Diabetes is a disease in which the body does not produce and/or properly use insulin i.e., is insulin resistant. According to the American Diabetes Association, 20.8 million people in the United States – or seven percent of the population – have diabetes. One out of every ten health care dollars spent in the United States goes to treat diabetic patients. The treatment of diabetes with subcutaneous insulin injections is associated with lack of compliance due to the pain of multiple daily injections. Hence, there is a big demand for insulin that can be administered without painful shots. Development of such an insulin delivery system without painful shots would open the way to a multibillion dollar market, while also making diabetics more treatment-compliant.

**Definition and Causes**

People with diabetes have high blood sugar because their pancreas do not make enough insulin and/or their liver, muscle, fat, and other body cells do not respond to blood insulin as they normally do in a healthy individual. The role of insulin is to move glucose from the bloodstream after a meal into liver, muscle, and fat cells, where it can be used as immediate fuel and also stored as glycogen, mainly in the liver, to be released for energy needs between meals when the blood sugar falls.

**Types of Diabetes**

- **Type 1 diabetes** is an autoimmune (some cases are idiopathic) disease, caused by the destruction of selective beta cells and resulting in natural insulin production deficiency.
- **Type 2 diabetes** comprises more than 90% of cases of diabetes and is seen mostly in adults. Obesity and failure to exercise are important predisposing risk factors. The latest research points to the novel “lipocentric” (lipotoxicity) theory, which states that high blood sugar (hyperglycemia), insulin resistance, and beta cell loss are secondary to the metabolic trauma caused by outside (ectopic) excessive lipid (fat) deposition due to excess caloric intake. In these type 2 diabetics, it is possible that in spite of elevated blood sugar and high (or low) blood insulin levels, glycogen from liver cells converted to glucose and released into the blood. These diabetics also need insulin with a different molecular make-up (change in the two amino acid chains and its disulfide bonds), which breaks insulin resistance in the cell, enhances the uptake of glucose, and stops glucose leaking from liver cells at the same time. Such a therapeutic agent, if developed to be effective orally, would seem to be “God’s Gift” to diabetics.
- **Gestational diabetes** is high blood glucose during pregnancy (4%) due to insulin resistance caused by placental hormones; reverses after birth of the baby and responds to insulin.
- **Miscellaneous group:** diabetes can stem from genetic defect-related metabolic syndromes, surgery, drugs, malnutrition, infections, and other illnesses.

**Diabetes: Symptoms, Diagnostic Tests, Complications, and Treatment**

Patients develop symptoms over a short (type 1) or long (type 2) period of time. These symptoms include increased thirst, urination, weight loss, increased appetite, fatigue, blurred vision, dry skin, numbness and tingling in limbs, slow-healing wounds and more infections than usual, disturbed sleeping, impotence in men, etc.

Diagnosis is made through urine, blood, and Ketones tests: fasting blood glucose level (higher than 126 mg/dL); random (non-fasting) blood glucose level (higher than 200 mg/dL);
oral glucose tolerance test (glucose level higher than 200 mg/dL after two hours); and HbA1c blood test (measures the average blood glucose during the previous two to three months).

There is hardly any organ in the body that is not adversely affected by diabetes, starting with the heart, blood vessels, brain, nerves, kidneys, gastrointestinal tract, limbs, etc., resulting in premature death. Diabetes is the seventh-leading cause of death: 193,140 deaths in 1996. Complications of diabetes are attributed to binding of proteins to sugar called excessive glycosylation as well as to a build-up of sorbitol inside the cells.

For type 1 diabetes and gestational diabetes, the treatment is subcutaneous injection of insulin. For type 2 diabetes, the treatment is threelfold: 1) exercise, reduce body weight, and drink arsenic-free water; 2) take oral antidiabetic medications and over-the-counter antidiabetic supplements such as cinnamon; 3) take insulin, if appropriate; about 30% of type 2 diabetics will also benefit from insulin therapy if testosterone blood levels are low. Taking insulin may ameliorate early diabetic condition.3

Insulin's Role in Transport and Storage of Blood Sugar Inside Cells

Cells have thin membranes with various kinds of receptors (locked doors) that can open or shut by entry and exit of biological and nutritional substances with specific keys like insulin and similar substances. Cells have these insulin receptors (locked doors with insulin receptors [IR] insulin-like growth receptors [IGFR-I, and II] on the cell membrane. These can be opened (activated) by insulin (the key) latching onto these receptors, activating various biological activities (i.e., opening the locked doors), and allowing large amounts of sugars, amino acids, and other nutrients, including electrolytes, to enter the cell. Insulin activates the various biological activities inside the cell needed for cell energy, protein synthesis, and cell division. Insulin is also needed to store blood sugar in liver cells as glycogen to be released when blood sugar falls.

Cancer and Insulin Receptors

Cancer and precancerous cells develop anaerobic (less oxygen) metabolism, as described by Nobel laureate Otto Warburg almost 75 years ago. Due to this metabolic defect, these cells produce only six ATP energy-loaded molecules for each molecule of sugar, instead of the 38 ATP molecules produced by normal cells. To overcome the energy defect, as the normal cells change to an anaerobic factory (cancer) needing lots of sugar, these cells develop three to ten times more insulin receptors to let three to ten times more sugar inside the cancer cells to meet the energy needs for their metabolic and multiplication processes. Abnormal precancerous and cancer cells have an additional supply of insulin directly deposited on these cells (insulin receptors) when a patient uses inhalation insulin, nasal and oral insulin sprays, or oral or rectal insulin, or the insulin is deposited into blood (in type 2 diabetics), which facilitates entry of sugar for cell multiplication. Even the nanomolar concentration insulin-like growth factors (IGF-I and IGF-II) are potent mitogens that can ultimately result in cancers.

If you visit www.Pubmed.gov and search for "insulin and cancer," you will find 17,089 citings; if you search for "insulin causes cancer," you will find 9,079 citings. This is one indication of the intense research underway on the relationship of insulin to cancer. All cancer and precancerous cells have three to ten times more IR and IGFR-I, which thrive on the high blood sugar and high insulin in which they come in contact. Even solitary, non-cancerous fibrous tumors have IGF receptors.4,8 Insulin receptors are over-expressed in all human cancers.9 A greater threat of tumors (cancers), infections, and other diseases looms on the horizon with the proposed use of inhalation insulin as well as with insulin oral or nasal insulin sprays, oral (swallowed) insulin, and rectal suppositories when used over the long term as stand-alone treatments.

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Development of Inhaled Insulin and Nasal and Oral Insulin Spray for Diabetes

Unprecedented demand for insulin-dependent diabetes mellitus therapy, coupled with the unmet need for non-invasive alternatives to subcutaneous insulin injection, make diabetes one of the most attractive profitable therapy areas for the pharmaceutical industry to develop inhalation, oral and nasal spray insulin, and oral or rectal pill hormone delivery of insulin-based products. (Exubera was the first such FDA-approved product in the market to deliver the insulin by inhalation insulin. Exubera has now been withdrawn from the market for safety reasons.) Important routes targeted for developing alternative (to subcutaneous injection) insulin delivery systems are the nose, mouth, lungs, skin, and digestive system.

Distribution of High Doses of Inhalation Insulin Used to Achieve the Blood Levels from the Lungs to Lower Blood Sugar

Inhalation and nasal and oral spray insulin is effective only when the calculated dose is at least three to five times the amount given under the skin by injection. Since only little more than ten percent of inhaled, aerosolized, or swallowed insulin is bio-available to reduce the sugar in the blood. Insulin has to be tagged
Effects of Using Insulin through Inhalation and Oral and Nasal Sprays

The above anatomical structures may also be constantly exposed to an onslaught by infection; chronic irritation from working in dirty, dusty, smoky environment; tobacco use (smoking, sniff, and chew); mechanical and chemical irritation from hydrocarbons, heat, and cold, chemicals, and noxious fumes; and irritation from acidic and alkaline food and drinks. Given these physical, chemical, and mechanical traumas, the cell structures affected by the inhaled, nasal, and oral sprayed insulin can undergo changes such as metaplasia, in which cells change from their original mature, differentiated type into another cell type; dysplasia, in which the cell change (different form) is indicative of an early step towards transformation into a tumor (cancer; for example, leukoplakia of the oral cavity); or heteroplasia, the abnormal cell growth of existing cells as seen in blood vessels of hypertensives and in bronchiolar asthmatics.

End Result of Long-Term Use of Inhalation and Nasal and Oral Spray Insulin

1. An initial transient irritation, causing cough, sneezing, shortness of breath, sore throat, and dry mouth
2. Many of the insulin particles are deposited on the oral-pharyngeal-laryngeal-tracheo-bronchial tree, mouth, and nose lining. This will increase the incidence of tumors of the oral cavity, tongue, larynx, pharynx, trachea, bronchial tree, lungs, tonsils, nasal mucosa, nasal air sinuses, nasal polyps, vocal cords, and any other structure where the insulin particulates are deposited.
3. Existing cancers of the lungs, mouth, and nasal cavity grow rapidly and spread farther due to direct deposit of insulin particles.
4. Increased incidence of cancer at the lower end of the esophagus due to their exposure to gastro-esophageal reflex disorder.
5. In smokers, excess insulin enters into blood, rapidly resulting in hypoglycemia.
6. Insulin, being a growth-promoting protein, can increase in smooth muscle cells in air passages, fibroblasts, many types of white blood cells in the lungs (including phagocytes, mast cells becoming larger), resulting in resistance to the passage of air in the respiratory tract (asthmatics) and a thickening of the lung alveoli lining, affecting the gas exchanges.
7. Insulin growth-promoting effect may lead to pulmonary (nasal or oral) blood vessel thickening, resulting in pulmonary hypertension and ASVD.
8. Inhalation and nasal and oral spray insulin may worsen pre-existing respiratory diseases. Singers may develop more vocal cord nodules and laryngeal tumors.
9. Inhalation and nasal and oral spray insulin may aggravate asthma, pulmonary fibrosis, sarcoidosis, tuberculosis, and chronic pulmonary afflictions, sinusitis, chronic infection of the oral and nasal cavity, existing chronic lung, oral, and nasal cavity diseases.
10. Due to rapid absorption of insulin, some patients may develop life-threatening hypoglycemia.
11. Our studies at Emory University School of Medicine have shown the pia-arachnoid membranes of the brain extend all the way to roof of the nose, extending to the base of the olfactory mucosa in the nose. That is why any inhaled infecting microbes (viruses and bacteria, e.g., meningococcus) from the nasal olfactory mucosa can reach the central nervous system (CNS) and be distributed with ease via inhaled, oral, or nasal spray insulin, resulting in brain infection.
12. Inhalation insulin and oral and nasal insulin sprays increase the
level of insulin antibodies from baseline levels of 6% to 35%. On the other hand, there is hardly any change in patients using subcutaneous insulin therapy. The adverse effects of inhaled insulin include retarding the action of soluble insulin in the blood and removing insulin as an immune complex by the immune (reticulo-endothelial) system, making less insulin available to lower the blood sugar at the cellular level.  

13. The studies show that patients with asthma have to inhale more insulin to achieve good metabolic control of blood sugar, which results in more insulin deposits. This raises the possibility of more adverse effects, such as lung cancers, with long-term use.  

We strongly recommend that these insulin-delivery methods not be used by tobacco users, by those with chronic oral-pharyngeal-esophageal-lung-nasal cavity diseases, or in anyone who has a predisposition to dysplasia, which can turn into cancer.

Future of Anti-Diabetic Insulin Therapies  
In spite of breakthrough claims in the news media, insulin injection still is the main therapy for insulin-dependent diabetics. Inhalation insulin has been withdrawn from the market due to increased incidence of lung cancer associated with its use as reported by us and confirmed by Pfizer. Nasal and oral insulin sprays have similar effects to inhaled insulin and should not be FDA-approved. Transdermal patches using absorption enhancers, ultrasound, iontophoresis, and various transdermal devices used to deliver insulin are cumbersome, unreliable, and not practical. Neutralizing the auto antibodies before they attack the insulin production of beta cells in type 1 diabetes and implantation insulin production of stem cells are still experimental and do hold promise. Important advancement can be made if we develop bioactive therapeutic agents that would stimulate the multiplication and the differentiation of new insulin-producing islets from preexisting pancreatic progenitor cells in islets and pancreatic ducts. Development of altered insulin protein that works even with the insulin resistance needs to be considered. Attempts are being made to develop long-acting subcutaneous injections of insulin, and other antidiabetic therapeutics agents are also on the horizon. Yet nothing safe currently exists to replace insulin shots. My advice to type 2 diabetics, "Heed the weight and cure the disease," still holds.  

At present, we have two patents pending for the painless delivery of insulin by subcutaneous injections and also a new locally applied transmucosal insulin delivery system.

Inhalation Insulin

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Inhalation Insulin

using existing insulin formulations that are safe and have been in use for decades. We hope to bring them to the market so that they will make insulin-dependent diabetics more compliant in testing blood sugar and using insulin — without the fear of painful shots.

Note: A longer version of this article excerpt (Part 1 of a two-part series), appears this month on www.TownsendLetter.com.

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Post Script: Word of Caution to Pharmaceutical Industry and FDA on the Development and Approval of Nasal and Oral Insulin Sprays and Oral and Rectal Insulin

Dr. T.R. Shantha sent detailed letters and published material to various drug companies involved in developing inhaled insulin and to the FDA about the dangers of inhaled insulin and possible development of cancers between the years 2005-2007. In October 2007, the Pfizer pharmaceutical company withdrew the only FDA-approved inhaled insulin (Exubera) from the market, taking a 2.5 billion dollar loss. Some of the other pharmaceutical companies stopped developing inhaled insulin also. Supporting Dr. T.R. Shantha’s research findings, on April 9, 2008, Pfizer announced findings of a connection between the development of six lung cancer cases and the short-term use of inhalation insulin.

Notes
11. Shen M, Hsu YM, Hsu KF, Chou CY. Insulin-like growth factor 1 is a potential stimulator of cervical cancer cell invasiveness and proliferation that is modulated by alphabeta3 integrin signaling. Cancer Res. 2006 May;66(10):4629-34.
17. Available at: www.Insulinnews.com-Inhalation insulin therapy.