Inhalation Insulin and Oral and Nasal Insulin Sprays for Diabetics: Panacea or Evolving Future Health Disaster

Part I

by T.R. Shantha, MD, PhD, FACA, and Jessica G. Shantha

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.[1] 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.[2] 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 threefold: 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 open or shut for the 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.

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.

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

➤

➤

to other substances to reach alveolar, oral, and nasal surfaces and be absorbed. Larger particles or liquids (containing insulin) are deposited in the mouth, throat, nasopharyngeal outlet, nose, and tracheo-bronchial tree alveolar macrophages.[10] When insulin passes through the nasal passage in exhaled air, some of these particles enter the nasal air sinuses and olfactory mucosa, which has direct connection to the brain.[15] The onset of action of inhaled and nasal and oral spray insulin is more rapid compared to that of subcutaneously injections.[11]

The Effect of Inhaled Insulin on Anatomical Structures

When one takes a breath of insulin powder/ liquid through an inhaler or via sprays, only a small part of insulin reaches the deep depths of alveolar, oral, or nasal blood and is distributed all through the body. Before insulin can reach and enter the bloodstream, almost 90% gets deposited directly on the following structures, exposing them to higher cancer development:

1. Oral cavity, tongue, tonsils, epiglottis, pharynx, larynx and vocal cords, trachea and bronchial air conducting tubes, nasal cavity, olfactory mucosa, and sinuses
2. Vocal cords: the space between the vocal cords is tight and creates a bottleneck for air passage, and all inhaled and exhaled insulin particles have to pass through that passage. Thus, the vocal cords receive the largest insulin deposits of any affected structure – and hence experience more adverse effects.
3. The esophagus: some insulin delivered by these methods is dissolved in the saliva and mucosa in the mouth, then ingested and deposited on the esophageal surface when swallowed.

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, snuff, 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 (GERD) and Barrette's disease from swallowed insulin dissolved in saliva
5. In smokers, excess insulin enters into blood, rapidly resulting in hypoglycemia.[12]
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.[13]
8. Inhalation and nasal and oral spray insulin may worsen pre-existing respiratory diseases.[14] 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.[15]
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.[16] 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.[17]
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.[18] 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.[19] 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.[17] 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

➤

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.

T.R.Shantha, MD, PhD, FACA
Jessica G. Shantha, Medical Student
115 Bayberry Hills
McDonough, Georgia 30253
Phone/Fax: 770-507-6564
Cell: 678-640-7705
shantha35@aol.com

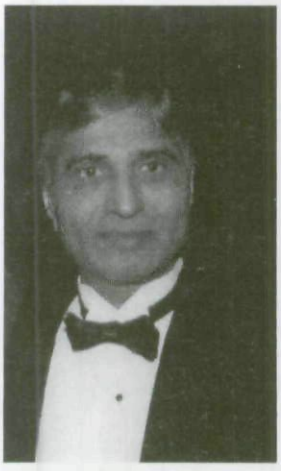
Post Script: Word of Caution to Pharmaceutical Industry and FDA on the Development and Approval of Nasal and Oral Insulin Sprays and Oral and Rectal Insulin

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.[20] 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.[25]

This is great victory for Dr. T. R. Shantha and his research findings (Shantha TR, Unknown health risks of inhaled insulin, *Life Extension*, September 2007: 79-82).[21] Can you imagine thousands of diabetics developing lung, gastrointestinal, oral and nasal cancers from the use of inhaled insulin? Dr. T. R. Shantha's timely report on the dangers of inhaled insulin saved thousands of diabetics from developing lung cancer and billions of dollars in their health care and litigation costs. We thank him for his research genius and for preventing this evolving health disaster and saving many hundreds from developing and suffering from lung, bronchial, oral, laryngeal, pharyngeal, and nasal cancers. The FDA should consider seriously his warning in this two-part series on insulin and take all precautions before they approve alternative methods to replace the subcutaneous insulin delivery system. Dr. T. R. Shantha firmly believes that nasal- and oral-sprayed insulin, oral insulin, or rectal insulin suppositories have similar effects to inhaled insulin. If these products are approved, there will be meteoric rise in oral, tongue, gum, cheek, tonsilar, pharyngeal, laryngeal, nasal cavity, gastrointestinal tumors (cancers), and infections, and countless other health hazards. FDA approval should be considered only after all the concerns are addressed. These insulin deliver systems should be approved for use under special circumstances only, not as replacements for subcutaneous insulin daily injections.

Notes

1. Diabetes – Definition: Diabetes is a life-long disease marked by high levels of sugar in the blood. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/001214.htm. Accessed September 26, 2008.
2. Dixon JB, O'Brien PE, Playfair J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA*. 2008;299(3):316-323.
   McGarry JD. What if Minkowski had been ageusic? An alternative angle on diabetes. *Science*. 1992;258(5083):766-770.
   Unger RH. Minireview: Weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. *Endocrinology*. 2003;144(12):5159-5165.
   Unger RH. Reinventing type 2 diabetes: pathogenesis, treatment, and prevention. *JAMA*. 2008;299(10):1185-1187.
3. Lichten E M, Testosterone's overlooked role in the treatment of diabetes in men. *Life Extension*. July 2007:23-29.
4. Li Y, Chang Q, Rubin BP, Fletcher CD, Morgan TW, Mentzer SJ, Sugarbaker DJ, Fletcher JA, Xiao S. Insulin receptor activation in solitary fibrous tumors. *J Pathol*. 2007 Apr;211(5):550-4.
5. Ryan CJ, Haqq CM, Simko J, Nonaka DF, Chan JM, Weinberg V, Small EJ, Goldfine ID. Expression of insulin-like growth factor-1 receptor in local and metastatic prostate cancer. *Urol Oncol*. 2007 Mar-Apr;25(2):134-40.
6. Mallikarjuna K, Pushparaj V, Biswas J, Krishnakumar S. Expression of insulin-like growth factor receptor (IGF-1R), c-Fos, and c-Jun in uveal melanoma: an immunohistochemical study. *Curr Eye Res*. 2006 Oct;31(10):875-83.
7. Dearth RK, Cui X, Kim HJ, Kuiatse I, Lawrence NA, Zhang X, Divisova J, Britton OL, Mohsin S, Allred DC, Hadsell DL, Lee AV. Mammary tumorigenesis and metastasis caused by overexpression of insulin receptor substrate 1 (IRS-1) or IRS-2. *Mol Cell Biol*. 2006 Dec;26(24):9302-14. Epub 2006 Oct 9.
8. Shen MR, Hsu YM, Hsu KF, Chen YF, Tang MJ, Chou CY. Insulin-like growth factor 1 is a potent stimulator of cervical cancer cell invasiveness and proliferation that is modulated by alphavbeta3 integrin signaling. *Carcinogenesis*. 2006 May;27(5):962-71. Epub 2006 Jan 7.
9. Belfiore A. The role of insulin receptor isoforms and hybrid insulin/IGF-I receptors in human cancer. *Curr Pharm Des*. 2007;13(7):671-86.
10. Heinemann L, Heise T. Current status of the development of inhaled insulin. *Br J Diabetes Vasc Dis*. 2004; 4(5):295-301.
11. Heise T, Rave K, Bott S, et al. Time-action profile of an inhaled insulin preparation in comparison to insulin lispro and regular insulin. *Diabetes*. 2000;49:A10
12. Himmelmann A, Jendle J, Mellen A, Petersen AH, Dahl UL, Wollmer P. The impact of smoking on inhaled insulin. *Diabetes Care*. 2003;26:677-82.
13. Aye M, Sheedy W, Harrison R, Thompson JS, Morice AH, Masson EA. Pulmonary vasodilation in the rat by insulin in vitro could indicate potential hazard for inhaled insulin. *Diabetologia*. 2003;46:1199-202.
14. Available at: www.Insulin news.com-Inhalation insulin therapy.
15. Heise T, Rave K, Bott S, et al. Time-action profile of an inhaled insulin preparation in comparison to insulin lispro and regular insulin. *Diabetes*. 2000;49:A10.
16. Shantha TR, Bourne GH. The "Perineural Epithelium": A new concept. Its role in the integrity of the peripheral nervous system. In: GH Bourne, ed. *Structure and Function of Nervous Tissues*. Volume I. New York: Academic Press; 1969: 379-459.
    Shantha TR, Nakajima Y. Histological and histochemical studies on the rhesus monkey (Macaca mulatta) olfactory mucosa. *Z. Zellforsch*. 1970;103:291-319.
17. Shantha, TR. Unknown health risks of inhaled insulin. *Life Extension*. September 2007; 79-82.
18. Hermansen K, Ronnemaa T, Petersen AH, Bellaire S, Adamson U. Intensive therapy with inhaled insulin via the AERx insulin diabetes management system: A 12-week proof-of-concept trial in patients with type 2 diabetes. *Diabetes Care*. 2004;27:162-7.
19. Henry RR, Mudaliar SR, Howland WC, et al. Inhaled insulin using the AERx Insulin Diabetes Management System in healthy and asthmatic subjects. *Diabetes Care*. 2003;26:764-9.



Dr. Shantha has published more than 125 research papers in distinguished journals such as *Nature*, *Science*, *New England Journal of Medicine*, *Journal of Cell Biology*, and others. He is the author of six books and the holder of seven patents. In 2005, Dr. T. R. Shantha received the distinguished physician award from the 42,000-member physician organization Association of Physicians from India (AAPI), and he was nominated for the Nobel Prize in physiology and medicine in 2007. Dr. Shantha is also the discoverer of the drug Terbutaline, which is used all over the world for treating priapism. A pioneer in alternative medicine, he has designed many innovative therapies, utilizing both traditional and alternative approaches, for the treatment of cancers and many other incurable diseases. Dr. Shantha has spent 53 years in medical research and in practice, is triple boarded, and is considered by many to be an expert on insulin potential therapy, hyperbaric therapy, and the treatment of both hyperthermia and pain.

Jessica G. Shantha is a medical student at the Morehouse School of Medicine.