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## Good News, Bad News: TrialNet's Bittersweet World

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By Robert S. Benchley



Early treatment of Type 1 diabetes focuses on prolonging the honeymoon period and helping the pancreas continue to produce insulin. The sooner treatment begins, the better the chances of prolonging pancreatic function. But what if it were possible to get a much earlier warning signal than we presently have of the onset of Type 1 diabetes? And how does the earliest-possible intervention affect outcomes for those predisposed toward Type 1 diabetes?

These are the kinds of questions being explored by TrialNet, an international network of researchers who are trying to find ways to prevent, delay and reverse the progression of Type 1 diabetes. According to Dr. Jay Skyler, TrialNet's chairman and Deputy Director for Clinical Research and Academic Programs at Miami's Diabetes Research Institute, TrialNet's mission is to conduct medical trials that advance the early detection of Type 1 diabetes to see if early intervention can reverse or slow the progress of the condition.

TrialNet was established in response to the Surgeon General's Healthy People 2000 report, which identified diabetes as a national health objective for the nation. In response to the report, Congress created the Diabetes Research Working Group, which recommended conducting new T1 clinical trials. Funding for TrialNet comes from the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Child Health and Human Development, the National Center for Advancing Translational Sciences at the NIH, the Juvenile Diabetes Research Foundation International, and the American Diabetes Association.



Dr. Jay Skyler: "Science doesn't move at a predictable rate. You never know what you are going to turn up as you move forward. This is my 20th year chairing these trials. Eventually I'll find the answer."

The most tangible result of the program has been implementation of a screening that identifies the risk of developing Type 1 diabetes among children and adolescents whose parents, siblings, or close relatives have the disease. Tens of thousands have taken the test, and through TrialNet's blood work will show that almost all of the kids who fit the profile above don't carry the antibodies known to lead to Type 1 onset, the need to know is urgent for those tested and the people who love them. A negative result produces a sigh of relief. A positive one can buy precious time.

### Finding Needles in a Field of Haystacks



Though it offers quick answers from screening for Type 1-predicting antibodies, TrialNet's research is a slow march, largely because it takes years to recruit subjects and develop meaningful study results. Screening for study subjects is carefully controlled. To sign up for TrialNet trials, participants must be 1 to 45 years of age, with a sibling, child or parent with T1; or 1 to 20 years of age, with a cousin, aunt, uncle, niece, nephew, half-sibling or grandparent with T1. Close blood relatives of people with T1 are studied because they are 10 times to 15 times more likely to develop diabetes than people lacking the familial relationship.

Although millions of people around the world have Type 1 diabetes, it's still extremely difficult to find enough test subjects to fill out TrialNet's trials, Skyler says. In one trial launched in 1994, researchers had to screen 100,000 people to get 711 who were qualified and willing to enroll. There are 197 affiliated study centers in the United States and Canada, and 31 in Finland, the United Kingdom, Italy, France, Germany, Sweden, Australia and New Zealand. Researchers cast a wide net to ensure that they can recruit enough subjects for the trials to be statistically valid.

"Even if you have a family member with T1, there's a 96% chance that you don't carry the antibodies indicating the possible presence of diabetes," Skyler says. "Of the remaining 4%, some people are ineligible for other medical reasons, some develop diabetes before we can conduct further screening, and some are unwilling to be subjects for further study."

Subjects who screen positive are monitored every six months. Skyler says researchers do everything possible to make sure being a participant is convenient for those who enroll because participants are considered research partners.

### TrialNet's Four Trials

TrialNet has four ongoing trials. In 2007, it began testing an experimental preparation of oral insulin to see if it could prevent or delay the onset of T1. An earlier study with oral insulin (1996-2004) delivered mixed results, says Skyler. "On the whole, it didn't work, but in some subgroups it showed promise," he says. "One subgroup demonstrated a potential 4 to 5-year delay. Another—a subgroup of the subgroup, people with higher levels of insulin antibodies—demonstrated a potential 10-year delay. We're now enrolling new subjects who fit those characteristics to see if we can confirm or refute our assumptions."

Another prevention trial will follow up prior research using a drug called Abatacept, which is currently used to control rheumatoid arthritis. In the earlier trial, the drug seemed to preserve pancreatic function better than a placebo, with no substantial side effects. "That's exciting," says Skyler. "It shows that the odds of seeing a beneficial effect are better when you initiate treatment early in the disease process, before substantial loss of beta cell function."

A third trial will test Teplizumab, an anti-CD3 monoclonal antibody drug used for immunosuppression, which seems to show promise of delaying diabetes onset. Again, the emphasis is on early intervention. Skyler says the trial is focused on people who don't quite have diabetes as defined by a glucose tolerance test, but who are almost there. "By intervening at that stage, we might have the best chance of keeping the disease from progressing further."

Protocol is still being finalized for the fourth trial, which is based on the "hygiene hypothesis" (See Insulin Nation's "[The Hygiene Hypothesis: Too Clean For Our Own Good?](#)"). The hypothesis theorizes that diabetes and other autoimmune diseases have become rampant because the developed world has become too clean, and our immune systems, left with little to do, sometimes attack healthy cells. The trial will involve oral delivery of the ova of porcine whipworms to keep the immune system busy, says Skyler. The worms will not grow and progress inside humans; the only exposure occurs as they pass through the intestinal system. The idea is to see if the worms give the immune system enough to do that the body doesn't attack the pancreas of people genetically disposed towards Type 1 diabetes.

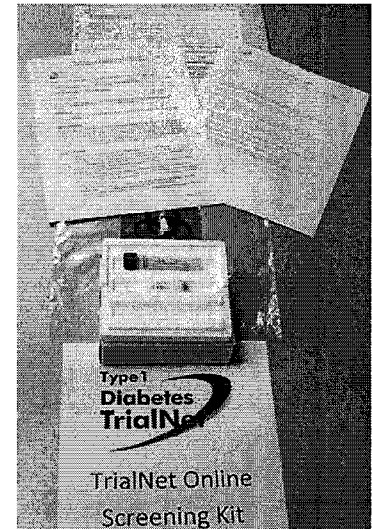
"This hypothesis may sound convoluted to many people," says Skyler. "But it makes good sense in animal models, not only for diabetes but also for all sorts of other immune diseases."

Most of the trials will be completed in the next five years. The timing depends on the speed with which TrialNet researchers can find subjects with the right risk characteristics.

TrialNet offers no silver bullets, just steady research that can lead to progress. In nearly 20 years of clinical research, Skyler has seen his share of false starts and dead ends, but there are also occasional glimmers of hope.

"I was asked to give a talk in 1984 entitled 'Diabetes in the Year 2000'. I listed things I thought would come to fruition; we're still working on them. I gave another talk in 1994, but I changed the title to 'Diabetes in 2021,' which will be the 100th anniversary of the discovery of insulin," he says. "Science doesn't move at a predictable rate. You never know what you are going to turn up as you move forward. This is my 20th year chairing these trials. Eventually I'll find the answer."

Those interested in learning more about TrialNet can visit [www.diabetestrialnet.org](http://www.diabetestrialnet.org).



After volunteers consent online to participate in TrialNet, they receive a screening kit in the mail, as shown, and will be directed to a local lab for a blood test at no cost to the volunteer. (File Credit: Courtesy of University of South Florida)