of diabetes. Physicians, who once reflected their

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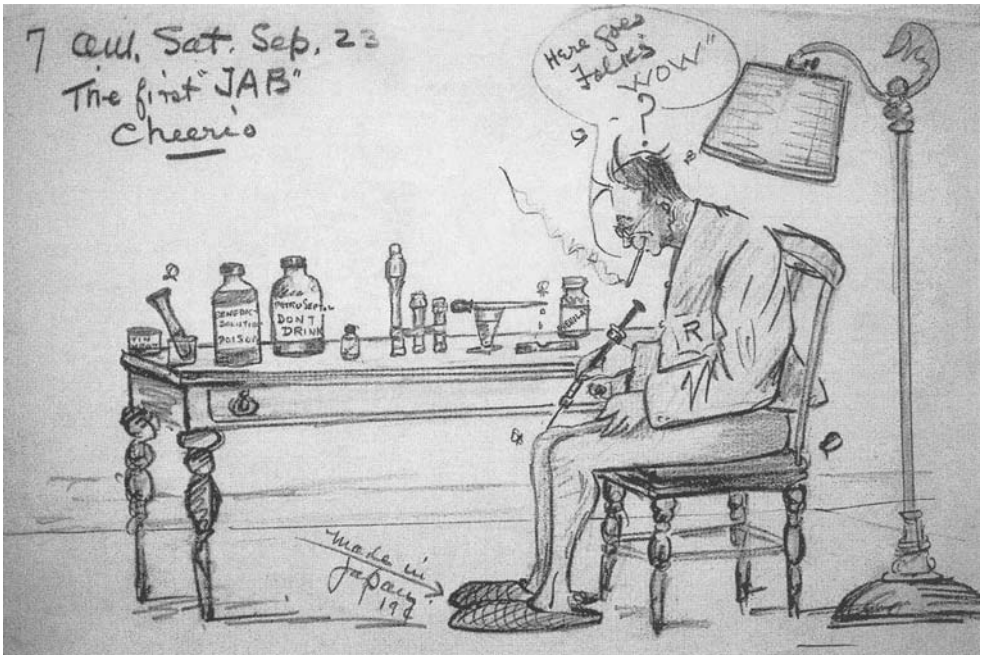

Fig. 1 'First Jab.' Guy Rainsford cartoon. Courtesy of the Joslin Diabetes Center

own fear of the needle back onto the people they treated, have learned—from their patients—that it is no kindness to delay the first injection of insulin, or the introduction of flexible multi-dose therapy.

Nonetheless, the dream of freedom from the needle persists, and rightly so: no one could watch a small child preparing to inject without wishing for a better alternative. The financial motive proved even more potent, for companies need investors, and investors have always been more than willing to waste their money on needle-free systems of insulin administration. NovoNordisk made the first major attempt to bring a non-injectable insulin to market with nasal insulin. Experience soon showed that this was not a realistic alternative, for despite the advantage of rapid absorption, bioavailability was low (the nasal dose needed to be 20-fold greater than the injected dose) and the rate of treatment failure unacceptably high [7]. The success of insulin pens may also help to explain why the project was quietly dropped.

At around this time Pfizer, a pharmaceutical giant with little track record in diabetes, teamed with Hoechst (later Aventis, later Sanofi-Aventis) to license a concept developed by Nektar, a small US biotech company. Inhalation therapy is based on the vast surface area of the alveoli (about 100 m^2, equivalent to half a singles tennis court), plus the observation that small proteins such as insulin (molecular mass 5700, diameter 2.2 nm) are readily absorbed from the alveoli into the circulation [8]. The problem is getting the insulin into the alveoli, for it is otherwise wasted within the pulmonary tree. Pfizer opted for an aerosol that dispersed dry insulin into very fine particles, without the use of absorption enhancers [9]. Patient expectations were high, and were further inflated by lavish promotion. The product was named Exubera, an ironic testimonial to the exuberant claims made on its behalf.

Despite an auspicious start, the regulatory trail proved arduous, for the new product had to stand comparison with the safety record of subcutaneous insulin administration. The first Phase 2 trials were completed by 1998, but not published until 2001 [10], for the product had encountered a snag: pulmonary function testing revealed a minor restrictive effect of therapy (see below). Subsequent experience tends to the view that this effect is non-progressive and reversible, but the regulatory authorities were not prepared to take a bet on it. The US Food and Drug Administration and other agencies therefore mandated pulmonary function testing.

By the time of its launch in 2006, over 2,500 patients had been treated, with a total exposure of more than 4,000 patient-years. Efficacy studies showed that Exubera was more rapidly absorbed than soluble insulin, and had a longer duration of effect. Dose-to-dose variability was comparable to regular insulin [8]. So far, so good. There were however a number of formidable limiting factors to its use. To begin with, the inhaler was bulky, awkward to use and difficult to dismantle; a later version was to be smaller, more user-friendly, and disposable, but reached the market too late. Dosing was complicated by the curious decision to dispense Exubera in milligrams rather than units. Although scientifically sound, doctors and nurses were now obliged to convert milligrams into units. Dosing was also inflexible: the powder comes in blister packs of 1 and 3 mg (corresponding approximately to 3 and 8 units), which then had to be combined to make up

the dose. The tedium of inhaling 36 units can easily be imagined. Conversely, this inflexibility also limited use in patients who are very sensitive to insulin, in whom 1 unit either way can make a big difference. Add to this the higher cost of inhaled insulin, the mandatory requirement for pulmonary function testing, the need to document needle phobia in countries such as the UK, and the unavoidable need to carry on injecting basal insulins, and it is easy to see that only the most determined of patients would feel inclined to persevere with this line of therapy.

Worse still, from the marketing standpoint, the insulin market was changing rapidly. Pens greatly simplified the speed and ease of injection, and the rapid-acting insulins (comparison with which was avoided) diminished the advantage conferred by the rapid uptake of inhaled insulin. Pen injection, already standard in much of Europe, spread rapidly in the USA, and especially when combined with the new analogues, already offered a much more flexible lifestyle for users of insulin.

Other companies were also interested in insulin inhalation. At least three other approaches are in development: AERx (NovoNordisk with Aradigm), AIR (Lilly with Alkermes) and inhaled insulin using Technosfere technology (Mannkind) [11]. Each has learned from Exubera and opted for flexible dosing, smaller devices and insulin dispensed in international units. Experience has shown that inhaled insulin works, achieving glycaemic control comparable to conventional insulin regimens in patients with type 1 diabetes. But is it safe? Is it needed? And will anyone ever make a profit from it?

Is it safe?

The lung is a relatively unexplored route of delivery for bioactive peptides, and there have been three major concerns in relation to insulin. The first, as mentioned above, relates to lung function. Exubera produces small, but consistent, decreases in FEV_1 (the amount of air exhaled in 1 s) and the DLCO (diffusion capacity of the lung) within the first week or so of treatment [12]; it is not yet clear whether the same applies to its competitors. The effect is minor, arguably non-progressive and reversible, and is not in itself a bar to inhalation therapy. The extensive lung safety programmes did however bring to light something previously described but largely overlooked: that there is such a thing as the diabetic lung [13]. People with diabetes have a reduced FEV_1 compared with non-diabetics, presumably as a result of microangiopathic or interstitial changes within the alveoli. So, do we risk converting a subclinical defect into a clinical problem by exposing the lungs to insulin? Experience to date is relatively reassuring, but the issue has not been laid to rest.

A second concern relates to the development of antibodies. The lung is immunologically very active, and peptides are not presented in the same way as under the skin [14]. Inhaled insulin, as it emerged, promotes more antibody formation than injected insulin, especially in those with type 1 diabetes. As in other situations in which the question has arisen, there was no correlation between insulin antibody levels and glycaemic control or rates of hypoglycaemia [15], but the observation contributes to our unease as we enter this hitherto unexplored territory. To underline the same point, we come to the third concern: insulin has trophic effects and is potentially carcinogenic. The risk of cancer formation may be small or non-existent, but cannot be fully excluded in the long term [16].

Do we need inhaled insulin?

Inhaled insulin is a luxury. We may desire it, but we don't need it. It has no unique advantage other than route of delivery, and there are cheaper and more effective means of administration. Its launch was based on presumed demand, backed by patient preference surveys, which, as we shall see, were deeply flawed. It was perceived demand that drove Exubera through the regulatory and reimbursement agencies in several countries, despite its high price. Even the National Institute for Health and Clinical Excellence (NICE) succumbed. But in the final analysis, and as many experienced physicians had predicted, the vast majority of informed patients voted to carry on with their needles.

Does this mean that there is no place for inhaled insulin? Not at all. We have lost a battle, but the war will continue. We do however need to scrutinise the rationale for its use with greater care. To begin with, everyone in the world of diabetes would wish for a viable alternative to insulin injections. Children have already been mentioned, and it would be highly desirable for adults also to be able to make a choice. Many have seen insulin inhalation as a convenient stepping stone to more conventional insulin therapy in, for example, those with type 2 diabetes who hesitate to take their first step in this direction. But, as everyone who works with patients will be aware, the imagined horrors of insulin injection greatly outstrip the reality, and most patients will make a smooth transition to insulin with the help of sympathetic counselling and support.

Most, but not quite all. A few patients simply refuse to take this step, and they too very much need our sympathy and support. 'Needle phobia' is an elusive concept, as NICE discovered, and comes in many shapes and forms. For practical purposes, it might be defined as an informed choice to sacrifice one's health and well-being rather than to submit to injections. This extreme form is mercifully rare, but less extreme—or less informed—degrees of

psychological resistance are relatively common in type 2 diabetes, and contribute to the burden of its complications. Few readers would doubt that education and emotional support are generally preferable to a gadget, but when all else fails, gadgets can be very useful. Inhaled insulin has already created its own need, and its withdrawal will generate considerable distress among those who currently rely on it. But as things stand, inhaled insulin meets a niche demand, and thus risks becoming an orphan drug.

Will there ever be a market for inhaled insulin?

The news on Exubera will inevitably provoke a reality check within the industry. On the face of it, the prospects do not look good. Merrill Lynch, in a Company Update issued on 24 October 2007, rated the chances of regulatory approval for Air Insulin (Eli Lilly and Alkermes) at 50%, and down-rated their estimate of 'peak global probably adjusted sales' at less than US $150 million [17]. Given that the development costs will greatly exceed this figure, it would take a brave decision to continue. But the story need not end here. Inhaled insulin is a viable form of therapy, and could potentially reach a much wider market. To do so however it would need to fulfil a number of searching criteria:

Safety Longer term safety data will be needed with respect to pulmonary function, but the theoretical risk of carcinogenicity, which has been raised with every new insulin preparation, should not prove a bar to further carefully monitored development.

Cost Inhaled insulin would need to be marketed at a competitive cost. As with most other drugs, commercial insulins are currently marketed at well above their production cost, and cheap large-scale production of generic human insulin could enable the price of subcutaneous insulin to be matched, despite the difference in bioavailability.

Convenience It will always be quicker and easier to inject insulin than to inhale it, but better, smaller devices could help to narrow the margin.

Competitiveness Current comparisons with injection regimens have been based on soluble (regular) human insulin, and the regulatory concept of non-inferiority. Future comparisons must be with optimised regimens using rapid-acting analogues, and will need to reach a higher standard of proof—second-best is not an option when it comes to glucose control.

What went wrong?

It is always easy to be wise after the event, although the warnings were there for those prepared to notice them [10]. Each new drug for diabetes is however launched on a cloud of uncritical optimism, often supported by over-optimistic reviews in the medical literature. Even so, it is revealing to ask why Pfizer, in earnest pursuit of another blockbuster, could have got things so hopelessly wrong. The answer, we believe, lies in the clash of two cultures: the culture of marketing and the culture of diabetes. Pfizer has been commended in some circles for its policy of putting a member of the marketing department in charge of each product development team [18]. Marketing, as we may observe, stands in relation to reality as heat stands to butter: therein lies its success. Totally ignoring the culture of diabetes—to which we will turn in a moment—the company assumed, as anyone who knows nothing about diabetes would, that the insulin injection is an evil to be avoided at all costs. Given this assumption, the rest followed naturally. Patient preference studies were typically based on surveys of patients *who had volunteered for trials of inhaled insulin*. Not surprisingly, those who were randomised to inhaled insulin were satisfied, and the others were not. On the same ruling assumption, negative signals were studiously ignored, despite all the practical obstacles described earlier. As the old saying has it, there are none so blind as those who will not see.

The retreat from Exubera conveys a further worrying signal. Drug development is driven by business, and business is driven by profit. Investors thus determine the direction of future therapy. Large pharmaceutical companies are relatively safe and profitable to invest in, provided the blockbusters keep coming, but—as the story of inhaled insulin has shown—innovative therapies tend to come from the smaller start-up businesses. This is all to the good, for patients can only benefit from greater diversity and more individually tailored therapy. The worrying signal from Exubera is that if the hurdle of drug development is too high, and the market too small, the necessary investment may never be made.

And, finally, what of diabetes? Diabetes, if diagnosed early, is nothing more than a very tiresome set of risk factors. These often enough progress from functional disturbance to structural damage, but this progression is by no means inevitable and can be prevented by effective management. Hence the concept of dangerous safety. Diabetes, as it is lived, is not a disease but a subculture. A subculture sets people apart from the rest of society in one key respect, e.g. religion or sexual orientation, but unites them in another. Membership of a subculture, often invisible to outsiders, carries with it a unique shared experience, a common language, and its own set of

recognition signals. Everyone who has the privilege of working with people with diabetes will understand this. Insulin injection carries automatic membership, but there are other entry levels to the subculture for those with diabetes without insulin, and for fellow travellers. We, as health professionals, fall into the latter category. Diabetes management is all about people with diabetes, and the speaker who, for example, states that a certain therapy will lower HbA_{1c} by 0.7% is clearly an outsider, let alone a self-confessed ignoramus. It is not that people with diabetes love their insulin injections, far from it, but they do know what works for them, and what doesn't.

So it was that Pfizer came, failed to see, and failed to conquer. And to all the patients who helped them with their studies, many of whom now depend on their product, to the medical teams who gave them their support, and to all who saw inhaled insulin as offering hope for the future, they have responded with the immortal words of Rhett Butler: 'Frankly, my dear, I don't give a damn.'

Duality of Interest C. Mathieu has consulted for Pfizer, NovoNordisk, Eli Lilly and Mannkind. E. A. M. Gale has no duality of interest to declare.

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