VOLUME 1 ISSUE 2

DIETRICH DIABETES RESEARCH INSTITUTE

DIABETES ASSOCIATION OF GREATER CLEVELAND

fighting the diabetes epidemic right here at home

DIRECTIONS

SUMMER 2005

DIRECTIONS

is a biannual publication of the Diabetes Association of Greater Cleveland's Dietrich Diabetes Research Institute (DDRI)

INSIDE

2005 DIABETES RESEARCH RETREAT

Stimulating Collaborative Partnerships

Excitement is mounting for the second all-day Diabetes Research Retreat at Executive Caterers at Landerhaven scheduled for Friday, November 18, 2005. The focus of this year's Retreat is "The Genetics of Diabetes" and several renowned speakers from across the country will present. Afternoon sessions will again be interactive opportunities to identify areas for collaborative efforts and initiatives that would have the greatest impact on the future of diabetes research in northeast Ohio.

This unique event reflects the interest that our first Retreat created throughout northeast Ohio – something that you should be proud of and excited about as well! Retreat 2004 was a groundbreaking achievement that served as the kick-off for a city-wide focus to address the challenges of diabetes research in northeast Ohio and plans for a centralized diabetes center here in Cleveland. The 2004 Retreat received press coverage in the *Plain Dealer* and in *Crain's Cleveland Business* (see "Creation of diabetes research center sought" on page 2).

Diabetes experts are working hard to understand, prevent, and provide the best treatments for diabetes – and many of them are doing their cutting-edge research right in your own backyard! To keep you informed and give you an appreciation for the amount, variety, and quality of diabetes research that is being conducted in northeast Ohio, look for 2005 Diabetes Research Retreat highlights in the Winter newsletter.■

WHAT RETIREMENT?

DDRI Consultant Harriet Fader Continues as Driving Force

Harriet L. Fader, CAE, DAGC's former President & CEO, continues her service to the diabetes community as Consultant to DDRI. As the visionary for the DDRI concept, Harriet accepted the position to increase the visibility of diabetes research efforts in the region, increase the recognition of DAGC and DDRI in the health care community as partners in diabetes research, and reinforce the role of DDRI as an independent contact point for the varied diabetes research efforts in northeast Ohio.

Among other activities during her "retirement", Harriet is also serving as the Chair of the Community Outreach Committee for Case School of Medicine's Task Force for the development of a citywide diabetes center and an NIH application to establish Cleveland as a diabetes center of excellence.

We are delighted that we all will continue to benefit from Harriet's expertise, dedication, and respect throughout the healthcare community as she works to advance DDRI and its mission.■

CREATION OF DIABETES RESEARCH CENTER SOUGHT

By Shannon Mortland

From Crain's Cleveland Business, January 10, 2005

Case Western Reserve University and the major medical centers in Cleveland are discussing creating a joint Center for Diabetes that would focus on research and education.

The creation of the center was discussed at a diabetes retreat last month attended by more than 200 local researchers. The retreat was held to discuss the research projects currently in the works at various local institutions, said Suzanne Johnson, research coordinator at the Diabetes Association of Greater Cleveland's Dietrich Diabetes Research Institute.

Dr. John Sedor, professor of medicine and physiology and vice president for research at MetroHealth Medical Center, said the retreat showed much diabetes research is being conducted locally and that there's great interest in collaborating on a centralized diabetes center.

"(The diabetes center) would be inter-institutional," Dr. Sedor said. "Anybody that wants to be part of it could be. Anybody working together to cross-pollinate is always more effective."

Institutions that already have shown interest in creating a diabetes center include the Cleveland Clinic, MetroHealth and University Hospitals Health System, said Dr. Ralph Horwitz, dean of the Case School of Medicine.

Dr. Horwitz said he hopes to form a task force in January to develop a plan for the diabetes center, which would focus on diabetes, obesity and metabolic syndrome. Metabolic syndrome is a group of risk factors, such as elevated blood pressure and obesity, that are found in one person.

Dr. Horwitz said he and Case are "very committed" to making sure the center is established and that it would become nationally known for its diabetes research.

Dr. Sedor said the ultimate goal would be for the center here to become a National Institutes of Health-designated diabetes center. The NIH now has 16 such centers at various universities across the country; it provides those centers with money to create collaborations among researchers doing high-level diabetes research projects.

A joint research effort is particularly important in Northeast Ohio because 1 in 16 local residents has diabetes, Dr. Sedor said. There's also a growing epidemic both locally and nationally of Type-2 diabetes in children - something that wasn't even discussed in medical schools 20 years ago, he said. So far, there's no explanation for the epidemic in children, but he said obesity might play a part in it.

Collaboration could help solve such mysteries, but working together hasn't always been easy, said Dr. F. Ismail-Beigi, professor of medicine and chief of clinical and molecular endocrinology at Case.

Dr. Ismail-Beigi said local medical centers often have felt like they were in competition with one another, and research grants usually are awarded to one institution. A joint diabetes center through which local researchers could apply for grants would make it easier for them to work together, regardless of their employer, he said.

Ms. Johnson said the Diabetes Association of Cleveland long has envisioned the creation of a research center and will do whatever it can to make the dream a reality.

"The idea is to bring all of these people together, to bring all of the available resources together," she said. "We're working in conjunction with Case and the hospitals to try to do what we can to make that happen." ■

KRISTIN DIETRICH GALLAGHER JOINS DAGC BOARD

Continuing the Family Tradition of Philanthropy

Kristin Dietrich Gallagher, daughter of DDRI funders Nancy and Richard Dietrich, is doing her part to further the mission of the Diabetes Association of Greater Cleveland. Krissy, who has type 1 diabetes, joined DAGC's Board of Directors this year. An avid runner, she also is volunteering as Co-Chair of the DAGC Run/Walk to Win the Fight Against Diabetes, presented by The Bonne Bell Company on October 29, 2005. ■

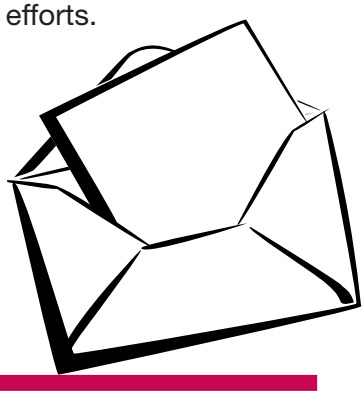
DIABETES RESEARCH MAKES A DIFFERENCE – AND SO CAN YOU!

Join the Fight

Is diabetes research important? If you or a loved one has diabetes, then the answer is YES!

DAGC and DDRI think research is important too. How important? One quarter of DAGC's operating budget supports research activities in northeast Ohio! DAGC funds Grants-In-Aid, Fellowships, and Summer Internships in Diabetes Research. Through the generous gift from the Dietrich family for DDRI, DAGC research activities have expanded to include the online Dietrich Diabetes Database, the first-of-its-kind Diabetes Research Retreat, professional Quarterly Meetings, electronic newsletters to researchers, the DDRI Website, and this newsletter.

How do we continue? Only with your help! Your generosity is critical to maintain DDRI and DAGC research efforts. Your donations to support research maintain and expand these vital services. Every dollar donated makes a difference – and every dollar donated stays right here in northeast Ohio!



You do make a difference! Use the enclosed donation envelope or go online to dagc.org.

PARTICIPANTS NEEDED!

Case Western Reserve University and Rainbow Babies and Children's Hospital are participating in a national multi-center research study funded by the National Institutes of Health. Our local partners in this effort include, The Cleveland Clinic, MetroHealth Medical Center, Kaiser Permanente, and The Children's Hospital Medical Center of Akron.

The TODAY Study wants to find the best ways to treat young people with type 2 diabetes. TODAY compares different treatment methods that include making changes in eating habits and physical activity and taking different combinations of medicines.

Participants are given diabetes care, medical exams, medicines, and diabetes testing supplies at no cost. Participants are seen by a team of doctors, nurses, and diabetes educators and learn how to take better care of type 2 diabetes.

To participate in the TODAY Study, one must:
- Be 10 – 17 years old
- Have had type 2 diabetes for less than 2 years
- Be English speaking

If you or someone you know would like to volunteer or find out more about the TODAY study, please contact:

Paul McGuigan, RN
TODAY Study Coordinator
Rainbow Babies & Children's Hospital
Phone (216) 368-8885
Email today@case.edu

SERVING THE PROFESSIONAL DIABETES RESEARCH COMMUNITY

DDRI as a Contact Point & Disseminator of Information

Diabetes is a complex disease that affects the whole body. DDRI is bringing a whole group of professionals in northeast Ohio together to solve its many puzzles.

Dietrich Diabetes Database

After months of development, the Dietrich Diabetes Database went live this June! The online database is another way that DDRI is stimulating local research. Researchers can view ongoing projects and contact other investigators with questions and ideas for future projects. The result of such collaboration is an enhanced combined effect called synergy, where the result is greater than the sum of its individual parts.

DDRI Quarterly Meetings

The Quarterly Meetings are another way to inform the northeast Ohio professional research community about varied diabetes research projects being conducted at our institutions and continue to encourage cross-institutional, cross-discipline collaboration. Each meeting focuses on a specific topic, with a panel of local experts sharing their research with the attendees. This year's third Quarterly Meeting will be presented in combination with the MetroHealth 2005 Research Festival on September 30, 2005.

MORE LONG TERM BENEFITS FROM TIGHT GLUCOSE CONTROL

The Body Remembers

Dr. Saul Genuth, Professor of Medicine at Case School of Medicine, announced an impressive finding at the June 2005 American Diabetes Association 65th Annual Scientific Session from the EDIC study – a follow-up of patients in the famous Diabetes Control and Complications (DCCT) study. Dr. Genuth is a Past President of DAGC, currently serves on its Medical Advisory Committee, and was a recipient of DAGC's first Grant-In-Aid in Diabetes Research. As the head of the NIH Epidemiology of Diabetes Interventions and Complications study (EDIC), Dr. Genuth shared the news that the intensive management of blood glucose that kept hemoglobin A1c levels closer to the normal value of 6% resulted in a 50% decrease in cardiovascular events like heart attack, stroke, and angina for those type 1 patients in the DCCT study – even years after the trial.

From 1983 to 1989, the DCCT study compared intensive treatment (trying to keep A1c values as close to normal as possible with frequent self-monitoring and a minimum of 3 injections of insulin per day or use of a pump) to what was a more conventional treatment at the time (one or 2 injections per day with daily urine or blood glucose testing and A1c around 9). After 6 1/2 years, the DCCT study was ended early and changed the way diabetes was treated when results showed conclusive evidence that intensive management reduced the development and the progression of eye, kidney, and nerve complications.

In 1994, almost all of the DCCT participants began the EDIC follow-up assessment. Both the intensive and conventional treatment group members eventually ended up with A1c levels around 8 as they continued self-management. The most startling results from the intensive control group are that the benefits of tight control are long-lasting benefits. The original intensive treatment group continues to show reduced risk of complications, even though their self-management shown by A1c levels is similar to the conventional treatment group. Researchers are now calling this effect "metabolic memory."

Analysis of EDIC data continues, but the message from Dr. Genuth and EDIC is clear:

The sooner you begin intensive management and the longer you can maintain that intensive attention to your glucose levels, the more you reduce your risk of complications.

So start now!■

DIABETES AND PREGNANCY

Another local expert featured at the June 2005 65th Annual Scientific Session of the American Diabetes Association was Dr. Patrick M. Catalano, MD, who presented recent research entitled, "Is Insulin Resistance During Pregnancy Different Between Women With Normal Glucose Tolerance and Those Who Have Gestational Diabetes?" as part of a symposia on Diabetes and Pregnancy.

Dr. Catalano, Professor and Chair of Reproductive Biology, Case Western Reserve University at MetroHealth Medical Center, is a world-recognized expert in gestational diabetes, glucose metabolism, and insulin resistance. Active nationally and locally, Dr. Catalano is the Chair of the Dietrich Diabetes Research Institute and is a former Chair of the DAGC Research Committee and a former Vice President of the DAGC Board of Directors.

According to Dr. Catalano, in women with normal glucose tolerance there are changes in insulin sensitivity which have a two-fold purpose: first, to store maternal nutrients (adipose tissue) in early pregnancy to meet the increased metabolic demands of both mother and fetus in late pregnancy; secondarily, there is a 60% decrease in insulin sensitivity in late gestation in order to provide nutrients and to allow growth and development of the fetus and placenta.

In contrast, in women who develop gestational diabetes, there is a significantly decreased insulin sensitivity prior to conception as compared to a weight-matched control group. Although women with gestational diabetes also have a 60% decrease in insulin sensitivity because their insulin sensitivity was already decreased prior to conception and beta cell function is not sufficient to maintain normal glucose tolerance, this combination results in impaired glucose tolerance which we define as gestational diabetes.

The mechanisms for these changes in maternal metabolism are related to placental factors and research is now focused on placental cytokines such as TNFα and leptin which can affect maternal nutrient metabolism and hence, fetal growth and adipocity (fat).■

THE FUTURE OF BIOMEDICAL RESEARCH IS HERE

West Quad Vision to Establish Cleveland as Leader

Development of the 14-acre West Quad at the site of Mt. Sinai has begun. Case and its hospital partners plan to create a collaborative biomedical center that will be at the forefront of medical research and care, attracting top researchers and biotech companies to the area and stimulating the local economy. Visit the Website http://westquad.case.edu for details and Webcam views of the project's progress.

MACULAR DEGENERATION CLINICAL TRIAL MAKES HISTORY

Featured on the July 26 NOVA scienceNOW program on PBS, Dr. Peter Kaiser, MD is making history with the first human clinical trial using RNAi to treat macular degeneration. Dr. Kaiser is an ophthalmologist at the Cleveland Clinic Cole Eye Institute specializing in eye diseases such as macular degeneration and diabetic retinopathy.

Dr. Kaiser was a recipient of the DAGC Grant-in-Aid for Diabetes Research in 2000 for a project that examined the use of steroid injections as a safe, effective treatment for vision loss from macular edema as compared to laser therapy. Look for more about Dr. Kaiser in a future DAGC newsletter. For more information about the accidental discovery of RNAi and this fascinating research, see www.pbs.org.

Congratulations TO NORTHEAST OHIO'S TOP DOCS!

In a recent survey by Northern Ohio Live, physicians were asked to name the doctors they would choose to care for their own family members. We are proud that many who made the list are physicians associated with DAGC and Camp Ho Mita Koda:

Pediatric Nephrology:

Ben H. Brouhard
(former DAGC Board President, former Camp Board Member, DAGC Honorary Director, current Medical Advisory Committee Member)

Endocrinology/Diabetes:

Robert S. Brenner
(former DAGC Board President, current Medical Advisory Committee Member)

Byron J. Hoogwerf
(current DDRI Task Force member, former DAGC Board President, current Medical Advisory Committee Member)

Jay S. Morrow
(former DAGC Board Member)

Thomas A. Murphy
(former DAGC Board Member)

Adrian M. Schnall
(former DAGC Board Member, current Medical Advisory Committee Member)

Daniel Weiss
(researcher with ACCORD clinical trial)

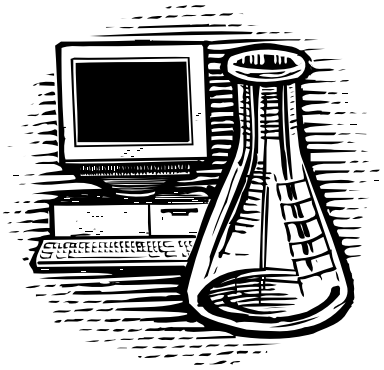
Pediatric Endocrinology/Diabetes:

William T. Dahms
(former DAGC & Camp Board Member, current Medical Advisory Committee Member, DAGC Honorary Trustee, former DAGC Grant-In-Aid recipient)

Douglas S. Kerr
(former DAGC & Camp Board Member, current Medical Advisory Committee Member, DAGC Honorary Director, former DAGC Grant-In-Aid recipient,former DAGC Summer Intern Sponsor)

Douglas Rogers
(Camp Ho Mita Koda Medical Director & current Camp Board Member)

Congratulations and our thanks to all of these dedicated professionals for the work they do to make a difference in the lives of those we serve!



What are stem cells?

Stem cells are primitive cells that can 1) divide and create more stem cells and 2) divide and specialize (or differentiate) to become many other types of cells. Think of them as "blank" cells that don't have any specific function yet. These cells eventually make up the various tissues and parts of the body – organs, blood, brain, etc. There are several basic kinds of stem cells:

Totipotent – These are the "master" cells containing all the genetic information needed to create all the cells of the body plus the placenta– they can do everything (totally potent). Human cells have this capacity only during the first few divisions of a fertilized egg.

Pluripotent – After 3 - 4 divisions of totipotent cells, the cells become increasingly more specialized. Because of their versatility and ability to make every cell of the body except the cells of the placenta, they are called pluripotent cells. These are the cells that people generally think of as **embryonic stem cells**.

Multipotent - Next, the cells are called multipotent, meaning they can give rise to several other cell types. These are cells that are specialized for a particular function. Multipotent cells can give rise to the cell types found in the tissue from which they were derived. Blood stem cells – called **hematopoietic** stem cells - specialize to other specialized blood cells like red blood cells, white blood cells and platelets. Skin stem cells give rise only to the various types of skin cells. Neither could make brain cells, for example.

Terminally differentiated - At the end of the series of cell divisions that make up the embryo the cells are specialized and permanently committed to a specific function.

What are embryonic stem cells?

Start with the **zygote** – the cell that results from fertilization of an egg by a sperm. This cell divides into 2 cells. These 2 cells divide. Each of the resulting cells divides. And so on. About 5 days after fertilization and before implantation in the uterine wall, you have about 150 cells. This assembly is called a **blastocyst**. Think of a volleyball smaller than a grain of sand that is filled with fluid and a baseball. The volleyball is made of the cells that would go on to form the placenta. The baseball, or **inner cell mass**, is a clump of about 30 **embryonic stem cells**. (After the end of the 8th week, the developing cells derived from the baseball become the fetus.)

For research, an egg is fertilized in a clinic in a glass dish or tube (***in vitro***) – not in a woman's body. Fertilized eggs that are not used for *in vitro* fertilization – and that otherwise would be destroyed and discarded – can be donated for research purposes. Informed consent is given from the donors. The inner cell mass from a donated blastocyst is removed and grown or "cultured" in another laboratory dish. As the cells continue to divide and fill the dish, some are put into new dishes to continue to divide. After six months, those original 30 cells of the inner cell mass have divided into millions of embryonic stem cells.

An **embryonic stem cell line** is a group of embryonic stem cells that have been grown in the lab (cultured) for six months or longer, have not "differentiated" (developed into a cell with a specific function), and appear genetically normal.

What are adult stem cells?

Many kinds of multipotent stem cells have been discovered in adults, and scientists believe that more will be discovered. Research is needed to find where they are in adult tissue and how many there are. These **adult stem cells** are used by the body to maintain and repair the tissue in which they are found. They do not come directly from the inner cell mass of the blastocyst, and so scientists are working to find out their origin in development.

These cells are often called **somatic stem cells** (meaning from the body) rather than adult stem cells. There are a number of different types of adult stem cells such as **hematopoietic** stem cells (blood cells), **neural** stem cells from the brain, and **mesynchymal** stem cells that can develop into bone, cartilage, and fat cells.

What does the future of stem cell research hold?

For over 40 years, scientists have conducted studies with the stem cells in adult tissue, so they have had a chance to see some promising results in certain areas. Research with embryonic stem cells has been occurring for a shorter time – just about 15 years - and there is much to be learned. But work with embryonic stem cells holds great promise.

Of course, there is a positive side to using adult stem cells. The controversy surrounding the use of embryonic stem cells is avoided and stem cells from sources like umbilical cord blood appear to hold great potential. In terms of therapeutics, using a person's own adult stem cells, when possible, does not hold the risk of tissue rejection.

From the perspective of patients and families with diabetes, we seek a cure. And we need stem cells that can develop into new insulin-producing islet cells. The continuation of both adult and embryonic stem cell research is critical to our understanding of the how diseases begin, how they progress, and the best treatment for them.

Why is stem cell research Important?

- More than 3,000 people die every day in the United States from diseases that could be treatable as a result of stem cell research - including diabetes. Stem cell research has the potential to launch a new era of scientific discoveries and revolutionize the practice of medicine by improving the quality and length of life.
- Stem cell research using embryonic stem cells and adult stem cells is being conducted throughout the US and the world. With it comes construction, capital expenditures, jobs, an influx of scientists, and renown for the area. Following the initial economic gains, commercialization usually occurs leading to further research, more funding to the area, and more jobs.
- By not investing in this area of great scientific promise, we also stand to lose more gifted scientific minds and entrepreneurs to those states and institutions that are actively pursuing treatments and cures for debilitating chronic diseases.
- There are over 18.2 million people in the US with diabetes and 40 million with pre-diabetes. Diabetes is an incurable disease that costs our nation over 132 billion dollars each year.
- What we stand to lose economically is dwarfed by the loss of life – more than 213,000 people a year – attributed to diabetes. These numbers increase daily and this health crisis is affecting more and more of our children and minorities each year. One in 16 people in northeast Ohio has diabetes.

STAY INFORMED

Learn about Stem Cells and Stem Cell Research

Exciting research is being done utilizing stem cells derived from a variety of sources that can, and we hope will, help and ultimately lead to a remarkable treatment option for those affected by diabetes. Want more information about all the sources of stem cells, what stem cells are, and the new suggested guidelines for research?

- A good place to begin to review and better understand stem cells, the current status of stem cell research, and all of the sources of stem cells is the National Institutes of Health Website section devoted to stem cells at http://stemcells.nih.gov. You will also find a glossary.
- Read the report from the National Research Council Institute of Medicine of the National Academies of Science's Committee on Guidelines for Human Embryonic Stem Cell Research. The report is intended to provide guidelines for conducting human embryonic stem cell (hES) research, both public and private, in a "responsible" manner and also provides background and history. http://www.nap.edu/books/0309096537/html
- Find out more about what's happening with adult stem cell research at The Center for Stem Cell and Regenerative Medicine here in Cleveland. http://ora.ra.cwru.edu/stemcell-center
- Check out the Advocacy section on the DAGC Website at www.dagc.org.

ASK THE EXPERT!

Mary Laughlin, MD

While the debate over embryonic stem cell research continues, many researchers are investigating adult stem cell sources for application in the treatment and cure of chronic diseases. Right here in Cleveland, scientists at The Center for Stem Cell and Regenerative Medicine are focused on treating diseases using adult human stem cells from a variety of sources and tissue engineering technology.

We have asked **Mary Laughlin, MD** from The Center for Stem Cell and Regenerative Medicine to tell us about The Center, stem cells from umbilical cord blood (UCB), and what promise they hold for people with diabetes.

Dr. Laughlin is an Associate Professor of Medicine and Pathology at Case Western Reserve University. She is the Director of the Allogeneic Bone Marrow Transplant Program at Case Western Reserve/University Hospitals Ireland Cancer Center and an internationally recognized expert in unrelated umbilical cord blood allogeneic transplantation (transplanting cells from a person not related to the recipient) for patients with blood disorders. Dr. Laughlin is also a founding member of **Arteriocyte**, a for-profit company developing stem cell therapies to treat the decreased blood supply caused by constriction or obstruction of the blood vessels (ischemia) in people with coronary artery disease, peripheral vascular disease, stroke, and renal ischemia.

• • •

Umbilical Cord Blood Derived Stem Cells in Diabetes

The total absence or low production of insulin by beta-cells avoids a proper control of glucose forcing diabetics to daily insulin injection for survival. **Islet cell transplantation**, including the **Edmonton protocol**, represents a hallmark in the cure of diabetes and has been successfully applied to more than 400 patients, resulting in insulin independence for periods longer than 4 years. However, transplantation trials for diabetes have to face the scarcity of islets available from cadaveric donors. Therefore, the finding of renewable sources of stem cells could circumvent this problem. In this respect, stem cells derived from **Umbilical Cord Blood (UCB)** are representing an interesting alternative. UCB stem cells display robust proliferation and the plasticity to differentiate to other cell types, including insulin-containing cells. The current therapeutic use in the future of bio-engineered insulin-secreting cells derived from UCB stem cells needs at present to fulfill several criteria. These criteria concern the type of stem cell to be used as starting biomaterial (e.g. UCB stem cells expressing the biomarker nestin), the optimal means to differentiate these cells for use in humans, the cell surface markers used to characterize the final cell product, as well as any potential transplantation-associated problems encountered including immune rejection. We will try to focus on these different aspects in order to emphasize the key points to consider for designing unified strategies for diabetes cell therapy utilizing cells derived from umbilical cord blood.

The lifesaving potential of stem cell transplantation for the treatment of diabetes has been a focus on ongoing investigation. A range of opinion exists within the general public and the scientific community about whether research with human embryonic stem cells is ethically acceptable. Further, the current paucity of human embryonic stem cell data has lead investigators to consider umbilical cord blood as a potential source of stem cells to derive islet cells for treatment of diabetes mellitus. Obvious advantages of this approach, if successful, would be fewer ethical hurdles compared with embryonic stem cells. Use of UCB as a stem cell source for research investigation and medical therapies has been approved by the Vatican and other religious groups. UCB is optimal as a stem cell source due to its high content of early developing stem cells, its robust proliferative capacity, low immunogenicity, low infectious contamination, and 'off the shelf' clinical application potential, with diverse representation of HLA genotypes present in banked frozen unrelated UCB grafts. UCB procurement poses no imposition on the normal birthing process and is not associated with ethical concerns in the arena of use of embryonic stem cells. UCB stem cell infusion has been routinely performed for hematology clinical use (approximately 3000 procedures) and to date no malignant transformation has been observed in any study patient. This potential risk in humans is a concern in the use of embryonic stem cells known to generate teratomas in animal study models.

Case Western Reserve University faculty member, Mary Laughlin, MD, was the first physician to transplant unrelated allogeneic umbilical-cord blood (UCB) in a child with leukemia, working with the transplant team at Duke University in 1994. She continued "bench to bedside" studies in children over the next 3 years, culminating in a NEJM paper in 1996 outlining UCB stem cell transplant outcomes [1]. Dr. Laughlin next carried the concept of this novel allogeneic stem cell source, UCB, into adult patients with hematologic disorders over the ensuing 5 years, culminating in a second NEJM paper in 2001 outlining results of this clinical trial in 68 adult hematology patients [2]. Further study over the ensuing 3 years has generated a third NEJM paper written in collaboration with Mary Horowitz (IBMTR) and Pablo Rubinstein (NYBC) comparing this novel hematopoietic stem cell source: UCB, with standard marrow procedures in more than 500 adults with hematologic disorders [3]. This ability and experience in carrying a novel allogeneic stem cell source

With Vincent Pompili, M.D., of University Hospitals of Cleveland and Case School of Medicine, Dr. Laughlin founded the first spin-out company from The Center, Arteriocyte. A current focus of Arteriocyte is to generate new blood vessels to replace or supplement those blood vessels that are not adequately supplying oxygenated blood to heart tissue in patients with heart disease. Using new technologies developed by the founders and Steven Haynesworth, associate dean of the College of Arts and Sciences at Case, multiple stem cell types derived from the blood are combined in a unique way and then infused into damaged tissues to grow new blood vessels.

Patients with heart vessel damage often are referred for angioplasty and/or artery bypass surgery. For patients who also have diabetes – and vascular complications involving various blood vessels throughout the body – these options are sometimes not successful. Arteriocyte intends to target those for whom the conventional approaches have been minimally effective, such as patients with heart disease and diabetes. Following NIH and FDA approval, patient testing should occur at University Hospitals later this year. In the study, stem cells will be drawn from the blood of patients with blocked or damaged heart vessels. These cells will be enriched in the laboratory then reinjected into the patient's damaged heart tissue with the expectation that the cells will trigger the growth of new blood vessels.■

forward from the laboratory into the clinic provides Dr. Laughlin, with her research team at Case, the experience and effective capability to apply and share this knowledge and background to apply stem cell therapies in the treatment of patients with diabetes.

Case School of Medicine ranks consistently among the nation's best medical schools with an individual curriculum and expanding medical research program. In 2000, the School of Medicine had a research budget of nearly $145 million, ranking it as the top medical research institution in Ohio. The School has approximately 500,000 square feet of research space. It is physically linked to University Hospitals of Cleveland through a series of tunnels, bridges and walkways. Basic and clinical research facilities overlap in location and strong interactions take place between Dr. Laughlin's laboratory in the Wolstein research center and clinical teams.

The Center for Stem Cell and Regenerative Medicine (CSCRM) is a multi-institutional center, founded in 2003 with a $19 million award over three years from the State of Ohio as a Wright Center of Innovation. Part of the award from the State of Ohio is funding the construction of a $2.3 million state of the art GMP cell production facility that is anticipated to be completed August 2005. CSCRM is composed of 28 investigators from CWRU, UHC, the Cleveland Clinic Foundation, Athersys, Inc, and the Ohio State University. The focus on non-embryonic stem cells by the founding institution researchers has resulted expertise in six adult stem cell types: Umbilical Cord Blood (UCB), Mesenchymal (MSC), Multi-potential adult (MAPC), Connective tissue progenitor (CTP), Hematopoietic (HSC), and Neural (NSC), investigating the areas of diabetes, cancer, hematopoietic, neurodegenerative, orthopedic, musculoskeletal, and cardiovascular research. Dr. Laughlin is a senior investigator in the CSCRM. Thus, the Center provides an excellent forum and resource for this study group.

Pancreatic islet cell transplantation as a treatment for diabetes has hitherto been confined to small patient cohorts with limited success. The results of islet cell transplantation before and after the advent of the new 'Edmonton protocol' of immunosuppression and management of the donor pancreas has achieved unprecedented success and renewed interest in this potential cure for diabetes. Central to recent improvements in the technique has been the transplantation of an adequate islet mass. Improved methods to procure, isolate, and purify islets for clinical use, are now being adopted as a new 'gold standard'. The use of new immunosuppressive drugs has further improved clinical results. Corticosteroid sparing-based regimens, and agents such as humanized monoclonal antibodies, are likely to form the mainstay of immunosuppressive protocols with the aim of achieving donor-specific tolerance. UCB as an alternative source of islet cells is also required to expand the technique in an era of reduced numbers of donor pancreata. Islet cell transplantation now forms the basis of a prospective multicenter trial under the aegis of the Immune Tolerance Network. The results of this are awaited, but it appears that islet cell transplantation may yet emerge as an effective treatment option for patients with diabetes.■

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Treat Yourself to a Cup of Green Tea With a Cinnamon Stick? - University of Scranton researchers found that both black tea and green tea lower blood glucose levels in rats. When fed the equivalent of less than 5 cups a day for humans for 3 months, diabetic rats also showed significantly lowered cataract formation.

Agricultural Research Service scientists discovered a compound MCHP in the cinnamon plant that acts as an antioxidant as well as helping to lower blood sugar levels. About 1/2 teaspoon of cinnamon powder (not cinnamon oil) lowered blood glucose, fat, and LDL cholesterol levels in volunteers with type 2 diabetes. Glucose levels began to rise when people stopped using the spice.■

Time to Learn the Metric System – No need to calculate your Body Mass Index (BMI) or your Waist-Hip Ratio. According to an article in the *British Medical Journal*, researchers in Sweden have shown that a waist circumference of 1 meter (39 inches) puts you at serious risk for insulin resistance. For both men and women of various ages and body shapes, a waist of less than a meter excludes insulin resistance. A recent study showed the same results in teens – waist size is a predictor of metabolic syndrome, future insulin resistance, diabetes, and heart disease!■

Diabetes Epidemic for Asian Americans – The Western diet may be contributing to the increased incidence of diabetes in the different Asian American populations. Studies show that the ideal body weight is lower and obesity begins at a lower weight class than that of caucasians. Returning to at least one native meal per day may help.■

Agent Orange and Diabetes – A 20-year Air Force study shows a link between type 2 diabetes in Vietnam veterans and Agent Orange, the defoliant containing dioxin sprayed from 1962 – 1971. A 166% increase in diabetes requiring insulin therapy was found in those veterans exposed to the herbicide. As levels of dioxin increased, the time of onset of diabetes shortened and the presence and severity increased.■

Gene Found to Contribute to Diabetes – Researchers have been looking at human chromosome 20 as a probable site for "diabetes genes" and are reporting that a gene has been found that is involved in the action of insulin. The gene Protein Tyrosine Phosphatase N1 (PTPN1) makes a protein that represses the insulin response. The more of this protein produced, the less the ability of the body to respond to insulin, leading to higher levels of blood glucose.

Some variants of this "diabetes gene" are protective and some are neutral. The protective variant of this gene is found in about 45% of caucasians, while the gene contributing to diabetes is found is about 35%. A similar pattern is found in Hispanic families, but not in African Americans. Investigation continues to find all of the genes involved in this complex process and which of those genes have an impact on the development of diabetes in different groups.■

Master Switch for Diabetes Found in Fatty Liver – We all know that those extra pounds put us at risk for serious health problems like diabetes and cardiovascular disease. Researchers at Joslin Diabetes Center now understand that the disease process starts in the liver. Obesity contributes to a fatty liver – and the liver accumulates fat faster than other organs and tissues. This fat in the liver appears to activate a "master switch", factor NF-kB. This factor triggers a low-grade inflammatory "cascade", or series of events, resulting in both elevated insulin and blood glucose levels indicating insulin resistance as in type 2 diabetes. In the cascade, researchers noted the marker C-reactive protein that is also a focus of cardiovascular studies. Researchers continue work on inhibiting this master switch with salicylates.■

"Carpal Tunnel" of the Feet – As diabetes patients live longer, they risk developing advanced complications like nerve problems in the extremities. News from the American College of Foot and Ankle Surgeons Annual Scientific Conference brings hope to many who suffer from neuropathy (nerve damage) and are in danger of amputation. Comparing many of the nerve problems in the feet of diabetes patients to carpal tunnel syndrome, one surgeon explained how a new approach might help delay nerve degeneration.

Nerves enlarge from water build up caused by elevated glucose levels. Since some of these nerves in the feet pass through "tunnels" of ligaments, blood flow is constricted and can eventually lead to nerve degeneration. With the new surgical approach, the tarsal tunnel is released; the nerve decompresses, regains blood flow, and regenerates. The best outcomes are seen when patients seek help as soon as they feel tingling or burning in their toes, before significant nerve damage has occurred.■

Protect Yourself From Neuropathy - According to a large British study published in the *New England Journal of Medicine*, the advice is the same for those with type 1 and type 2: To prevent diabetic neuropathy (nerve damage leading to sensations of pain and/or numbness, tingling or "pins and needles" in the feet and hands), continue with tight glycemic control, watch your weight, do not smoke, and get your blood pressure under control.

And don't forget to learn more about diabetes, find out about the signs of complications (eyes, feet, heart, kidneys, nerves), and ask questions when you see your doctor – be your own health advocate!■

Technology Speeds Bench to Bedside – The CORE (Center for Outcomes Research) Diabetes Model is a multi-national health economic model that uses data from major clinical trials. Using computer simulation, the CORE Diabetes Model can make cost predictions and evaluate clinical outcomes from short-term clinical trial information. With this insight into implementing diabetes treatment guidelines, information from studies that would normally take years to conduct & analyze are quickly translated into effective treatment strategies for diabetes patients.

One report predicts that the US would save around $72 billion of the 132 billion dollar estimated healthcare cost of diabetes if patients with type 1 and type 2 controlled their A1C levels to the recommended 6.5 or 7 percent ($35-$50 billion savings in direct costs like hospitalizations; another $15-$22 billion savings in indirect costs such as lost time at work, disability, and premature death). The report also stressed how tight control of blood glucose and A1C levels helps reduce complications – for every 1% reduction in A1C levels, diabetes complication rates drop more than 25%!

In another recent report, a CORE analysis supported insulin pump therapy over multiple daily injections for type 1. The study projected that use of the pump could increase life expectancy by 10 months. In addition, the lifetime treatment costs of complications with pump therapy saved over $18,000 per life year saved.

Man's Best Friend – Dogs are being trained to detect the smell of a person with blood sugar levels that are too high or too low. About 25 dogs have completed the $4,000 to $20,000 training. These diabetic alert dogs can signal the owner when they need to eat or when they need to take more insulin. For more information, see www.heavenscentpaws.com or www.k94life.org or Assistance Dogs international for a complete listing.

Coffee for Hypoglycemia? – New studies show a significant reduction in nighttime episodes of hypoglycemia (excessively low blood sugar leading to weakness, disorientation, and possible brain damage or coma) in type 1 patients who consume normal amounts (around 250 mg.) of caffeine daily. The underlying mechanism is unclear, but both frequency and length of nighttime hypoglycemia were reduced.

Heart Disease in Teens – Teens with type 1, particularly boys, show early signs of cardiovascular disease and atherosclerosis (thickening of artery walls). Conditions were worse with those who smoked, inhaled second-hand smoke, or had high cholesterol or lipid levels.

Teens and Technology – One way to help teens remember to check blood sugar is to use PDA alerts. Using special software, they can also upload readings, insulin doses, and daily carb intake. The new approach makes it more likely for the kids to test and seems to lead to better control. In another study, kids who got text message reminders to test on their cell phones also tested more often. It may be that other tools like email and instant messages or even watch alarms will also help. The overall message is to find the reminder method that works best for your teen and your family.

Insulin Triggers Diabetes – The autoimmune system normally protects the body from foreign cells; in autoimmune disorders like type 1 diabetes, the T-cells mistakenly begin to turn against a person's own body. Scientists have known that the immune cells (T lymphocytes or T-cells) attack the beta islet cells that produce insulin in the pancreas. What they didn't know until recently was what triggered the series of events that led the body to destroy its own beta cells.

After years of research, 2 separate studies point to insulin as a trigger (antigen) setting the destruction in motion. The exciting discovery opens new possibilities for potential treatment, but first scientists need to find the specific proteins on the insulin molecule that the T-cells recognize and try to defend against.

Autoimmune Regulatory Gene Identified – Roquin, a gene involved in regulating the immune system in mice, has been identified and might help in developing treatment for type 1 diabetes. Roquin acts on a molecule found on the surface of the T-cells. Mutation of the gene results in an overactive immune response by the T-cells, leading to beta cell destruction. A nearly identical, corresponding gene has been identified in humans. Researchers will proceed to study the human Roquin gene and the molecule on the T-cells in people with and without diabetes. The hope is to find ways to prevent the development of diabetes and also prevent the immune system attacks on regenerated or transplanted beta cells.

Beta-cell Production Continues in Type 1 – Evidence now indicates that the production of beta cells continues in the pancreas, even in 88% of people tested who have had diabetes for years. Previously it was thought that the insulin-producing cells were completely destroyed. The researchers noted that the cells have a high death rate, demonstrating that new cells are being formed and continue to be destroyed by the autoimmune response of the body. Finding a way to inhibit beta cell destruction could reverse diabetes. The rate at which the new cells are being produced and how they are produced remain the focus of further study.

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