Chapter 28

Research and Diabetes

INTRODUCTION

Banting and Best received the Nobel prize for their discovery of insulin in 1921. It was believed that a “cure” for diabetes had been found. Before the discovery of insulin, people with the more severe form (now called type 1) lived only about one year. Insulin was not a “cure,” but did save lives. Years later, we began to see and understand the long-term complications of diabetes.

Four Common Research Questions

The four questions about research asked most often are listed below:

1. When will there be a cure?
2. When will continuous glucose testing (no finger pokes) be available?
3. Can diabetes be prevented (type 1 or type 2)?
4. Are there advances in preventing diabetic complications?

There has been wonderful progress in diabetes research over the last ten years. The next ten years will likely show even more progress.
1. A CURE: ISLET/WHOLE PANCREAS TRANSPLANTS

The following research shows promise:

**Islet Transplantation**

In 2001, successful islet cell (the cells that make insulin) transplants were done in Edmonton, Alberta, Canada. Drs. A.M.J. Shapiro, E.A. Ryan, R.V. Rajotte and team reported:

- 16 patients had received islet transplants
- the “cure” rate (off insulin) was 70 percent (11 of 16 patients)

All patients had “hard to manage” diabetes. Most were having reactions (unconscious episodes or seizures) as a result of not recognizing lows (“hypoglycemic unawareness”). For this reason they were willing to take the three medicines needed after receiving the transplant.

**Major reasons for their success may have been:**

- receiving an adequate number of islets (usually with two transplant operations)
- not using steroids as part of the treatment. Steroids have been helpful in preventing rejection of other organ transplants. Steroids cause insulin resistance and raise blood sugar levels.
- the medicine cyclosporine was not used
- their use of new medicines that help the body accept the new islets

The Edmonton results were very exciting and other research centers were invited to see if they could repeat the findings. As a result, over 100 patients have now had islet transplants at numerous centers (including the Barbara Davis Center). Approximately 90 percent of patients remain off insulin for one year and approximately 50 percent of those reaching three years have remained off insulin. Even if a small dose of insulin is again needed, the transplanted islets may still be very helpful. However, the results have been somewhat variable, and one center discontinued their program due, at least in part, to patient complications. In addition, it was reported at the 2005 ADA meeting that the three immunosuppressant medicines being used in the “Edmonton-Protocol” were causing kidney damage. Thus, future research will need to focus on the use of the other anti-rejection medicines.

Dr. Bernhard Hering (University of MN) and his team have reported success for eight patients using just one donor pancreas per patient. Their method of preparing the islets differs from the Canadian group. They are also using a new anti-CD3 antibody to help prevent rejection. Five of their patients remained off insulin for more than one year.

These reports are very exciting and offer hope for the future. You can keep up to date on the progress at [www.islet.org](http://www.islet.org)

**However:**

- there are not enough human islets
- the medicines used to prevent rejection still cause side effects
- the medicines must be taken for the person’s lifetime (at the time of this publication)
- the medicines are costly

This procedure is currently used only in people with diabetes that is hard to control. These people often have severe low blood sugars due to “hypoglycemic unawareness.”

**The main goals for the future for islet transplantation involve:**

- getting islets from an easier source (such as pig islets)
- continued evaluation of new medicines to prevent rejection
- use of new medicines which allow “tolerance” of the new islets so that potent immunosuppression medicines do not have to be taken indefinitely
- protecting the transplanted islets from the immune system (so diabetes does not reoccur)
Whole Pancreas Transplantation

Type 1 diabetes can be cured by a whole pancreas transplant. The medications needed are the same as those given after any organ is transplanted (e.g., kidney, liver, heart). The medicines have improved but still have harmful side effects. Some of these are:

✔ infections
✔ low white blood cell counts
✔ an increase in the risk for cancer

If a kidney transplant is needed due to kidney failure, so that the immunosuppressive medicines are needed anyway, a pancreas transplant may also be done. This may be done at the time of the kidney transplant or at a later time. Approximately 80 percent of the pancreas transplants are still functioning after one year.

In summary, the most important goal at this time is to keep in good sugar control. This will help prevent complications. Then, when a cure becomes routinely possible, the person will be able to benefit from this miracle.

2. CONTINUOUS GLUCOSE MONITORING (CGM)

This area is now covered primarily in Chapter 7 on blood glucose monitoring. However, in addition to becoming a part of routine care, CGM will continue to be an important area of research as more accurate sensors (the cannula placed under the skin) and monitors become available. The major problem in the past has been the lack of accuracy in detection of low blood sugars (and frequent “false sensor” lows), particularly during the night. As between 50 and 75 percent of severe lows occur during the nighttime sleeping hours, an accurate nighttime sensor will be valuable. The National Institutes of Health (NIH) has supported an independent evaluation of the devices and sensors through a consortium of five centers called “DirecNet” (see Figure 1). This is important as commercial companies obviously tend to present their best data as they must sell their products to survive.

The three CGM devices most likely to be helpful in the near future are the Navigator system from Abbott/Therasense, the Guardian from Medtronic/Mini-Med and the DexCom STS. All will have alarms to warn about high and low sugars. All will have the ability to read the subcutaneous glucose levels on the face of a monitor or pump. Although still a hope for the future, having accurate CGM devices available will be an important step in developing a reliable “closed-loop” pump in which the CGM determines pump insulin output (the “bionic pancreas”).

3. PREVENTION OF DIABETES

Prevention of Type 1 Diabetes

It is now possible, for many people, to predict that diabetes will occur. This is done by measuring the following antibodies in the blood:

✔ insulin autoantibody (IAA)
✔ GAD-antibody
✔ ICA512 antibody
✔ fluorescent ICA antibody

Type 1 Diabetes/TrialNet (T1D/TrialNet)

The National Institutes of Health (NIH) and the Juvenile Diabetes Research Foundation (JDRF) and the American Diabetes Association (ADA) have wisely decided to support research aimed at preventing diabetes. The assumption is that if you can recognize who is at risk years before disease onset (which is now possible), there must be some way to prevent the disease. A consortium of 14 centers in the U.S. and Canada and five centers in Europe and Australia are working together to identify people at high risk. Multiple agents will then be used to try to prevent the disease onset. Families having a first or second degree relative who started insulin treatment prior to age 40 years can be screened for the above antibodies. Hopefully, as a result of the studies, diabetes may be able to be prevented in future generations.
The phone number to call to be screened is: 1-800-425-8361. More information is available on the website: www.diabetestrialnet.org.

The T1D/TrialNet consortium is also doing studies in people with recently-diagnosed diabetes to attempt to halt the destruction of the insulin-producing islet cells. It is now known that if a person continues to make some of their own insulin, the course of the diabetes will be easier. The eye and kidney complications are less likely, and severe low blood sugars (Chapter 6) and ketoacidosis (Chapter 15) are less likely. The above number can be called for more information (or go to the website above).

The third approach of T1D/TrialNet is to try to prevent the initial autoimmune reaction against the islets from occurring. In this study, mothers in their last trimester of pregnancy or infants in the first six months after birth are eligible. As the group in which type 1 diabetes is increasing the most is children under age five years, studies starting early in life are important. The number above (or the website) can be contacted for more information.

Prevention of Type 2 Diabetes

The Diabetes Prevention Program (DPP) is discussed in Chapter 13. The DPP studied 3,234 people with impaired (not diabetic) oral glucose tolerance tests. (They were close to having type 2 diabetes.) The results of the DPP were released in 2002. (N Engl J Med 346:393-403, 2002.)

Results:

✔ 30 minutes of activity per day (five days per week) with a low-fat diet and weight-loss reduced the risk for developing type 2 diabetes by 58 percent
✔ taking metformin (glucophage) also reduced the chance of getting type 2 diabetes (by 31 percent)

People with a strong family history of type 2 diabetes now have a clear way to lessen their risk of getting this disease.

4. CLINICAL ADVANCES IN DELAYING THE COMPLICATIONS OF DIABETES

The good news!

The life span for people with type 1 diabetes has increased. In the March, 1999 “Diabetes Care Journal”, an article indicated:

✔ The well-being of patients with type 1 diabetes greatly improved in the last 50 years. This has been shown in studies from Europe and the U.S.
✔ The main reasons for this improvement are:
  ● the risk of developing diabetic kidney disease is less
  ● kidney disease is diagnosed at an earlier stage
  ● treatment with ACE-inhibitors or other high blood pressure medicines

The bad news!

Families often do not bring in the two overnight urines for the microalbumin testing. The healthcare providers cannot always remember to ask you to do this.

If you or your child has had diabetes for:

✔ at least three years
and
✔ has reached puberty (usually 11-13 years of age)

The two overnight urines should be collected every 12 months. Families must help by making sure these important tests are done yearly.

Directions for the collections can be found at the end of Chapter 22. There has been one change in how to collect them.

There have been too many large containers of urine in the lab. We now ask that you:

✔ measure and record the total volume of each of the two overnight collections at home
take a small portion of each sample and place it in separate small containers

bring the two containers (one for each night) to the clinic for testing

Urine is sterile. Measure the urine volume using a cooking measuring cup. Measuring containers and tubes can also be picked up at the clinic during a routine clinic visit. Please label the tubes. Also fill out the form with the times and volumes. (The form can be found at the end of Chapter 22.)

In summary, the life span and quality of life for people with diabetes keeps getting better! Reducing the risk of kidney disease is the major reason.

There is less kidney disease because …

- glucose control is better
- blood pressure control is better
- fewer people with diabetes are smoking
- with use of the microalbumin test, kidney damage is found earlier
- early kidney damage can be reversed before it becomes permanent

The other risk associated with type 1 or type 2 diabetes is cardiovascular disease (particularly heart attacks and stroke). Prevention is discussed in Chapter 11, Normal Nutrition. Not smoking, regular exercise and control of blood pressure and blood lipids are all important in the prevention of cardiovascular disease. In addition, evidence was reported from the DCCT (Chapter 14) at the 2005 ADA meeting that good sugar control helps reduce the risk for heart attacks.

DEFINITIONS

ADA: American Diabetes Association. They are involved with promoting care, education and research for type 1 and type 2 diabetes.

Bionic pancreas: A man-made device that would turn off or turn on insulin based on glucose levels. This type of device is currently in the research phase.

DPT-1: Diabetes Prevention Trial-Type 1. The first large trial in the U.S. to see if type 1 diabetes can be prevented. It has been followed by Type 1 Diabetes/TrialNet.

FDA: Food and Drug Administration.

JDRF: Juvenile Diabetes Research Foundation International. This organization helps to fund research on type 1 diabetes.

Tolerance: (As used in this chapter.) The body’s acceptance of foreign tissue without needing medicines to prevent rejection.

QUESTIONS AND ANSWERS FROM NEWSNOTES

When is a cure coming?
I am asked this question almost daily in clinic. I do not know the answer other than to say that progress is being made.

Which do you think will come first, a safe cure or the ability to prevent type 1 diabetes?
A cure is, of course, already possible if one is willing to take the medicines that may be risky. If enough people are willing to enter studies such as DPT/TrialNet, I would guess we will be able to prevent the onset of some cases of type 1 diabetes before we can easily cure those who already have it.
Example of data from child in the DirecNet research studies who wore two continuous glucose monitoring systems (CGMS) devices (solid lines). He also had blood drawn from an IV line for blood glucose levels (black dots). The two CGMS devices (Medtronic MiniMed) followed the drop in glucose following IV insulin and the subsequent rise following food. It is hoped that the subcutaneous monitors will eventually result in a “closed-loop” pump (“bionic pancreas”) in which glucose levels control pump insulin output.
Table 1
Type 1 Diabetes/TrialNet

People can call 1-800-425-8361 to find out the nearest place to go to obtain the free ICA screening test.

1. **Screening (Phase 1):** Islet cell antibody (ICA) tests

   - The four antibodies used in screening are:
     - GAD antibody
     - ICA512
     - IAA (insulin autoantibody)
     - Fluorescent ICA (if one or more of the antibodies listed above are present)

   ✔ If one antibody is found, a second sample will need to be drawn to confirm the result. If the antibody is present in the second sample, then the person can enter Phase 2.

   ✔ If more than one antibody is present, a second sample can be drawn for confirmation OR the person can go directly into Phase 2.

2. **Phase 2:** The following tests are done:

   - Oral glucose tolerance test (OGTT) - to make sure diabetes isn’t present
   - Islet cell antibody test (as described above)
   - HLA (looking for the 0602 protective gene)
   - HbA\text{1c}

   *In a few cases an additional test will be required:*

   - Intravenous glucose tolerance test (IVGTT)

   With all of the test results, the person can be provided with a risk level related to the development of diabetes (within the next five years).

   The risk levels are: less than 25 percent, 25-50 percent and greater than 50 percent.

3. **Phase 3:** The Phase 2 tests (minus the HLA) are repeated every six months

4. **Oral Insulin Trial**

   Oral insulin was studied in the initial Diabetes Prevention Trial – Type 1 (DPT-1). Because a subgroup showed a favorable effect in delaying the onset of diabetes, a second study will now be done. The oral insulin trial is a double-blinded study in which the participants will receive either 7.5 mg of insulin or a placebo once daily and will not know which they are taking. The insulin taken by mouth does not have any low-blood sugar effect, as it is broken down into smaller particles by the stomach acid.

   The participants in this trial have a 25-50 percent chance of developing diabetes in the next five years.

   In order to enter this study, the Phase 2 test results must show:

   - a positive ICA test (x2)
   - a positive IAA (insulin autoantibody) test (x2)
   - normal insulin production on one IVGTT
   - no protective genes (HLA-DQ 0602)
   - a normal oral glucose tolerance test (OGTT)
   - a mixed meal test (MMT) is done shortly after entering the trial
Some day,
A CURE!