
Series: Molecular Medicine Institutions

The Joslin Diabetes Center

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The Joslin Diabetes Center in Boston was established in 1898, more than 25 years before the discovery of insulin, and has been at the forefront of diabetes research, treatment, patient and professional education ever since. Joslin is affiliated with Harvard Medical School and has enjoyed a rich history of important discoveries and innovations. These include:

- Pioneering the team model of diabetes care and involving the patient in understanding and managing his own disease—a concept established by founder Elliott P. Joslin, M.D. and his colleagues in the early years of this century;
- Emphasis on tight control of blood sugars as a means of preventing diabetes complications. This controversial focus of the Joslin-style of patient care endured ridicule in many quarters for over 60 years until the nationwide Diabetes Control and Complications Trial proved conclusively that tight blood sugar control reduces complications;
- Development of clinical protocols by Priscilla White, M.D., and those who followed her, that raised the fetal survival rate for diabetic women from only 50% at mid-century to over 96% today;
- Seminal work in the development of laser photocoagulation to treat diabetic eye disease;
- Identification of the means to tell who is most likely to develop type 1 diabetes years in advance of symptoms and the identification of treatment strategies now in nation-

wide NIH clinical trials, to see if this form of the disease can be prevented;

- Multiple discoveries related to the fundamental mechanisms of insulin action, islet cell regulation and mechanisms of tissue injury to vascular tissues in diabetes.

Current Research and Clinical Programs

The current research program involves more than 200 staff members, including 30 top-level investigators. The research program has shown immense growth over the past 15 years, growing from a program with an annual budget of \$6 million in 1985 to over \$25 million in FY 2000. The research program encompasses 11 sections, representing a full range of basic and clinical research activities: Behavioral and Mental Health; Cellular and Molecular Physiology; Clinical Physiology and Clinical Research; Eye Research; Genetics and Epidemiology; Immunology and Immunogenetics; Islet Transplantation and Cell Biology; Metabolism; Molecular Biology; Vascular Cell Biology; and Nephrology.

The Joslin Clinic offers services including adult diabetes and endocrinology, pediatric diabetes and endocrinology, ophthalmology, mental health, diabetic pregnancy, and diabetes care. In 1999, the Clinic formed a joint venture with CareGroup and Beth Israel Deaconess Medical Center to further strengthen its ability to provide the complete range of diabetes services patients require. Joslin has also broadened its patient care and professional education activities beyond Boston in the past decade, establishing more than 20 Joslin Centers at selected sites around the United States

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and conducting an estimated 90 continuing medical education programs reaching more than 30,000 physicians, nurse practitioners and other diabetes care providers each year. Both the clinic and research activities are housed in a facility that takes up most of a city block in Boston's Longwood Medical Area of Harvard teaching hospitals.

Research Strengths

One of the key features in the design of the Joslin Research Program has been to create an environment in which there is both breadth and depth. A breadth of topics is needed to cover the many areas of knowledge which are required for research into diabetes and its complications. A depth of expertise is found in most areas where there are several investigators with common interests and overlapping areas of expertise that maximize both individual and group productivity. In addition, because of the breadth of the research programs needed to deal with both type 1 (insulin-dependent) and type 2 (non-insulin dependent)

diabetes and their complications, many investigators at Joslin have areas of expertise outside the diabetes field, including areas related to basic biochemistry and cell biology, genetics, immunology, vascular biology, visual and renal physiology, growth and development, and cancer.

Since all members of the Research Division are also full-time faculty of Harvard Medical School, there is also considerable interaction and collaboration with non-Joslin investigators who have related interests and complementing research expertise. Joslin researchers have particularly close interactions with colleagues at the Beth Israel Deaconess Medical Center, Dana-Farber Cancer Institute, Children Hospital, Brigham and Women's Hospital, Harvard School of Public Health, and Harvard Medical School. At the same time, Joslin has its core laboratories and infrastructure to provide its researchers with most of their critical needs and up-to-date technologies.

Joslin researchers are very strong in many areas, including insulin signaling, islet cell biology, immunology, pathophysiology of diabetic complications, genetics, exercise physiology and other areas. This strength is evidenced by the very impressive list of more than 3000 publications produced since the founding of the Center, the invitations to speak at many national and international meetings, and the receipt of major awards inside and outside the diabetes field. For example, in 1999 alone, Research Director and Center Director C. Ronald Kahn, M.D. was elected to the National Academy of Sciences and the Institute of Medicine. Morris F. White, Ph.D., a senior investigator in the Research Division, was named the Outstanding Diabetes Researcher under age 45 by the American Diabetes Association and Lloyd M. Aiello, M.D., director of the Clinic's Eye Institute, was named the Outstanding Physician Clinician by the American Diabetes Association.

About the President and Research Director

In January 2000, Dr. C. Ronald Kahn became the President of Joslin Diabetes Center. He has served as Research Director of Joslin Diabetes Center since 1981 and, in 1998, was named Director and Executive Vice President of the Center. He is also the Mary K. Iacocca Professor of Medicine at Harvard Medical School.

His special research interests include: insulin action and insulin resistance particularly as it relates to type 2 diabetes; the genetics of diabetes; and the pathophysiology of diabetes. Much of the work in the Section on Cellular and Molecular Physiology, which he heads, centers around understanding the mechanism of action of insulin and related hormones, how insulin action pathways are altered in diabetes and other disease states, and how insulin action can be mimicked or improved as an approach to the treatment of diabetes.

Since the initial discovery by his laboratory that the insulin receptor is an insulin-stimulated enzyme with protein tyrosine kinase activity, the Kahn laboratory has focused its attention on how this early signal is converted to the final effects of insulin on metabolism and growth, how insulin signaling is altered in insulin-resistant states such as type 2 diabetes, and what the impact of genetics is on these functions. Following the activation of the receptor kinase, several intracellular substrates become tyrosine phosphorylated. The best studied of these are two related high molecular

weight proteins, termed insulin receptor substrates 1 and 2 (IRS-1 and IRS-2). These phosphorylated proteins serve as docking sites for other intracellular signaling proteins (SH2 proteins) and link insulin stimulation to two major intracellular cascades: one is the pathway mediated by an intracellular enzyme phosphatidylinositol 3-kinase (PI 3-kinase) and the other is the Ras pathway. This forms an important point of diversion in insulin signaling and several potential points of regulation in disease.

Current projects in the laboratory include defining the roles of the IRS proteins and PI 3-kinase in the insulin-signaling pathway through the creation of new cell lines and animal models in which these proteins are either eliminated by a genetic "knock-out" or increased by overexpression. This has led to identification of previously unrecognized pathways of signaling and creation of the first polygenic model of type 2 diabetes in rodents which resembles human type 2. This lab also has used molecular genetic techniques to identify novel intermediates for the PI 3-kinase pathway and regulation of calcium flux by insulin in important target tissues, such as skeletal and cardiac muscle.

Dr. Kahn also is characterizing the alterations in insulin-signaling at a molecular level in insulin-resistant states, especially type 2 diabetes (NIDDM), and determining how this signaling system interacts with other hormonal and metabolic signals. Both genetic and acquired alterations in multiple steps of these signaling pathways have been observed. The Kahn laboratory is studying ways to overcome this insulin-resistance and improve diabetes control in humans and in rodents. These researchers also have defined novel interactions between the insulin-signaling pathway and the action of vasoactive hormones, such as angiotensin II, which may contribute to the association between diabetes, hypertension and accelerated cardiovascular disease.

Dr. Kahn is a 1964 graduate of the University of Louisville and received his medical degree from the University of Louisville School of Medicine. He completed internship and residency training at Barnes Hospital, St. Louis, before joining the Diabetes Branch of the National Institutes of Health, where he served from 1970–1981—first as a Clinical Associate (fellow), then Senior Investigator, and finally



Chief of the section on Cellular and Molecular Physiology. He came to Joslin as Research Director in 1981, and was named Director of the Center in 1998.

Dr. Kahn is the recipient of numerous awards and honors. In addition to being elected to the National Academy of Sciences and the Institute of Medicine, he has received an honorary doctorate from the University of

Paris, and the top research awards of the American Diabetes Association, Juvenile Diabetes Foundation and International Diabetes Federation. He is a past president of the American Society of Clinical Investigation, past Chair of the Congressionally mandated Diabetes Research Working Group and a current member of the Advisory Council of the National Institute of Diabetes and Digestive and Kidney Diseases.