

20 years Commemorating the Founding of HBDI the Genetics Division of NDRI

“The HBDI has a remarkable history of pioneering efforts, including creating and proving the utility of collaborative international efforts with meticulously collected and characterized collections of DNA and other samples that provided a base for the remarkable growth in our knowledge of the genetics of Type 1 diabetes.”

– George Eisenbarth, M.D., Ph.D., Director, Barbara Davis Center for Childhood Diabetes

It was November in Monaco. The year was 1985, when more than 130 prominent immunologists, pathologists, geneticists, biochemists and endocrinologists convened in this trendy principality for “The World Conference on Diabetes Research,” sponsored by JDF and the World Health Organization. At this scientific symposium, the idea for HBDI – the Human Biological Data Interchange took form. JDF founder Lee Ducat, who also founded the National Diabetes Research Interchange in 1980, co-chaired the conference with scientists K.G.M.M. Alberti, M.D., Ph.D., and Paul Lacy, M.D., Ph.D., along with Carol Lurie, who chaired JDF’s coordination of the event. At that meeting, scientists heard about the important work NDRI was doing to provide pancreas and other tissues for diabetes research, in particular for islet cell transplant studies. What Lee heard, was that scientists needed families for study.

At the Monaco conference, Åke Lernmark, Ph.D., then a professor at the Hagedorn Research Laboratory in Denmark and an NDRI advisor, planted the seeds for a new NDRI initiative. “You know,” he told Lee, “we really need to push to find the Type 1 diabetes genes.” Previously, families in small numbers were willing to donate blood samples to grow cell lines for study, but much larger collections were needed, he said, to push genetic research forward.

On the flight back to Philadelphia, Lee thought about how she could make this happen. For NDRI, she had designed the systems to collect tissue and medical history data from surgical, transplant and *post mortem* donors all around the country. NDRI systems could serve as a model for this new thrust. She had worked with families from JDF for nearly two decades. She knew how dedicated they were, but collecting medical histories and coordinating blood draws from entire families

would be a challenge. Systems had to be designed for blood collection nationally, and cell immortalization, storage and distribution to scientists. In the early 1980s registries were not the popular core of patient research studies, and a Type 1 diabetes registry was non-existent.

HBDI is born

The JDF leadership was interested in this project and both NDRI and JDF would move forward to fund and establish this new genetic resource for Type 1 diabetes



George Eisenbarth, M.D., Ph.D.

research – HBDI, the Human Biological Data Interchange. Once again, a long road of creative thinking and hard work lay ahead. Lee and her committee of scientific experts pressed forward. Lee set about recruiting top immunologists and genetic experts to serve on the first HBDI scientific advisory committee, and Åke Lernmark, Ph.D., who was then Professor of Medicine, University of Washington, Seattle, and George Eisenbarth, M.D., Ph.D., who was Chief of the Section of Immunology at the Joslin Diabetes Center, agreed to chair the effort. Members of that first HBDI Steering Committee included Pablo Rubinstein, M.D., Director of Immunogenetics, New York Blood Center, Graeme Bell, Ph.D., Associate Professor of Biochemistry and Molecular Biology and Medicine, Howard Hughes Medical Institute, Janice Dorman, Ph.D., Assistant Professor, University of Pittsburg, Jurg Ott, Ph.D., Professor, Department of Genetics, Columbia University, M. Alan Permutt, M.D., Washington University School of Medicine, Michael J. Sheehy, Ph.D.,

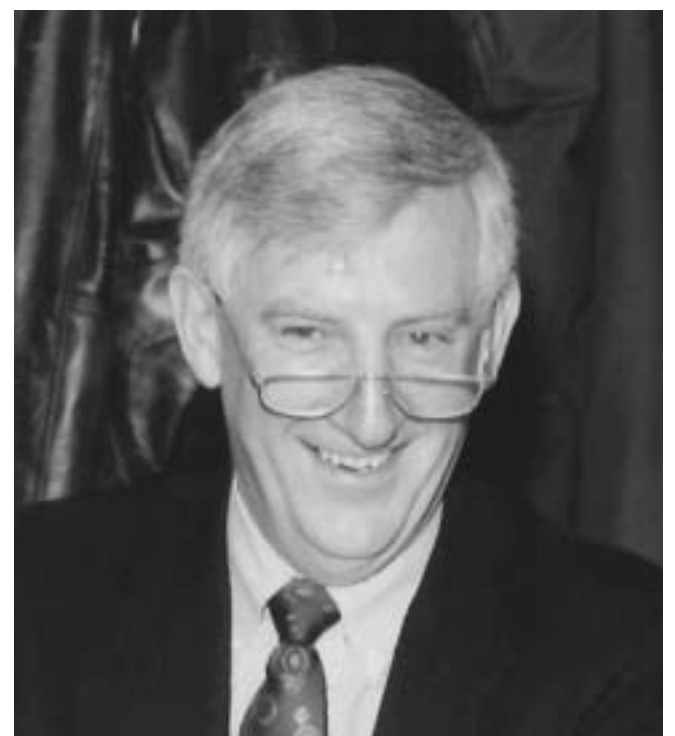


Åke Lernmark, Ph.D.

Scientific Director, American Red Cross Blood Services, Richard Spielman, Ph.D., Associate Professor of Human Genetics, University of Pennsylvania School of Medicine, Howard Tager, Ph.D., Louis Block Professor, University of Chicago Medical School, Gerard McGarrity, Ph.D., President, Coriell Institute for Medical Research, Sara King, JDF Director of Research Programs, and Fran Jacoby, JDF Volunteer Chairman.

Under the direction of the co-chairs and steering committee, HBDI began to seek simplex families with one proband with Type 1 diabetes and to prioritize the recruitment of multiplex families with two Type 1 affecteds. The systems were put in place and coordinators trained to work with families to obtain informed consent, collect blood and medical histories. Specialized blood collection kits were designed to make it

easier for physicians, venopuncturists and nurses to collect blood samples and ship them to the cell repository. Blood samples were immortalized into cell lines and DNA aliquots through a solid relationship with Coriell Institute for Medical Research to ensure a renewable resource from these Type 1 families. Scientists needed statistically significant numbers of families to study, so recruitment continued first with 100 families, then 500 to the 600 immortalized families available for study. The HBDI database grew to over 6,000 families registered, 35,000 individuals and 100,000 extended family members.



Noel Maclaren, M.D.

Throughout the next decade, HBDI family recruitment led to the creation of the largest registry of patients with Type 1 diabetes and their families for research. Enriching the collection were families from Canada, England, Ireland, Scotland, Puerto Rico, Chile, Australia, the

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Netherlands, Italy, Israel and France, some recruited by scientists who shared these families from their own collections. Two major contributing scientists were Noel Maclaren, M.D., then Professor and Chairman of the Department of Pathology and Laboratory Medicine, University of Florida, Gainesville, and HBDI Co-Chairman George Eisenbarth, M.D., Ph.D., Executive Director, Barbara Davis Center for Childhood Diabetes in Denver.

“Search for the Diabetes Genes”

In the early 1990s “The Search for the Diabetes Genes,” a legislative effort was launched to fund research to find the genes that cause diabetes and its complications. Lee worked to facilitate a Capitol Hill Conference on The Genetics of Diabetes in April 1990, co-chaired by Senator Jake Garn, who had donated his kidney to his daughter with Type 1 diabetes, Senator Strom Thurmond, whose daughter has diabetes and Senators Arlen Specter (R-PA) and Tom Harkin (D-IA), Chair of the Senate Appropriations Subcommittee, and with Congressman Louis Stokes (D-OH), who strongly endorsed the initiative along with others from government, the scientific community and the public. Senators Thurmond and Garn joined Lee in testimony to Congress to press for increased funding support. A unanimous vote by the National Diabetes Advisory Board added weight to the appeal and by 1992, Congressional appropriations had increased to support the search for the diabetes genes.



Senator Tom Harkin

NDRI groundbreaking conferences on genetics of rare and common diseases

Continuing the momentum in support of research focused on the genetics of Type 1 diabetes, in October 2000, NDRI gathered top geneticists for the first international conference on “The Genetics of Complex Diseases.” Åke Lernmark, Ph.D. co-chaired the conference with Noel Maclaren, M.D., then Chairman of the NDRI Board of Directors. The agenda featured a day of roundtable discussions on the genetics of complex diseases, Type 1 diabetes, autoimmune thyroid disease, and autism. Francis Collins, M.D., Ph.D., then Director of the National Human Genome Research Institute, was recognized as “Scientist of the Year” for his monumental achievement expediting, coordinating and completing the sequencing of the human genome.

NDRI sponsored a second groundbreaking conference in Washington, in 2003, “The Genetics of Rare Disease – Window to Common Disorders,” for which Francis Collins, M.D., Ph.D., served as Honorary Chair and led the creative process of designing the conference. More than 300 attended from major university centers, NIH and other government agencies, voluntary health organizations and corporations to consider new strategies for the study, prevention and treatment of common and complex diseases. In 2008, Dr. Collins agreed to

spearhead yet another NDRI conference, “Therapeutic Insights from New Diabetes Gene Discoveries.” He called the series of roundtable discussions a “true landmark” in diabetes research, highlighting the most recent discoveries of more than a dozen new diabetes genes, which established new subtypes of diabetes. “What we experienced was an up to the minute summary of all the new discoveries of genetic factors in Type 1

and Type 2 diabetes, along with a highly sophisticated discussion of how these new discoveries may shed light on disease pathogenesis,” he said. “What is more, the private sector researchers focused on how best to capitalize on these new discoveries to target new pathways toward therapies that could never have been dreamed of before.”

Co-organizers of the international genetics conference “Therapeutic Insights from New Diabetes Gene Discoveries” were Francis Collins, M.D., Ph.D., presently Director of the National Institutes of Health, David Altshuler, M.D., Ph.D., Associate Professor of Genetics and Medicine, Harvard Medical School, Christopher Austin, M.D., Director, NIH Chemical Genomics Center, Andrew Hattersley, D.M., FRCP, Professor, Molecular Medicine, Peninsula Medical School, Exeter, UK, Stuart Schreiber, Ph.D., Professor and Chair, Department of Chemistry and Cell Biology, Harvard University, and John Todd, Ph.D., Professor of Medical Genetics, Cambridge Institute for Medical Research, UK.

The Keynote speaker was Peter Goodfellow, D.Phil., former Senior Vice President for Discovery Research at GlaxoSmithKline, UK. Recognized as “Distinguished Scientists” were Andrew Hattersley, D.M., FRCP, for his breakthrough research in the discovery of the genes for monogenic/neonatal diabetes; John Todd, Ph.D., for his genome wide association studies to elucidate inheritance of Type 1 diabetes and pathways involved in disease development, and David Altshuler, M.D., for his discoveries in the genetics of Type 2 diabetes. Francis Collins, M.D., Ph.D., was presented with NDRI’s first “Benjamin Franklin Distinguished Scientist Trophy.”

HBDI – an international resource for genetic research for future studies

HBDI families still hold secrets ready to be discovered. Because these families have been tracked for up to 20 years, the HBDI resource is the oldest registry of families with Type 1 probands. The HBDI resource is a rich storehouse of genealogical and medical history data containing information on complications, surgeries, transplants, physician updates and rare and autoimmune diseases, from nearly 35,000 primary members and over 100,000 extended members of 6,700 families affected by Type 1 and/or 2 diabetes as well as control families. Cohorts within the database include: 3,500 simplex families, 700 multiplex families, 450 three generation families, 300 families with twins/triplets, 1,300 families with autoimmune diseases, 300 families with clustering of autoimmune diseases, 1,500 families with clustering of complications, 2,700 families with Type 2 diabetes, 3,000 families with other diseases, rare and common, and 100 control non-diabetic families. Within the database are individuals with



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– Francis Collins, M.D., Ph.D.



Senator Arlen Specter

SCIENTISTS NEED FAMILIES TOO

If you're living with diabetes, please call to help science.

Families like yours have valuable information about the genetics, the causes and the cure for diabetes.

Call: **800-345-4234** to inquire about participating.



HBDI The Human Biological Data Interchange

onset from birth to age two, valuable for the study of diabetes subtypes as well as families with two to four Type 1 members, families with early onset and rapid development of complications.

HBDI's biorepository contains some 350,000 aliquots of DNA, cell lines, buffy coats and sera from close to 600 highly characterized families with Type 1 diabetes. Currently there are 175 enrolled scientists and a collection of 99 publications based on the study of 28,152 HBDI family biomaterials. This collection was one of the first to offer HLA typing of families using the latest PCR-based methods of DNA amplification performed by Henry Erlich, Ph.D., and Janelle Noble, Ph.D. at Roche Molecular

Systems. Studies in many different labs showed that the major genetic contribution to Insulin Dependent Diabetes susceptibility comes from the region of chromosome 6 containing the HLA genes. The HBDI catalog of coded family pedigrees makes it easier for researchers to view and request families and individuals for study. HBDI families have been important resources for the Type 1 Diabetes Genetics Consortium and the International Histocompatibility Working Group of investigators who performed micro-satellite typing on families from the registry.

HBDI has served 175 scientists resulting in 99 publications

Genetic research advances through the use of HBDI families

Increasing numbers of published studies throughout the last two decades chronicle the research advances emerging from the data and material available from the HBDI resource. The HBDI repository has been a key element in the discovery of Type 1 diabetic susceptibility genes. It has also contributed to discoveries of associations of diabetes with single nucleotide polymorphisms (SNPs), with extended haplotypes and with either risk for or protection from Type 1 diabetes conveyed by those DNA features. Studies have also contributed to understanding potential mechanisms of how genetic mutations lead to Type 1 diabetes development and disease progression. After the *American Journal of Human Genetics* announced the availability of the immortalized cell lines and DNA for research in 1990, it took only four short years for John Todd, Ph.D., University of Oxford, and colleagues to publish evidence that Type 1 diabetes susceptibility is influenced by a number of different genes. Quickly following this work, there were multiple studies from John Todd, Ph.D., Jin-Xiong She, Ph.D., University of Florida, and Tim Magnus, M.D., University of Calgary, utilizing HBDI repository samples to identify specific Type 1 diabetes susceptibility genes including IDDM3, IDDM4, IDDM7, LYP, IDDM8 and CTLA-4. Many studies were able to determine risk and protection in Type 1 diabetes conveyed by HLA haplotypes including studies led by Henry Erlich, Ph.D., George Eisenbarth, M.D., Ph.D., Janelle Noble, Ph.D., and John Todd, Ph.D.

For the past 10 years, major studies based on HBDI families have looked at the impact of single nucleotide polymorphisms (SNPs) on the risk of developing Type 1 diabetes. This work by Patrick Concannon, Ph.D. and Francesco Cucca, Ph.D., for example, showed that although one specific allele in PTPN22, which encodes for LYP, is a major risk variant for Type 1 diabetes, other variants also can contribute to development of Type 1 diabetes. Other studies by Henry Erlich, Ph.D. and John Todd, Ph.D. indicated that genes such as IL18, IL4R, MICA, and MICB, do not play a role in Type 1 diabetes risk.

Using the HBDI family resource, researchers have explored genetic factors that are involved in autoimmune disorders, that are frequently clustered in

families with Type 1 diabetes. In 1999, George Eisenbarth, M.D., Ph.D., and colleagues demonstrated that there was a correlation between both a specific HLA allele and the presence of 21-hydroxylase autoantibodies, but the group also showed that the presence of autoantibodies alone was not sufficient for disease progression. In 2005, Yaron Tomer, M.D., and his team demonstrated that there were common and also unique genes associated with Type 1 diabetes and thyroiditis. Dr. Jin-Xiong She, in 2005, demonstrated that the known Type 1 diabetes susceptibility gene PTPN22, was a critical player in multiple autoimmune disorders.

In 2007, the work of David Greenberg, Ph.D., Director, Division of Statistical Genetics at Columbia University, and Cristina Monti, Ph.D., at the University of Pavia, Italy, along with NDRI Research Director John Lonsdale, Ph.D., and staff showed that familial clustering among HBDI families exists for diabetic complications and that the severity and progression of retinopathy appear to be familial. Subjects were classified based on when diabetes was diagnosed and on medical histories documenting the presence or absence of microvascular complications, retinopathy, neuropathy, and nephropathy in those subjects. Utilizing data from 8,114 Type 1 diabetic patients among 6,707 HBDI families, they determined that the presence of a complication in siblings increased the risk for that same complication among probands for all three classes of microvascular complications, supporting the idea that the complications themselves are inherited. Furthermore, female probands were at a

higher risk to develop retinopathy than male probands. Finally, if a parent had Type 2 diabetes, the risk of complications was also higher. A parent with Type 1 diabetes did not seem to affect risk of complications.

Dr. Greenberg and the team are working to determine the specific chromosomal loci variations that contribute to microvascular complication risk. Using a subset of affected sibling pairs, both with and without microvascular complications, they have already found that four specific loci may either contribute to, or offer protection from, the development of microvascular complications in Type 1 diabetic patients. They are currently in the process of isolating specific single nucleotide polymorphisms which play a role in this process in order to more fully elucidate the genes that are involved in the development of microvascular complications.



"You need a huge collection of families to do these studies, and that is why the HBDI/NDRI collection is so unique, 6,700 families is a resource that cannot be duplicated anywhere in the world...these are impressive numbers for anyone who is interested in population characteristics."

—David Greenberg, Ph.D.

In 2009, a team of investigators led by Yaron Tomer, M.D., Mount Sinai Medical Center with David Greenberg, Ph.D., Columbia University Medical Center, studied an HBDI subset of 88 families with 448 individuals and identified three chromosomal loci that show linkage when individuals have either Type 1 diabetes or autoimmune thyroid disease, or both. The discovery of these linkages demonstrates that there is a shared genetic susceptibility to Type 1 diabetes and autoimmune thyroid disease involving mostly immune regulation genes, suggesting that perhaps dysregulation of the immune system plays an important role in the development of both Type 1 diabetes and autoimmune thyroid disease. As Dr. Greenberg has commented, "You need a huge collection of families to do these studies, and that is why the HBDI/NDRI collection is so unique, 6,700 families is a resource that cannot be duplicated anywhere in the world...these are impressive numbers for anyone who is interested in population characteristics. The data, the collection of families, is probably the only collection in the entire world where we can even approach the question of the familiarity and the genetics of complications." ■



Yaron Tomer, M.D.

20 years Commemorating HBDI



First International Conference the Genetics of Complex Disease



Lee Ducat and George Eisenbarth, M.D., Ph.D.



Richard Spielman, Ph.D., and John Todd, Ph.D., FRCP



Lee Ducat and Åke Lernmark, Ph.D.



Senator Jake Garn and his family



Richard Spielman, Ph.D., and Arthur Caplan, Ph.D.



Senator Strom Thurmond and his family



Peter Goodfellow, D.Phil., FRS
Keynote Speaker, Genetics of Diabetes Conference



Frances Ashcroft, B.A., Ph.D., D.Sc.



Francis Collins, M.D., Ph.D., NIH Director
Genetics of Diabetes Conference Co-chair



Andrew Hattersley, D.M., FRCP and David Altshuler, M.D., Ph.D.



Discussion group from the Genetics of Diabetes Conference