

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

## Part 2

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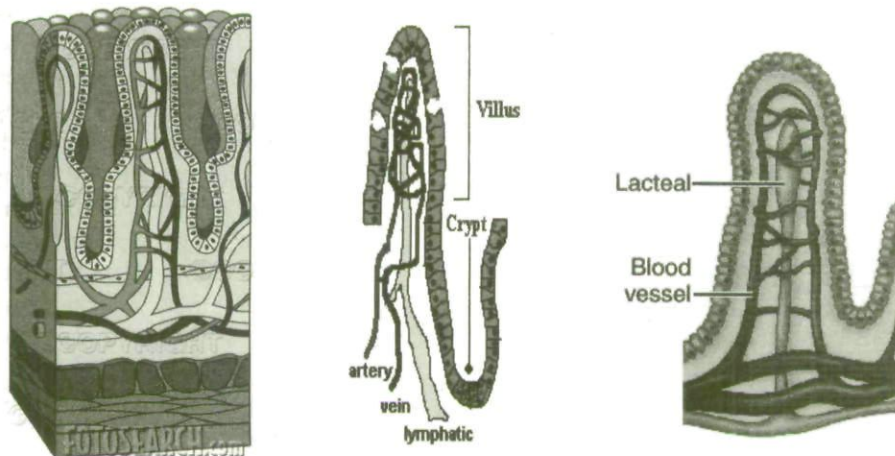
In Part I of this article, we discussed diabetes treatments and the dangers of alternative inhalation insulin delivery systems when used as a replacement for insulin shots.<sup>1,2</sup> In recent times, we have seen the research we discussed supported. Six cases of lung cancer, as well as six deaths, have already resulted from the use of inhalation insulin, and 30 cases of pancreatitis have been reported with the use of the anti-hypoglycemic agent Byetta (Exenatide: oral and injectable forms). With this inhalation insulin debacle, many research centers and

pharmaceutical companies are now scrambling to find other alternative methods of delivery to replace painful subcutaneous insulin injections and help make diabetics more compliant. Here, in Part 2, we want to discuss the pros and cons of oral (swallowed) and rectal insulin for diabetics as an alternative treatment to both the standard injectable insulin and the failed inhalation insulin therapy.

To understand how oral insulin works, it is important to have anatomical and histological knowledge of the liver and gastrointestinal tract. The

liver is part of the digestive system. It weighs three pounds and performs about 500 different functions in addition to playing an important role in maintaining blood glucose levels. The liver receives 75% of its blood from the digestive tract (portal veins), which contains nutrients, including sugars, and 100% of the insulin from the pancreas, which pours into the liver in response to elevated blood sugar. The liver receives 25% of its blood supply from the heart (hepatic artery), hence only 25% of the subcutaneous insulin reaches the liver. The liver removes glucose from the blood with the help of insulin when blood glucose levels are high after meal and stores it as glycogen. When the glucose in the blood falls below physiological levels, the liver cells liberate stored glycogen as glucose with the help of another pancreatic hormone, glucagon.

The small intestine has millions of finger-like projections in the lumen called villi (velvety surface), lined by single layer of epithelial enterocyte cells. The enterocyte have hundreds of additional extensions on their exposed surface towards the lumen, called microvilli, which are like tiny



Cross-section of intestinal villi showing layers of mucous membrane and blood supply  
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hairs ("brush border") coated with glycoprotein layer. These constitute a semi-permeable membrane of the gut interior wall and are the first structures to come in contact with food and oral insulin. These enterocytes on the gut lining live only for three to five days before they are shed into the gut lumen and replaced by new cells from the crypt. The enterocyte cells with microvillus and glycoprotein coating are involved in absorbing oral insulin, digesting food with sugar, liquids, secretions, etc. and they also act as barrier to prevent unwanted particulate matter from entering the bloodstream. The villi increase the intestinal absorptive surface area 300-fold and microvilli 600-fold, providing a massive absorption surface of the gut lumen for oral insulin. The center of the villi contains tiny blood vessels and are lymphatic. They collect the absorbed digested material from the guts, including insulin taken orally, and empty it into the portal vein to the liver and through thoracic lymph duct to heart.

Crypts of Lieberkuhn are invaginations of the epithelium at the base and between the villi, like the web of the fingers. The base of the crypts contains stem cells that divide and provide the source of all the epithelial cells in the crypts and the lining of the gut and its secretory cells. The colon does not have villi projections but does have crypts with multiplying stem cells replenishing shed cells.

### Oral Insulin Preparation

An oral insulin preparation contains protective agents that prevent the destructive action of digestive acids and enzymes and facilitators of insulin absorption. These agents should be non-toxic to the intestinal lining and should not have any adverse effects when absorbed. Some developers of oral insulin claim that oral delivery reaches the liver three times more effectively than subcutaneous injection. Unfortunately, these manufacturers forget that oral insulin does not enter fully into the portal blood to be delivered to the liver like naturally

produced pancreatic insulin. As described below, no more than 25-40% reaches the liver, giving oral insulin a 0 to 15% advantage over the injectable form – not a three-time advantage, as claimed. Note: there are many formulations of oral insulin being developed, and this is not the place to describe each individual form.

### Oral Insulin's Path

The lining epithelium (enterocytes) on the villi of the intestines plays an important role in the digestion and absorption of intestinal contents (food), including oral insulin. When oral insulin is taken on an empty stomach, the following occurs:

1. Oral insulin can be inactivated by digestive enzymes, diluted with food and many liters of digestive juices, and deposited in the crypts (Crypts of Lieberkuhn) between the villi. Some of it can be trapped in the diverticulas; part of it can be mechanically dislodged, mixed with food remnants, and evacuated with the next bowel evacuation.
2. Oral insulin attaches to the glycoprotein lining of the microvilli to be absorbed by the enterocytes and its microvilli and transported as described below.

Once oral insulin is absorbed by the enterocytes (villi-lining cells), what happens to this absorbed insulin?

1. Insulin is deposited inside the cells of the villi.
2. Oral insulin from enterocyte cells is transported to blood vessels in the center of the villi and carried to the portal circulation, then to the liver, as with natural insulin.
3. Oral insulin from enterocyte cells is transported to the lymphatic ducts (called lacteals) in the center of the villi situated next to the blood vessels, then delivered to systemic circulation, in which it acts like subcutaneous injected insulin.
4. Oral insulin deposited in enterocyte cells is picked up by billions of plasma cells (immune system) that line below the enterocytes in the lamina propria of the intestines.

5. Some of that insulin is also picked up by the muscle layers and fat in the intestinal wall and used to transport the glucose to these cell layers.
6. Insulin within the enterocyte-lining cells of the villi is shed into the lumen of the intestine without entering the circulation. Every hour, 1/120th (or 20% of it in 24 hours) of the cells lining the villi are shed into the gut lumen; part of it is digested and absorbed, and the rest is evacuated as excreta along with the insulin it has absorbed.

### Insulin Receptors and Cancers

As described in Part I of this series, when insulin comes directly in contact with the cells, it has a more adverse stimulatory effect on dividing stem cells in the crypt and on dysplastic, precancerous, and cancerous cells, which have up to ten times more insulin receptors compared to the single insulin receptor in normal cells. Can you imagine adding a cell stimulant to these multiplying dysplastic cells, especially in constantly multiplying crypts and polyps? Even solitary, non-cancerous fibrous tumors similar to polyps besides other types of cancers have more insulin receptors that facilitate the entry of large amounts of glucose into these cells, promoting their growth, multiplication, and spread.<sup>3-8</sup>

### Possible Health Consequences of Oral Insulin

How will oral insulin, its preservatives, and absorption enhancers affect the gut wall? Can these enhancers cause exfoliation of the lining cells and the breaking of adhesions between lining cells of the gut, resulting in breaching of the barrier between blood and food? If so, can this result in leaky gut syndrome, which can lead to many gastrointestinal (GI) diseases like irritable bowel syndrome, celiac disease, Crohn's disease, IBS, diarrhea, autoimmune diseases, and infections (bacterial, viral, molds, and fungi) and an untold number of





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➤ other diseases? Does anyone know the full effect of oral insulin, which is a powerful growth factor, on the intestinal parasites? Many factors need to be considered: All the following concerns need to be addressed by any pharmaceutical or research centers developing oral insulin for diabetics:

1. What will be the effect when we take oral insulin along with any of the following:

- Antibiotics, which can lead to the overgrowth of abnormal flora in the gastrointestinal tract (bacteria, parasites, candida, fungi)
- Alcohol and caffeine (with strong gut irritants-healing effect of insulin)
- Foods and beverages contaminated by parasites like *Giardia lamblia*, cryptosporidium, and *blastocystis hominis*; by bacteria like *helicobacter pylori*, klebsiella, citrobacter, pseudomonas, and others; mold and fungal mycotoxins in stored grains and fruit and refined carbohydrates. Can these bacteria go wild due to oral insulin?
- Chemicals in fermented and processed food (dyes, preservatives, peroxidized fats influenced by oral insulin)
- Those patients with enzyme deficiencies (e.g., celiac disease, lactase deficiency causing lactose intolerance)
- Non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin, ibuprofen, indomethacin, etc.; corticosteroids, narcotics, blood thinners; hormones (in birth control pills and other medications). Would oral insulin intensify the absorption of hundreds of oral medications, resulting in adverse toxic effects?
- Chemotherapy and radiation therapy cause immune system destruction and damage to the multiplying crypt cells and enterocytes of the villi, resulting in denudation of the intestinal

lining (villi). When we take oral insulin in these situations, what will happen to the oral insulin and what will be its effect on these damaged intestinal lining cells? Will the oral insulin help in healing by stimulating cells to multiply and replace the damaged cells? Or will oral insulin aggravate damaged genetic conditions of cells, leading to infections and tumor development? Or will more oral insulin be absorbed in these situations?

2. Dysbiosis (also called dysbacteriosis) is a microbial imbalance inside the gut resulting from antibiotic use, chemotherapeutic agents, etc. There are billions of beneficial microbial colonies inside our gut that carry out a series of helpful and necessary functions and protect the body from the penetration of pathogenic microbes. Can the use of oral insulin for long time decrease their ability to check growth, allowing an overgrowth of harmful colonies, with subsequent local (thrush) and systemic damage, including leaky gut syndrome, allergies, and other diseases? Conversely, can oral insulin restore the intestinal flora to homeostatic state?
3. It is estimated that the human gut contains 1000 species of ten trillion bacteria. These play a role in gastric ulcer, autism, cancers, fatty liver, ADHD, leaky gut syndrome, inflammatory bowel diseases, etc.<sup>9</sup> According to Dr. J. Nicholson of Imperial College in London: "almost every sort of disease has a gut bug connection somewhere."<sup>9</sup> He says that "if you mess around with gut microbes, you mess around the brain chemistry in major ways." How will health will be affected by the changes oral insulin, with its preservatives and absorption enhancers, makes in the gut microbial environment? Before the oral insulin methods are approved, their effect on gut flora should be studied to prevent any future diseases comparable

to those caused with the use of inhalation insulin.<sup>1</sup>

4. Destruction of villi and microvilli of the intestines by oral insulin containing biochemical additives can lead to malabsorption of nutrients and persistent osmotic diarrhea, often accompanied by fever, as seen in celiac disease and Microvillus Inclusion disease, etc.
5. Insulin-containing particles impacted (stuck) at the crypts are not absorbed into circulation. Crypts of the gut contain stem cells and are in a dynamic state of cell division to replace the inner lining of the gut. Direct contact with oral insulin will surely enhance the growth and multiplication of these cells, leading to increased incidence of polyps and cancers.
6. Direct contact between oral insulin and precancerous cells in the gut lining and polyps can result in their multiplication and transformation into cancers.
7. When impacted in diverticulas, the insulin-containing oral formulation may enhance the infection of any local cysts (as shown with inhaled insulin) with increased incidence of diverticulitis. This may also stimulate the cell growth, causing cancers in the diverticulas.
8. There are 183,000 plasma cells for each cubic millimeter below the villi cells (in *lamina propria*).<sup>10</sup> The absorption of insulin through the lining of the intestinal mucosa will stimulate these cells, which will then become over-active and produce large amounts of immune globulins (IgA, IgG, IgM, and IgG). Patients with inflammatory bowel disease have a higher percentage of some of these immune globulins, which may even increase more, due to the supply of oral insulin growth factor. The effect of overstimulation of these plasma cells by oral insulin is unknown.
9. One of the outcomes of inhalation insulin (oral spray and nasal spray insulin) was an increase in the level of insulin antibodies from baseline levels of 6% to



35%. In contrast, there is hardly any change in the patients with subcutaneous insulin therapy.<sup>1</sup> Orally administered insulin can result in massive insulin antibody production from plasma cells (in *lamina propria*). The adverse effects of such antibodies include retarding the action of soluble insulin in the blood and removing this insulin as an immune complex by the immune (reticulo-endothelial) system, making less insulin available to lower the blood sugar.

10. Low doses of orally administered auto-antigens suppress auto-immunity by inducing antigen-specific regulatory T-cells in the gut, which act by releasing inhibitory cytokines at the target organ. Because type 1 diabetes is an autoimmune disease, the studies made on rats using insulin not only failed to prevent type 1 diabetes, but when insulin was administered with an adjuvant, this actually accelerated the diabetes by destroying insulin-producing cells in the T-cell activated immune system.<sup>11</sup> Can you imagine the acceleration and/or complete destruction of insulin-producing cells in the pancreas due to use of oral insulin with adjuvant? Type 2 diabetes may be converted to type 1 diabetes as the result of insulin antibodies and antibody-containing T-cells of the immune system attacking insulin-producing beta cells in the pancreas. Oral insulin should not be used unless the product is free of these adverse effects as demonstrated through large-scale human studies.
11. Gastrin is a peptide hormone, synthesized and released from stomach (gastric antral G cells). Increased gastrin in the blood (hypergastrinemia) is found in peptic ulcers; treatment of GERD with proton pump inhibitors (PPI); secretion of gastrin from tumors, (gastrinomas- ZES); endocrine neoplasm; atrophic gastropathy;

in PPI therapy, and a host of other conditions. High gastrin in the blood causes benign and cancerous tumors in GI tract.<sup>12</sup> Gastrin stimulates the growth and proliferation of epithelial cells, the normal mucosa, and the multiplying crypts of the villi, predisposing for colorectal cancer, due to increases in angiogenesis and inhibition of apoptosis by gastrin.<sup>13-16</sup> Because insulin stimulates cell multiplication (carcinogenic), taking oral insulin should further increase incidence of gastrointestinal tract cancers, due to synergistic action with gastrin growth factor in the above conditions. Hence, if oral insulin is approved, those with these conditions and those who use PPI should be warned about adverse outcomes.

12. It has been observed that gastric acid suppression, using H<sub>2</sub>-receptor antagonists (cimetidine) and PPI, is associated with an increased risk of community-acquired pneumonia,<sup>17</sup> risk of *C. dif* infection,<sup>18</sup> hip fractures<sup>19</sup> due to low calcium absorption, and interference with osteoclasts' acid production.<sup>20</sup> What will be the result of H<sub>2</sub>-receptor antagonists (cimetidine) and PPI use with long-term use of oral insulin on these conditions?
13. In familial polyposis (FAP), an inherited genetic condition of the colon and rectum, adenomatous, swollen, and thickened multiple tumor polyps develop on the inner lining of the bowel. Polyps turning into cancers are a major cause of death in these patients. Can you imagine giving these patients oral or rectal suppository insulin, which promote cell division, making polyps larger and turning them into cancers? In diabetics with this condition, oral and rectal (suppository) insulin should be contraindicated.

It is only a matter of time before oral insulin for diabetics will be formulated and marketed. But we

still don't know the full effects of the prolonged use of this form of insulin on our 30-foot-long intestinal lining with its billions of cells, trillions of gut bacteria (flora). The health risk for these treatments may take a long time to unravel as did that with the use of Avandia (oral anti-diabetic agent), Vytorin (anti-cholesterol drug increasing the incidence of cancer), Vioxx, (used for pain resulting in heart attack deaths), and, more recently, Exubera (lung cancers) and Byetta (pancreatitis).

### Rectal Insulin Suppository

The absorption and effect of insulin suppository (rectal) is much different than that of oral insulin due to anatomical differences in blood supply to the rectum. It is important to note that when the insulin is absorbed from the rectal mucosa (mostly from the lower half of the rectum), it won't reach the liver in the same way that oral (25-30-40%) and natural pancreatic insulin (100%) does. It reaches middle and inferior rectal veins, which drain to the systemic circulation (inferior vena cava) then into the heart and on to the liver. Superior rectal veins drain to the portal veins that enter the liver. To reach the superior rectal vein's absorption-draining area, a suppository has to be deposited about four inches from the anus, which is not possible. Hence, the action of insulin suppository when absorbed is similar to subcutaneous injection. Rectal insulin absorption is unpredictable and erratic at best. Besides the social difficulty in inserting the suppository, it can get mixed with fecal remnant if the rectum is not completely empty and evacuated with the next bowel movement. Like inhalation, sprayed, or oral insulin modes, this method of delivery has a carcinogenic effect on the rectal mucosal cells with which it comes in contact.<sup>1</sup>



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## Word of Caution to FDA and Pharmaceutical Industry

Oral insulin, if developed and FDA-approved without any health hazards, would be a multibillion-dollar product. One of the developers claims that the oral insulin is a "breakthrough method of delivering insulin orally" that "could bring relief to millions...only an oral capsule mimics the physiological delivery of insulin." These are spurious claims. Such exaggerated claims are not new to this industry when promoting a new product and promoting pharmaceutical company stocks. I recommend that inhalation, oral, and nasal insulin sprays not be FDA-approved. They should not be used by tobacco users, asthmatics, persons with chronic oral-nasal-pharyngeal-esophageal-lung diseases, those with other precancerous lesions (leukoplakia) of the lungs, mouth, and nose. Oral or rectal insulin should never be used by those who have familial polyposis. The FDA must fully investigate the health risks, including the concerns we have enumerated, and mandate post-approval surveillance in addition to pre-approval studies by the developers of these products.

Editor's Note: An extended version of this article is available at [www.TownsendLetter.com](http://www.TownsendLetter.com).

## Notes

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