The first patient to receive a dose of insulin was 14-year-old, 65-lb Leonard Thompson. He received an impure injection of 15 ml, which was described as “a thick brown muck,” on January 11, 1922. His blood glucose fell slightly, and because of the impurities in the extract, he developed an abscess at the site of one of his injections.1

Since then, a plethora of purer forms of insulin and insulins with various time action profiles have been produced, approved, and administered.2 Protamine zinc insulin was introduced in the 1930s. NPH was introduced in the 1940s. The lente series was introduced in the 1950s. Advances in chromatography in the 1960s and 1970s led to the production of highly purified insulins. In the 1980s, recombinant DNA technology was used to produce human insulin. Insulin was the first drug ever produced by recombinant technology.

More recently, DNA technology has led to the ability to synthesize insulin analogs. To date, more than 300 insulin analogs have been produced, approved, and administered.2 Protamine zinc insulin was introduced in the 1930s. NPH was introduced in the 1940s. The lente series was introduced in the 1950s. Advances in chromatography in the 1960s and 1970s led to the production of highly purified insulins. In the 1980s, recombinant DNA technology was used to produce human insulin. Insulin was the first drug ever produced by recombinant technology.

More recently, DNA technology has led to the ability to synthesize insulin analogs. To date, more than 300 insulin analogs have been produced.2 While the purity of insulin has increased and the needle size for injections has decreased, thus reducing the discomfort associated with subcutaneous insulin injections, no method of insulin delivery other than injection is currently available.

The concept of nasally administered insulin first appeared in 1935.3 Unfortunately, low bioavailability and great variability in absorption found in research done thus far have demonstrated that nasally administered insulin is not particularly practical.

Several years ago, interest in the possibility of administering insulin via the pulmonary route surfaced. Since that time, several methods have evolved that may eventually bring this idea to fruition. This article briefly reviews the physiological and pharmacological basis for pulmonary insulin and discusses several of the more salient systems currently being evaluated in the United States.

Rapid-Acting Pulmonary Insulin
Recent technological advances have made it feasible to deliver insulin to the alveolar space. Here, it is rapidly absorbed into the alveolar capillaries and disbursed throughout the systemic circulation. Alveolar epithelium measures ~100 m² (the size of a tennis court).4 This extremely vascularized surface is very permeable, making inhaled insulin an attractive alternative to injections. The absorptive ability of the alveolar surface stands in contrast to the thick layered mucosa of the upper airways and the bronchial tree, which are relatively impermeable to peptide drugs.

Until quite recently, insulins administered via the pulmonary route in human studies were soluble, rapid-acting formulations. Technology is now available that may allow for the pulmonary administration of longer-acting, as well as rapid-acting, insulin compounds.

Two of the more well-known and highly publicized inhalation systems are those from Inhaled Therapeutics of San Carlos, Calif., which is working in collaboration with Pfizer and Aventis, and from Aradigm Corporation of Hayward, Calif. These two systems use different technology to deliver insulin via the pulmonary route.

The Inhaled Therapeutics system uses a fine-powdered formulation. The particle size used in this system is less than 5 μm in diameter.4-5 Particles of this size are able to reach the deep lung with slow, deep inhalation. Larger particles are more likely to become lodged in the upper airway, while smaller particles will be partially exhaled.3

Inhaled Therapeutics uses a technology it developed called “PulmoSol powder technology” to create the right-sized particles to reach the deep lung. These particles are highly soluble and quickly dissolve upon reaching the alveoli. They then pass a single cellular layer into the circulation.

IN BRIEF

Various methods of insulin administration other than injection have been sought since the discovery of insulin. For the past several years, systems that deliver insulin via the pulmonary route have been developed and evaluated. Based on available data, pulmonary insulin appears to be safe, efficacious, and well accepted by patients. This article describes the technology behind several of these pulmonary administration systems and outlines the most recent data from clinical trials evaluating pulmonary insulin.
Powdered aerosolized particles can contain up to 95% pure drug, in contrast to aqueous aerosols, which typically contain only 1 or 2% drug and about 98% water. These powdered aerosols carry approximately five times more drug in a single breath than does a metered-dose inhaler system and much more drug than do liquid or nebulizer systems.

The PulmoSol glass stabilization system creates chemically stable insulin particles. Using a fast-drying technique, the system places insulin into an amorphous, glassy state. This state has many of the properties of a liquid but the viscosity of a solid.

Insulin from this system will be available in “blister packs” and will remain stable at room temperature for up to 2 years. The device used with the Inhaled Therapeutics system is the size of a mechanical flashlight and is very easy to use.

The other system being evaluated in the United States is that being developed by Aradigm. This system uses a hand-held inhalation device that is regulated with microprocessors to produce a consistent dose using commercially available liquid insulins. Liquid insulin is inserted into the device, and the aerosol delivers particles 2–3 μm in size directly to the alveoli. The Aradigm system circumvents any problems encountered in converting peptides into powders.

Recently, a new drug delivery system has been developed that facilitates the absorption of peptides and proteins via the pulmonary route. This system is known as Technosphere. The Technosphere insulin is an ordered lattus array of Technosphere and recombinant human insulin.

Pharmacodynamic trials of this system have reported a rapid onset of metabolic effect in a dose-dependent manner. Inhalation of Technosphere insulin was very well tolerated.

In one study of Technosphere insulin involving 12 patients with type 2 diabetes, the maximum metabolic effect was greater and the duration of action was shorter with inhaled Technosphere insulin than was observed with subcutaneous regular insulin. This small study concluded that inhaled Technosphere insulin may be superior to regular human insulin administered subcutaneously for prandial insulin supplementation in patients with type 2 diabetes because of its greater onset, its shorter duration of action, its low within-subject variability, and its convenience.

Another small study of the Technosphere insulin system in healthy volunteers reported high bioavailability (25.8% of that with subcutaneous and 14.6% of that with intravenous administration) and an onset of action similar to that seen with intravenous regular insulin. The study concluded that more research was required to determine the feasibility of Technosphere insulin as a candidate for future drug development.

**Long-Acting Pulmonary Insulin**

Several investigators have evaluated methods of prolonging insulin absorption from the lungs of rodents. In one study, a porous aerosol particle containing 20% insulin and 80% poly(lactic acid-co-glycolic acid) was reported to demonstrate sustained release of insulin into the blood over a period of several days. Bioavailability of the inhaled particles was 87.5% of that with subcutaneous injection of the sustained-release particles.

Unfortunately, the doses required in this trial were very high. Doses of 9 mg of powder were administered to rats weighing 0.3 kg. This would be roughly equivalent to a 2,100-mg dose for a 70-kg human—a mass probably too large to be inhaled on a regular basis.

Recently, a unique, porous, dry-particle aerosol technology known as AIR was developed with both fast-acting and slow-acting pulmonary insulin formulations. AIR technology uses particles with a small aerodynamic size (1–3 μm), a low density (<0.1 gm/ml), and large geometric particle size (10–20 μm).

These particles can be very easily aerosolized from a simple inexpensive inhalation device, which effectively delivers the particles to the deep lung and provides systemic absorption and high bioavailability.

The size and approximate shape of the AIR inhaler device is that of a standard marker pen. The insulin is contained in blister packs. The inhaler requires no power source and uses patients’ breath to deliver large amounts of powder with a single breath.

The long-acting AIR insulin exhibits a pharmacokinetic profile similar to that of human insulin (Humulin L), and the fast-release AIR insulin displays a pharmacokinetic profile similar to that of human insulin in rats.

**Clinical Trials**

Numerous clinical trials have demonstrated the effectiveness, safety, and acceptability of inhaled insulin in both type 1 and type 2 diabetic patients. There are summarized in Table 1.

One trial evaluated 51 patients with type 2 diabetes. The study began with a 1-month run-in period, after which patients were randomized to either inhaled insulin or subcutaneous insulin for 3 months. Patients treated with inhaled insulin used the inhaled product before meals, along with a bedtime injection of ultalente. Patients randomized to the subcutaneous therapy injected insulin two or three times daily.

Baseline HbA1c levels were similar in both groups. Patients self-monitored blood glucose levels four times daily, and these values were reviewed weekly.

At the end of the trial, both groups had experienced a mean 0.7% reduction in HbA1c levels. The patients in the inhaled insulin group lost a mean of 0.4 kg, whereas those treated with subcutaneous insulin gained an average 1.1 kg. Pulmonary function tests in these patients were unchanged.

In another trial, 62 subjects with type 2 diabetes who were treated with sulfonylureas, metformin, or both, entered a 3-month treatment period...
After a 1-month run-in.13 These patients were randomized to receive their preexisting oral agent therapy or the oral agent therapy plus one or two inhalations of insulin three times daily. Patients self-monitored their blood glucose four times daily. Baseline HbA1c levels were similar between the two groups.

At the end of 3 months, the patients in the oral agent arm experienced a mean 0.13% reduction in HbA1c values, while those in the oral agent–plus–inhaled-insulin arm experienced a mean 2.28% reduction in HbA1c values ($P < 0.001$). There was one report of hypoglycemia (54 mg/dl) in the inhaled-insulin arm. Pulmonary function tests in this trial were unchanged.

Inhaled insulin has also been evaluated in patients with type 1 diabetes. In one study, 70 patients were randomized to either inhaled insulin three times a day plus bedtime ultralente or to continue on their prestudy regimen of two to three insulin injections per day. Patients self-monitored their blood glucose levels four times a day with a pre-meal glucose target range of 100–160 mg/dl. Baseline HbA1c levels averaged 8.53%, whereas those in the inhaled-insulin arm averaged 8.51%.

After 3 months of therapy, there was no statistically significant difference between HbA1c levels in the two groups. The subcutaneous group had a mean HbA1c of 7.7%, and the inhaled-insulin arm had a mean HbA1c of 7.87%. Ten severe hypoglycemic events occurred in patients in the subcutaneous arm of this study, whereas only eight events occurred in the inhaled-insulin group.14 The incidence of mild hypoglycemic episodes was similar between the two groups. Pulmonary function tests were unchanged.

Eighty percent of the patients in the inhaled arm opted for a 1-year extension. Participants in the extension could choose whether to have inhaled-insulin or subcutaneous-injection therapy. A 15-item questionnaire was used to assess patient satisfaction during the parent study at baseline and at 3 months and again 1 year later. Of those on inhaled insulin in the 3-month trial, 81% chose to remain on inhaled insulin. Nineteen percent of patients originally on inhaled insulin switched to subcutaneous. Of the patients on subcutaneous insulin in the parent study, 79% switched to inhaled insulin and 21% continued with subcutaneous insulin.

Subjects treated with inhaled insulin had significantly greater improvement in global satisfaction and in convenience/ease of use ($P < 0.01$) compared to those on subcutaneous insulin. Glycemic control remained stable during the 1-year extension. The data suggested that inhaled insulin was preferred over subcutaneous insulin and resulted in greater patient satisfaction.

Patients in three of the above-mentioned studies12–14 were evaluated for sustained efficacy and pulmonary safety while using insulin during 2 years of outpatient therapy. Pooled data from these three trials yielded an average HbA1c of 8.0% at the end of the 3-month trial. Average HbA1c levels at the end of 2 years remained at 8.0%.

Forced expiratory volumes in 1 s (FEV1) were a mean of 3.2 liters at baseline and at 24 months. Diffusion capacity was a mean of 25.6 ml/min/mmHg at baseline and 24.4 ml/min/mmHg at 24 months. The authors concluded that these results suggest sustained long-term clinical efficacy and pulmonary safety in patients being treated with inhaled insulin.16

A pharmacokinetic/pharmacodynamic trial was carried out in 18 C-peptide–negative type 1 diabetic patients. Each study utilized a glucose clamp over 600 min and measured the area under the curve for insulin, the t-max of metabolic effects than does subcutaneous insulin.

15

### Table 1. Summary of Phase 2 Trials

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>N</th>
<th>Duration of study (not including run-in period)</th>
<th>Treatment arm/change in HbA1c from baseline</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2</td>
<td>51</td>
<td>3 months</td>
<td>• Inhaled insulin/0.7%</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Subcutaneous insulin/0.7%</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>62</td>
<td>3 months</td>
<td>• Oral agent/0.13%</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Oral agent plus inhaled insulin/2.28%</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>70</td>
<td>3 months</td>
<td>• Subcutaneous insulin (2–3 injections/day)/0.83%</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Inhaled insulin plus subcutaneous insulin (once daily)/0.64%</td>
<td></td>
</tr>
</tbody>
</table>
ly in development. Based on available data, pulmonary insulin appears to be effective and safe.

While the majority of insulin delivery systems being evaluated use rapid-acting insulin, systems are also being developed that may allow for the administration of long-acting insulins. Ease of administration of pulmonary insulin may lead to better compliance and better glycemic control in the long run.

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