Concept, Strategies, and Feasibility of Noninvasive Insulin Delivery

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OBJECTIVE — To comprehensively review the progress to date on the development of alternative routes for insulin delivery.

RESEARCH DESIGN AND METHODS — Study data were collected through a Medline review.

RESULTS — Proof of principle has been established for many routes of administration including dermal, nasal, oral, buccal, and pulmonary insulin delivery.

CONCLUSIONS — Of all the approaches to date, pulmonary delivery appears to be most feasible. Ongoing phase III studies will ultimately determine safety, tolerability, and efficacy before approval for clinical use.

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The therapeutic insulin era began on 11 January 1922 with the first clinical use of insulin by Banting and Best. In <2 years, insulin moved "from the realm of hypothesis to the reality of treatment" (1). In the ensuing 80 years, scientists uncovered the basic pathophysiology of diabetes, gradually elucidated insulin's structure, and focused their attention on developing better insulin formulations (e.g., NPH, lente). In this regard, the development and availability of rapid-acting (e.g., lispro, aspart) and basal insulins (e.g., glargine) have allowed for the routine use of very physiological insulin regimens.

However, despite significant research, the first effective noninvasive delivery systems for insulin are only now in development, marking a new milestone in effective management of diabetes. There is a clinical need for such because insulin therapy is central to the treatment of people with type 1 diabetes. Intensive insulin therapy, in particular, is associated with better long-term clinical outcomes. The progressive decrease in β-cell function evident in the pathogenesis of type 2 diabetes means that the majority of patients will eventually fail on oral therapy and will require insulin therapy at some point. Furthermore, oral agent failure is just one of a number of situations where insulin therapy might be indicated in patients with type 2 diabetes (2).

Despite the benefits of tight glycemic control, which ultimately can only be achieved with insulin in type 2 diabetic patients, there is reluctance on the part of physicians and patients to initiate insulin therapy (2). Factors such as weight gain, social stigma, lifestyle restriction, injection anxiety, sense of guilt or failure, and perception of worsening disease may affect patients' attitudes. Although hypoglycemia and weight gain are also perceived as barriers, these factors should not discourage the start of insulin. This reluctance contributes to poor glycemic control, and any advances that can help to minimize such concerns clearly have a place in diabetes management.

NONINVASIVE INSULIN DELIVERY

— Originally, insulin was administered intramuscularly. It soon became clear that subcutaneous injections were just as effective but considerably less traumatic (3). Over the years, researchers have suggested transdermal, ocular, oral, buccal, nasal, rectal, vaginal, and uterine delivery systems (3,4). However, subcutaneous administration has remained the route of choice, although the original researchers recognized the limitations. Best wrote the following in 1974: "We hope for and expect more physiological methods of giving insulin" (1).

Until recently, many believed the low bioavailability of insulin delivered noninvasively meant such methods would not be clinically realistic. This view is no longer sustainable in light of recent history, and during the next few years, several novel delivery devices could be launched that may result in improved glycemic control for many patients.

The following exemplify the different approaches tried during the history of insulin delivery and the current status of development (Table 1).

Jet injectors

Jet injectors are devices that administer insulin without needles by delivering a high-pressure stream of insulin into subcutaneous tissue and were first proposed over 40 years ago (3,5). It was suggested that insulin doses delivered may be more precise and more quickly absorbed than subcutaneous needle delivery; but in reality, the time-action profile of intermediate-acting insulin may be altered with these devices (5). Further, discomfort associated with this technique may be comparable to, if not greater than, that associated with injections. This method may benefit selected cases, such as those

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Abbreviations: DL_{CO}, carbon monoxide diffusing capacity; HIM2, hexyl-insulin-monoconjugate-2; iDMS, insulin diabetes management system.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Potential noninvasive insulin delivery options*

- Jet injectors
  - Deliver high pressure stream of insulin
  - May benefit selected cases (e.g., severe lipoatrophy); suggested that use be advocated only for those who develop problems with other injection routes
- Transdermal
  - Iontophoresis
    - Electrical current used to enhance transdermal insulin delivery; proof-of-principle from animal studies; human studies needed
  - Low-frequency ultrasound
    - Use of low-frequency sound wave to augment delivery of insulin and other macromolecules across human skin
  - Transfersomes
    - Composite phosphatidylcholine-based vesicles with similar permeability to water, although 1,000 times larger
    - Transdermal delivery of insulin with bioefficiency ≥50% of the subcutaneous dose
    - Administration over a 40-cm^2 skin area may supply sufficient basal insulin to a typical type 1 diabetic patient
- Intranasal
  - Nasal administration of certain proteins (e.g., oxytocin, desmopressin, and calcitonin) is now well established
  - Permeability enhancers are generally required to augment insulin bioavailability; insulin bioavailability is typically in the range of 8–15% with enhancers
  - Nasal irritation is common (e.g., with lecithin, bile salts, or laureth-9 as enhancers).
  - Nasal tolerance and high rates of treatment failure are major limitations
  - Recent clinical studies have shown more promising results (e.g., with gelified nasal insulin)
- Oral
  - Enteric
    - Oral enteric insulin delivery has limited bioavailability
    - Insulin is too large and hydrophillic to readily cross the intestinal mucosa
    - Polypeptides undergo extensive enzymatic and chemical degardation
    - Only around 0.5% of a dose of oral insulin reaches the systemic circulation
    - Several methods used to promote bioavailability
    - Ongoing phase I and II clinical trials with new formulation suggest a bioavailability of ~5%, which may result in an acceptable glucose-lowering effect
  - Buccal
    - Liquid aerosol insulin is sprayed into the buccal cavity without entering the airways
    - A liquid formulation of human recombinant insulin with added enhancers, stabilizers, and a non-chlorofluorocarbon propellant delivered via a metered dose inhaler in clinical trials
    - Efficacy studies are preliminary and safety reports are scarce
- Pulmonary
  - High permeability and large surface area provide a favorable anatomy for protein/drug uptake
  - Very rapid absorption of insulin after inhalation mimics time-activity profile of fast-acting insulin; appropriate for premeal delivery
  - Appears comparable to subcutaneous insulin on glycemic parameters for both type 1 and type 2 diabetic patients
  - Several pulmonary insulin delivery systems are in development and in phase III testing (see Fig. 1)

with severe insulin-induced lipoatrophy (3). However, it has been suggested that jet injectors should be advocated only for people who develop problems with other injection routes (5).

Transdermal

Human skin is an extremely effective barrier in protecting against the entry of foreign proteins. Attempts to overcome this skin barrier to allow insulin transfer have included techniques to weaken the barrier with chemical substances, ultrasound techniques, or electric current (6).

Iontophoresis. Iontophoresis refers to the concept of achieving transdermal delivery of a protein (e.g., insulin) by direct electric current. An analogous concept may be the passive transdermal medication patches currently used to deliver nicotine for smoking cessation programs or hormone therapy for postmenopausal women. However, iontopheresis differs by using a low-level electrical current in the process, enhancing the delivery of drug ions into the skin and surrounding tissues. Depending on the net charge of the insulin molecule, the applied electrical potential has been shown to increase the rate of insulin transfer across skin (6,7). Proof of concept has been shown in studies demonstrating that iontophoretic delivery of bovine insulin in a study of depilated diabetic rats produced a concentration-dependent reduction in plasma glucose levels (8). Interestingly, efficacy did not appear as high in nondepilated rats. This result suggests that the creams used acted as a penetration enhancer only in animals treated in advance with a depilatory cream, rather than having their hair removed with scissors, or that the depilation per se was effective in reducing the skin's barrier function. However, iontophoretic delivery of a monomeric human insulin analog produced a significant fall in plasma glucose in the rats, suggesting that the type of insulin may be a factor (8). With this technique, the rate of insulin transfer may be appropriate for the coverage of basal insulin requirements (6).

Low-frequency ultrasound. Low-frequency ultrasound has been demon-

strated to increase, by severalfold, the permeability of human skin to macromolecules. Researchers estimate that permeability achieved by 1 h of sonophoresis performed three times daily would allow a typical daily dose of insulin (~36 units) to be delivered via a transdermal patch (9). Although this approach is potentially feasible, the insulin delivery rate may not provide for physiological replacement.

Transfersomes. Transfersomes are lipid vesicles made of soybean phosphatidylcholine that are flexible enough to pass through pores much smaller than themselves with a similar permeability to water, despite being much larger (10). Animal and human data demonstrate that when the vesicles are loaded with insulin and applied to intact skin in a sufficient quantity, glucose levels are significantly reduced because it is observed that transfersomes transport the insulin with at least 50% of the bioefficiency of a subcutaneous injection (10). The application of insulin-laden transfersomes over a skin area ≤40 cm^2 would provide the daily basal insulin needs of a typical patient with type 1 diabetes according to research estimates (10).

Intranasal

Nasal administration of certain proteins—such as oxytocin, desmopressin, and calcitonin—is well established. These are highly potent molecules that are smaller than insulin (4). Insulin delivered using nasal administration reaches the systemic circulation, although various factors—including dose, timing, and frequency of administrations—influence its bioavailability. For this reason, most nasal formulations incorporate permeability enhancers to augment the low bioavailability to levels typically between 8 and 15% (11,12). However, these can cause nasal irritation—a formulation based on lecithin was associated with nasal irritation, and up to 100% of patients report irritation with formulations containing bile salts, whereas 25–50% experienced irritation with laureth-9 (12–14).

A study in 17 subjects with type 2 diabetes concluded that intranasal insulin could be effective in reducing postprandial glycemia by 50–70% (15). However, a study involving 31 subjects with type 1 diabetes found that the intranasal insulin dose needed to reach given markers of glycemic control was some 20 times higher than that of subcutaneous administration. Moreover, serum insulin concentrations increased more rapidly and declined more quickly during nasal administration than during subcutaneous administration (16). The authors concluded that intranasal insulin treatment was not a realistic alternative to subcutaneous insulin because of the low bioavailability and high rate of treatment failure.

Two recent studies in small numbers of people with diabetes report more encouraging results. One of ten severely hyperglycemic subjects with type 2 diabetes, who had failed on oral agents, reported that three preprandial doses of intranasal insulin (with or without one bedtime injection of NPH) gave comparable glycemic control to NPH b.i.d., although mean HbA_{1c} levels were high (9.4 ± 0.5 vs. 8.8 ± 0.2%). Nasal insulin alone achieved adequate glycemic control in 3 of the 10 subjects (7.6 ± 0.3%) (17). A 6-month study of a gelified sprayed nasal insulin containing absorption promoters in 16 subjects with type 1 diabetes showed that twice-daily NPH plus three preprandial nasal insulin doses (plus nasal supplementation in case of unexpected hyperglycemia) was as efficient as NPH b.i.d. plus three preprandial regular insulin injections. Although nasal tolerance appeared better than that with the previously reported lyophilized form, 4 of the 16 subjects discontinued because of treatment-related side effects. It was suggested that the absorption promoters played an additional role in intolerance (18). Nasal administration appears promising, but intolerance and high rates of treatment failure may prove difficult to overcome.

Oral enteric

Insulin's oral bioavailability is limited because *1)* insulin is too large and hydrophilic to readily cross the intestinal mucosa and 2) polypeptides undergo extensive enzymatic and chemical degradation, in particular by α-chymotrypsin (19,20). In the case of insulin, this enzymatic barrier is more important than that posed by the mucosa (19). Another major barrier for oral insulin administration, besides gastrointestinal proteolysis, is that no selective transport mechanism exists (6). The epithelial cells of the intestine do not normally transport macromolecules such as insulin and therefore may require extremely high doses to achieve some measurable insulin absorption (6,21). Other barriers that exist include the unpredictable transit time and the delayed absorption of encapsulated insulin (6). These factors may explain why ~0.5% of an oral insulin dose may reach the systemic circulation (22). Because of these obstacles, it would be extremely difficult to consider oral insulin therapy as a physiological option for premeal dosing (6). However, researchers have tried several steps to promote the bioavailability of oral insulin, including attaching caproic acid molecules and coating with chitosan, which stabilize degradation and improve permeability; facilitating absorption (e.g., with salicylates); concurrent administration with protease inhibitors; and entrapping insulin within microparticles (23–26). Other approaches have demonstrated that the chemical modification of insulin with fatty acids could improve insulin absorption from the intestine (27). In addition, engineered polymer microspheres were demonstrated to increase gastrointestinal absorption of insulin (28).

The most promising oral insulin to date is hexyl-insulin-monoconjugate-2 (HIM2), a native recombinant insulin with a small polyethylene glycol 7-hexyl group attached to the position B29 amino acid lysine, currently in development (Nobex Corporation, Research Triangle Park, NC). Preclinical pharmacokinetic and safety data for HIM2 are beginning to emerge. Ongoing phase I and II clinical trials suggest that oral HIM2 has a bioavailability of ~5% and may result in an acceptable glucose-lowering effect (29).

Oral buccal

A buccal system delivering a liquid aerosol formulation of insulin via a metered dose inhaler (Oralin) has been developed by Generex Biotechnology (Toronto, Canada). The buccal insulin preparation is a human recombinant insulin with added enhancers, stabilizers, and a nonchlorofluorocarbon propellant. To date, however, efficacy studies have only been presented as abstracts, safety reports of buccal insulin are scarce, and the majority of the previously mentioned abstracts did not assess side effects. Further review must await the results of the peer-reviewed reports.

Pulmonary delivery

Pulmonary delivery of insulin appears to be the first reported alternative to injections. Specifically, 3 years after the initial

Exubera (Nektar Therapeutics, Pfizer; Aventis SA)
- In late phase III development
- Dry-powder insulin formulation packaged in individual blisters of 1 or 3 mg
- Faster onset of action than sc regular insulin and lispro; reproducibility of all pharmacokinetic and pharmacodynamic parameters demonstrated
- Effective as monotherapy or combination therapy in patients with type 2 diabetes inadequately controlled on oral hypoglycemic agents (phase II and III studies)
- Comparable glycemic control (HbA_{1c}) to conventional sc insulin in insulin-treated type 2 diabetic patients and to conventional or intensive sc insulin in type 1 diabetic patients in phase II and III studies
- Associated with improved patient satisfaction

AERx iDMS (Aradigm Corporation; Novo Nordisk A/S)
- In early phase III development
- Liquid insulin formulation packaged in individual strips and dosed in single units
- Uses microprocessors to produce the correct rate and depth of breathing, ensuring consistent delivery regardless of breathing ability
- Faster absorption and onset of metabolic effect than sc insulin
- Comparable pharmacodynamic variability compared with sc insulin in patients with type 1 diabetes
- Preliminary clinical efficacy data suggest glycemic control comparable with sc insulin in patients with type 2 diabetes

AIR (Alkermes; Eli Lilly)
- Developmental phase undisclosed
- Uses particles formulated with a low density porous structure of 5–30 μm diameter
- The device aerosolizes the particles from blister packs and is breath-activated
- Sustained-release formulation also investigated

Aerodose (Aerogen)
- In phase II development
- A breath-activated multidose inhaler that delivers liquid insulin
- Aerosolization time, but not particle size, has an impact on metabolic effect
- Shorter time to peak action than sc insulin, comparable reproducibility, and a linear dose-response relationship for pharmacodynamic parameters

Spiros (Dura Pharmaceuticals)
- Development on hold (phase I)*
- Delivers a dry-powder formulation through a handheld battery-powered multidose system
- A new powder dispersion system (Spiros-S2) should achieve efficient delivery at low inspiratory flow rates (15-30 l/min) without Spiros' electromechanical components

Technosphere (Pharmaceutical Discovery Corporation)
- In phase I development
- Formulation involves an ordered lattice array of Technosphere dry-powder microparticles and recombinant human insulin
- The approach appears appropriate for prandial insulin supplementation

Figure 1—*Pulmonary insulin delivery systems in development. *Dura Pharmaceuticals is now part of Elan Pharmaceuticals. Development is on hold. sc, subcutaneous.*

clinical use of insulin, it was reported that insulin can be administered as an aerosol and could produce a decrease in blood glucose (30). However, it was 46 years later that the pivotal study of inhaled insulin offered proof of principle (31). Specifically, Wigley et al. (31) showed that delivering pork-beef insulin using a nebulizer produced a prompt increase in plasma immunoreactive insulin in three subjects without diabetes and four subjects with diabetes and that hypoglycemia showed a temporal relationship with the increase in plasma immunoreactive insulin. During the next 22 years, several

studies confirmed that pulmonary delivery was possible (32,33). Bioavailability was low—between 20 and 25% of that associated with subcutaneous insulin—but the predictability of the blood glucose response was at least as good. It was suggested that technological modifications, such as optimizing particle size and regulating the effect of breathing, might enhance absorption and improve biological response. This proved to be an accurate prediction (33).

The reality of pulmonary insulin becoming a viable alternative to injections is in large measure due to the inherent anatomic advantages that make it an ideal route for the administration of insulin. Specifically, the lung provides a vast (50–140 m^2, ~500 million alveoli) and well-perfused absorptive surface (34). The lung lacks certain peptidases that are present in the gastrointestinal tract, and "first pass metabolism" (i.e., immediate hepatic degradation by the absorbed insulin) is not a concern (34). In addition, the presence of a very thin alveolar-capillary barrier allows for a rapid uptake of peptides in the bloodstream and a rapid onset of action after inhalation (34). The exact mechanism of insulin absorption across the pulmonary epithelium remains unclear, although it is likely to involve transcytotic and paracellular mechanisms (35). Nevertheless, it was evident from the early studies that after inhalation into the lungs, insulin is rapidly absorbed with peak plasma concentrations being reached after 15–40 min (31,33). The rapid absorption of inhaled insulin has been consistently demonstrated with recent devices and makes inhaled insulin appropriate for premeal use.

Experience gained with asthma treatment has facilitated the development of pulmonary delivery systems for insulin. Early asthma drug delivery devices for pulmonary absorption included nebulizers, metered dose inhalers, and dry-powder inhalers (36). These devices proved useful in the management of local respiratory diseases such as asthma but are not designed to deliver drugs deep into the alveoli for systemic drug delivery. Conventional asthma inhalers have poor lung delivery efficiencies, and even in well-controlled human studies, there is considerable variation. Such systems are not clinically effective for pulmonary insulin delivery. The early challenge therefore was to develop an inhaler that delivers insulin to the "deep lung."

Despite anatomic advantages offered by the pulmonary bed to insulin uptake, potential limitations must be overcome for effective drug deposition. These factors include type of propellants used, air flow speed, losses within the device and the environment, particle size, drug clearance, drug deposition into the throat and bronchial tubes, drug absorption, patient compliance, and the potential impact of concomitant diseases, all of which can influence insulin delivery (37–39). Size and particle velocity are recognized as two major physical factors affecting optimal deep-lung deposition of an inhaled drug (35). For optimal deposition efficacy, particles should have low velocity and be between 1 and 3 μm in diameter. After the aerosolized drug reaches the deep lung, it must be absorbed with high enough bioavailability to make the delivery system feasible. Most of the devices currently in development will use a liquid or dry-powder insulin formulation for the generation of the insulin aerosol (Fig. 1). In addition, the development of inhaled insulin with these formulations varies from subcutaneous delivery by the fact that both components (the insulin formulation and the device) need to be studied as a unit (6). In this regard, the specific device has a major impact on the metabolic effect of the applied insulin. As stated by Heinemann, "Even the best insulin formulation becomes ineffective if the inhaler does not generate an aerosol with appropriate features" (6).

CURRENT DEVELOPMENTS IN PULMONARY DELIVERY

Exubera

The Exubera system is one of the more extensively investigated in terms of clinical development. Developed by Nektar Therapeutics (San Carlos, CA), it is currently being clinically assessed by Pfizer (Groton, CT) and Aventis Pharma (Frankfurt, Germany). This system delivers a fine dry-powder formulation (<5 μm in diameter) of regular short-acting human insulin to the deep lung in a reproducible and efficient manner. The number of individual blister packs inhaled controls the dose. The insulin dry powder is packaged into a single-dose blister containing 1 or 3 mg, with the 1-mg blister corresponding to ~3 units of insulin. The pack is inserted into the inhalation device (similar to a nebulizer) where a pneumatic mechanism punctures it and disperses the powder in a discrete cloud into the air chamber, which ensures consistent delivery (40). The insulin cloud is inhaled slowly at the beginning of a deep breath; the volume of the holding chamber is <20% of a deep breath. Early studies demonstrated reproducible pharmacokinetics and postprandial control with this device comparable to subcutaneous regular insulin (41).

Inhaled insulin therapy in insulin-treated patients with type 2 diabetes has been assessed (42). Patients received one or two inhalations of insulin before each meal plus a bedtime Ultralente injection (Humulin U; Eli Lilly, Indianapolis, IN). Glycemic control, as assessed by HbA_{1c} levels, was significantly improved compared with baseline. When compared with patients who were randomly assigned to receive continued subcutaneous insulin, HbA_{1c} levels were comparable between groups. A subsequent 24-week phase III study involving 298 subjects also showed comparable HbA_{1c} control in patients with type 2 diabetes treated with an inhaled insulin regimen versus a subcutaneous insulin regimen (41).

The study by Skyler et al. (43) enrolled 73 patients with type 1 diabetes. Patients received their usual daily insulin regimen of two to three injections or premeal inhaled insulin plus a bedtime Ultralente injection for 12 weeks. Inhaled insulin provided comparable HbA_{1c}, fasting, and postprandial glucose levels compared with subcutaneous injection. A 24-week phase III study, involving 334 subjects with type 1 diabetes, compared treatment with premeal inhaled insulin plus a single bedtime injection of Ultralente to treatment with a conventional subcutaneous insulin regimen consisting of two to three injections of regular/NPH insulin per day (41). Subjects in the inhaled insulin group achieved comparable changes in HbA_{1c} to those in the subcutaneous group. Preliminary reports also show that this system may be effective in patients with type 2 diabetes who were inadequately controlled on oral hypoglycemic agents. Those receiving inhaled insulin monotherapy or inhaled insulin combined with an oral agent achieved greater improvements in HbA_{1c} than those on oral agent therapy alone (41).

AERx
This insulin diabetes management system (iDMS), developed by Aradigm and now in collaboration with Novo Nordisk, creates aerosols (1- to 3-μm diameter particles) from liquid insulin. It uses microprocessors to guide the correct rate and depth of breathing, triggering insulin at the optimum moment in the inspiration-expiration cycle. This aims at consistent delivery of insulin, regardless of a patient's breathing ability (44). In a study of 18 subjects with type 1 diabetes, insulin administered by the AERx iDMS shows faster absorption and onset of the metabolic effect than subcutaneous insulin (45). A study in healthy volunteers suggested that changes in the inhaled volume and depth of inspiration influenced pharmacokinetics of insulin delivered using this system (44). Upper respiratory tract infections do not seem to induce any clinically relevant changes in pharmacokinetics or pharmacodynamics (although t_{max} is significantly reduced) (46), whereas the dose may need to be adjusted upward in asthmatics (47).

Preliminary clinical efficacy and safety data are now emerging for this system. A 12-week study in relatively poorly controlled insulin-treated subjects with type 2 diabetes suggests that pulmonary insulin administered via the AERx iDMS immediately before meals (plus bedtime NPH) is as efficacious in terms of HbA_{1c} reduction as premeal subcutaneous insulin (also with bedtime NPH) (48).

AIR (Advanced Inhalation Research)
The AIR system uses particles formulated with a low-density porous structure of between 5 and 30 μm in diameter. The device aerosolizes the particles from blister packs and is breath-activated. The system is being developed by Alkermes and Eli Lilly in two forms: a sustained-release AIR insulin with a pharmacokinetic profile similar to Humulin L in rats and a fast-release formulation that shows pharmacokinetics similar to Humulin R (49).

Dura's Spiros
This pulmonary delivery system (currently on hold) delivers a dry-powder formulation through a handheld battery-powered multidose system. The device delivers consistent doses to the lung across a wide range of inhalation flow rates. The company's latest development is a new powder dispersion system (Spiros-S2) that should achieve efficient delivery at low inspiratory flow rates (15–30 l/min) and without Spiros' electromechanical components.

Aerogen's Aerodose
Aerogen's Aerodose is a breath-activated multidose inhaler that delivers liquid insulin to the systemic circulation. A study in 13 healthy volunteers suggested that aerosolization time, but not particle size, had a significant impact on the metabolic effect of insulin delivered using the Aerodose device (50). In a study of 15 subjects with type 2 diabetes, insulin delivered using the Aerodose device had a shorter time to peak action than subcutaneous insulin and gave comparable reproducibility of dose (51). A further study in 24 insulin-naive subjects with type 2 diabetes revealed a linear dose-response relationship for pharmacodynamic parameters, suggesting pharmacological predictability with this system (52). It is currently on hold after initial phase II clinical trials.

Pharmaceutical Discovery Corporation's Technosphere/Insulin
The ordered lattice array of Technosphere dry-powder microparticles and recombinant human insulin provides yet another inhaled insulin system demonstrating "proof of concept." Several studies using the euglycemic clamp have been performed in healthy volunteers and patients with type 2 diabetes. The data demonstrate that this system will provide for a rapid systemic insulin uptake (t_{max} ~12–14 min), a fast onset of action (~20–30 min), a short duration of action (~2–3 h), and a low within-subject variability (53,54). The approach appears appropriate for prandial insulin supplementation.

Adverse events and benefits
The frequency and nature of adverse events reported with inhaled insulins appear, in general, to be comparable with subcutaneous insulin, with the exception of cough (although this decreases in incidence and prevalence with continued use) (43). Subjects treated with inhaled insulin may develop an increase in serum insulin antibody levels, but these levels thus far have not been related to any significant clinical change (41,55). Smoking, however, appears to greatly enhance insulin absorption (56). Pulmonary function tests, including forced expiratory volume in 1 s, forced vital capacity, total lung capacity, and carbon monoxide diffusing capacity (DL_{CO}) have been conducted for all inhaled insulin studies. Some studies reported a statistically significant decrease in the more variable DL_{CO} relative to subcutaneous insulin (41). Further studies are ongoing to characterize the insulin antibody and DL_{CO} changes, including whether a difference of this magnitude has any clinical significance, as well as any mechanistic or methodologic basis. One of the most important and beneficial findings to date, however, is that patient satisfaction is enhanced with inhaled insulin treatment compared with subcutaneous insulin injections (57,58).

CONCLUSIONS — There is a long history of attempts to develop novel routes of insulin delivery that are both clinically effective and tolerable. The various approaches that have been studied to date have involved strategies that are designed to overcome the inherent barriers that exist for protein uptake across the skin, gastrointestinal tract, and nasal mucosa. Nevertheless, the "proof of concept" for many of these approaches appears to have been established. However, it does appear that the most clinically viable system to date may be pulmonary delivery. Two of the devices for pulmonary delivery are in phase III testing, and the results thus far demonstrate comparable efficacy to that of subcutaneous insulin. The pulmonary safety and tolerability data will need to be established before these devices are clinically available. Thus, 25 years after Best hoped for and expected "more physiological methods for giving insulin," systems are in place to achieve his hopes and expectations.

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