

### What do a vampire bat and a Gila monster have in common?

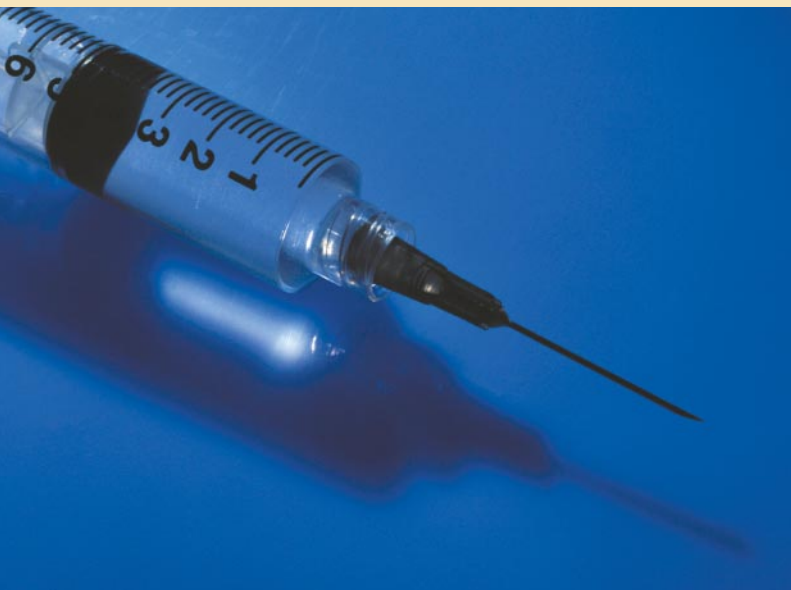
No, they're not the stars of the latest horror flick, but they are the stars of some of the latest drug development research in the area of diabetes and diabetes complications.



### The Gila Monster

At the American Diabetes Association 64th Scientific Sessions in Orlando, researchers presented the results of not one but *two* clinical trials evaluating a new drug called exenatide in patients with type 2 diabetes. Exenatide is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. The Gila monster is native to the Southwestern United States and is one of only two species of venomous lizards. The lizard eats only four times a year and, when not eating, is able to turn its pancreas off, stopping the release of insulin. When it's time to eat again, it secretes the hormone exendin-4 to turn its pancreas on and stimulate insulin secretion.

Researchers have found that exenatide can stimulate insulin secretion in humans, too. When a person eats a meal and blood glucose levels rise, hormones in the gut called incretins act on the pancreas to increase insulin production. Because exenatide exerts its effects on incretin receptors, it is categorized in a new class of antidiabetic drugs called incretin mimetics. When administered, exenatide essentially stimulates the incretin effects and thereby stimulates the pancreas to make more insulin.



Both of the randomized, blinded, placebo-controlled clinical trials performed with exenatide showed progressive weight loss and lower blood glucose levels in patients who received either 5 or 10 $\mu$ g subcutaneous injections twice daily. Trial results were presented by Dr. Ralph DeFronzo of the Texas Diabetes Institute and Dr. David M. Kendall of the Park Nicollet International Diabetes Center. Patients in the studies had type 2 diabetes, and were not able to control their blood glucose levels adequately with metformin (Glucophage), or metformin combined with a sulfonylurea drug (such as Glucotrol or Amaryl). Normally, patients with type 2 diabetes who cannot achieve glucose control with oral medications are prescribed additional oral medications or insulin injections. Exenatide, which causes weight loss, could become a new alternative to making the move to insulin, which causes weight gain. Side effects of exenatide injections were few and mainly included mild to moderate nausea. These trials described here were Phase III clinical trials, which is the last phase of clinical trial before a drug can be considered for Federal Drug Administration (FDA) approval.

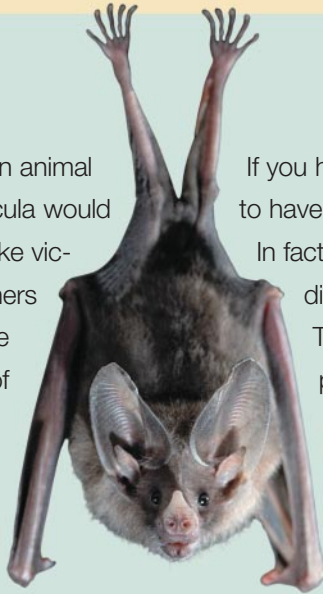
Exenatide may mean good news for people with type 1 diabetes as well. In addition to stimulating insulin secretion, the drug appears to promote pancreatic islet recovery and new growth. A Phase I trial led by Dr. Kristina Rother and collaborating investigator Dr. David Harlan, both at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), is currently underway to determine whether exenatide can be safely used to improve pancreatic beta-cell function in patients with type 1 diabetes. The study enrolls adults with long-standing type 1 diabetes who still have some residual beta-cell function. Because stimulation of growth of new beta cells may activate the underlying autoimmune process, half of the study participants will receive immunosuppressive drugs. Investigators plan to study the effects of exenatide alone, immunosuppressive drugs alone, and a combination of exenatide and immunosuppression on insulin secretion and glycemic control. Another human trial studying exenatide combined with an anti-CD3 monoclonal antibody (an immunosuppressant) is scheduled to begin early next year and will be led by Dr. Kevan Herold at Columbia University in New York. This study is based on successful research in mice where a combination of an anti-lymphocyte serum and exendin-4 led to remission of diabetes in 88% of mice studied (Ogawa N, List JF, Habener JF, Maki T: Cure of Overt Diabetes in NOD Mice by Transient Treatment With Anti-Lymphocyte Serum and Exendin-4. *Diabetes* 53:1700-1705, 2004).

Exenatide is being developed by Amylin Pharmaceuticals in the U.S. According to its website, Amylin currently plans to market exenatide in an injectable pen/cartridge delivery system, pending the necessary FDA approvals. ■

## The Vampire Bat

It may seem somewhat absurd that an animal whose name conjures images of Dracula would be able to help in the recovery of stroke victims, but that is exactly what researchers have found in the saliva of the vampire bat. Vampire bats in tropical regions of South and Central America take in up to 50 grams of blood daily by biting animals such as cows. Similar to a mosquito which secretes enzymes to prevent blood from clotting when it bites, the vampire bat also secretes a protein in its saliva that prevents an animals' blood from clotting while it is feeding.

In the mid-1980s the German biotechnology company PAION GmbH discovered that the vampire bat enzyme was genetically similar to an already known anti-clotting substance but was more potent. Currently there is only one FDA approved drug (IV rt-PA) for treating a stroke caused by blood clots blocking blood supply to the brain, and this drug can only be administered within three hours of the onset of stroke symptoms. Many stroke victims arrive at the hospital too late and are unable to receive this drug. Researchers in the U.S. at the University of Louisville in Kentucky are now testing the ability of the protein found in vampire bats, known as desmoteplase, to break up clots in the blood vessels of stroke victims up to nine hours after the onset of symptoms. Desmoteplase is the first drug to be developed in a new class of blood clot-dissolving agents.



If you have diabetes, you are much more likely to have a stroke, heart disease, or heart attack.

In fact, more than 65 percent of people with diabetes die from heart disease or stroke. This makes it the number one killer among people with diabetes. Development of a new drug to treat stroke may help save lives in the future. Desmoteplase is currently in Phase II clinical trials, and larger scale studies in humans in the U.S. must be successfully completed

before researchers can seek FDA approval. According to the PAION GmbH website, desmoteplase was recently granted fast track status by the FDA. Fast track status is only granted for drugs that address an unmet medical need in a serious or life-threatening situation. Fast track designation means that the review of clinical trial results will be expedited, and the FDA will work closely with the developers of fast track drugs to ensure the final testing of the drug is designed in such a way as to support its quick approval. If the upcoming trials are successful, it is possible that a Biologics License Application (BLA) for desmoteplase would be submitted to the FDA as early as 2007. ■

### Do you know the warning signs of a stroke?

- weakness or numbness on one side of your body
- sudden confusion or trouble understanding
- trouble talking
- dizziness, loss of balance, or trouble walking
- trouble seeing out of one or both eyes
- double vision
- severe headache