Testimony
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On Behalf of
Juvenile Diabetes Research Foundation International
Regarding Federal Support of Juvenile Diabetes Research
Before the

Senate Permanent Subcommittee on Investigations

Introduction:

I would like to thank Chairman Levin, Senator Collins, and distinguished members of the subcommittee for this opportunity to speak before you. My name is Hugh Auchincloss. I'm a Professor of Surgery and a transplant surgeon at Harvard. I'm also the Director of the Juvenile Diabetes Research Foundation Center for Islet Transplantation at Harvard Medical School. Finally, I have served for the past three years as the Chairman of the Medical Science Review Committee of the Juvenile Diabetes Research Foundation.

I want to speak today about the extraordinary advances that have occurred recently in the effort to cure type one diabetes. I also want to talk about the very significant problems that remain to be overcome, and about the equally significant opportunities that are available today to solve these problems.

What has been accomplished?

Let me talk first about what has been accomplished. Members of this committee have already heard about the success of the "Edmonton Protocol" for islet cell transplantation. This protocol uses a combination of immunosuppressive medicines, islet cell isolation procedures, and techniques for their transplantation that has led to the elimination of insulin therapy for the vast majority of patients who have undergone the full procedure. The success of this protocol has changed the field of islet transplantation dramatically. Two years ago the results of islet transplantation were dismal. Today, we now expect that most patients who undergo the procedure will truly be able to say

that they used to have diabetes.

What remains to be done?

As dramatic as this accomplishment is, much more needs to be done before we can turn to the children in this room and say that we have cured diabetes.

1. In the first place, the patients who have undergone the Edmonton protocol, or other variations of this approach, have actually given up one disease (their diabetes) for another one (the requirement for life-long immunosuppression). All of these patients will need to take a combination of several medicines which prevent rejection of their islets but which also diminish their body's capacity to fight infections and the development of cancers. They will need to take these medicines for the rest of their lives, if they wish to stay off insulin. This trade-off has been justified for a small number of adult patients who truly can no longer tolerate their insulin therapy and for patients who already need kidney

transplants (and thus need immunosuppressive treatment anyway). However, it is not a reasonable trade-off for young children. Therefore, we need to accomplish what is referred to as "tolerance-induction": the re-programming of the immune system so that it treats transplanted tissues from a donor as if they were a natural part of the recipient's body. The Immune Tolerance Network, sponsored jointly by the NIH and the JDRF, is working to initiate clinical trials to accomplish this goal. However, there is still no clear road map for how this can be done and much more research and effort will be needed to bring this effort to fruition.

2. The second remaining problem is that children who have type one diabetes face an additional immunologic problem when we attempt to replace their insulin-

producing cells. Not only will transplanted islets be subject to rejection because they come from a different donor, they will also be subject to immunologic destruction because they are islets, and thus the targets of the original autoimmune condition that caused the disease in the first place. Therefore, even if we learn to accomplish transplantation tolerance and perform islet replacement without immunosuppressive drugs, we will still need to learn how to reprogram the immune system so that these children no longer have autoimmunity.

3. The third remaining problem is that even if we could transplant islets without rejection and without recurrent autoimmunity, we do not have remotely enough islets to go around. Even if we used every available cadaver-donor pancreas for islet transplantation, we

would have only enough islets to cure 0.1% of all the people with type one diabetes. Despite all the efforts that we are making to increase the number of donors and to improve the yield of islet isolation, we still have no hope of finding enough islets from human cadaver donors to cure this disease.

There are at least seven different ways in which more islets might be obtained. Scientists are actively exploring all of them.

1. We might learn to transplant islets from animal donors. This is called xenotransplantation. We have tried this approach, and have, so far, been miserably unsuccessful.

2. We might learn to genetically engineer other types of cells so that they produce insulin in a regulated fashion. For example, liver cells (which are abundant) might be made to secrete insulin on demand.

3. We might develop immortalized lines of insulin-producing

cells that could proliferate indefinitely. We would need, however, to learn how to shut off this proliferation reliably after transplantation to prevent what would otherwise be a transplanted cancer.

4. We might learn to grow cultures of islets so that we could increase the islet yield from each cadaver donor. But so far, whenever we have gotten islets to grow, they have also stopped producing insulin.

5. We might learn to produce new islets from their precursors within the pancreas. So far, however, we're not even sure where these precursors are located and our best efforts to produce new islets from them have yielded only droplets, not the bushels that we need.

6. We might learn to produce islets from so-called adult stem cells. These are cells that have been found in bone marrow, cord blood, and other sites

that appear to be capable of differentiating into many different human tissues. However, despite some recent advances, scientists have been unable to turn these cells into insulin-producing cells, even after thirty years of work.

7. Finally, we might learn to differentiate embryonic stem cells into insulin-producing cells. We know that these ES cell lines can be made to proliferate to produce almost unlimited quantities of offspring. In addition, during the past year, scientists have succeeded in guiding cells of this type to turn into what have been called "pre-islets". These differentiated offspring have produced insulin, but not yet in normal quantities. It was a dramatic step forward in this field, making this the most promising avenue of research toward developing an endless supply of insulin-producing

cells for transplantation.

We do not know which of these approaches might someday solve the critical problem of islet supply. All of these approaches have been attempted. I urge you, on behalf of the JDRF and all the children with type one diabetes, to enable and support research in every one of these areas.

Unfortunately, the most promising of these approaches - the use of embryonic stem cells - is opposed by some. I fear that the opposition is often based on misunderstandings. First, the embryonic stem cells that are most promising are derived from the left-over products of in vitro fertilization. They are derived from clusters of cells that are today sitting in freezers all across this country that are due to be discarded. Another misunderstanding is the idea that adult stem cells are just as good as embryonic stem cells. Someday, we may learn that that is true. However, we do not know today whether it is true or not. On the contrary, there is considerable scientific evidence suggesting that embryonic stem cells have major advantages over any other source of cells.

The JDRF has taken a strong leadership position advocating the continued scientific investigation of embryonic stem cells as a possible source of new islets and of tissues to treat numerous other diseases of both children and adults. We urge Congress and the NIH to support federal funding for this research as well.

Thank you for the opportunity to speak to you today. I would be happy to answer any questions.

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