Five Decades of Diabetes Patient Care: The Time of My Life

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My diabetes mentor, Dr. Joseph T. Beardwood, Jr., a professor in diabetes and metabolic diseases at the University of Pennsylvania, was the spark that kindled my lifelong passion for a career devoted to diabetes. One of the seven original founders of the American Diabetes Association (ADA) and its third president (1942–1944), Dr. Joe stimulated me to join the ADA and encouraged my activities in patient care and education and diabetes research.[1]

In 1954, Dr. Charles H. Best lectured to our senior class at Temple Medical School. I have never forgotten his message. As a scientist, his major job was to be at the research bench. This required most of his time and prevented him from teaching medical students, residents, and practicing physicians. However, he urged us to follow new research findings and to act as "translators" for primary care physicians. I accepted that suggestion and have served my colleagues as a "thought leader" ever since. Dr. Best died on April 4, 1978.

It has been a joyride to observe and participate in the growth and development of scientific research and clinical knowledge of diabetes during my entire professional career. The cascade of new information in our field has been almost beyond belief.

In the Beginning

During my residency, 1951–1954, Dr. Beardwood's team included a gem of a fulltime hospital diabetes nurse educator. On twice-daily rounds, Mary Travis taught me to prescribe insulin and diets, to control blood glucose levels, and to write perioperative orders. She was an excellent role model for the office staff I subsequently hired and trained in 1954.

My first office and hospital practice in Trenton, N.J., was restricted to diabetes, which encouraged inexperienced primary physicians to refer patients to our care. Some pediatricians were uncomfortable treating type 1 diabetes and happily referred children to us. My practice suddenly burgeoned, however, when the town's busiest, elderly diabetes specialist died, and most of his patients transferred to us.

I had much to learn, so my path led me to the Joslin Center in Boston in 1954, where I had direct contact with the senior staff: Dr. Howard F. Root, Dr. Alexander Marble, Dr. Priscilla White, Dr. Robert F. Bradley, and Dr. Leo P. Krall.[2] I never dreamed that I would be appointed medical director of the Joslin Centers for Diabetes at St. Barnabas, Princeton Division in New Jersey, in 1994.

IN BRIEF

"To provide clinical care and education to children and adults with diabetes has been a privilege," says Arthur Krosnick, MD, FACP, CDE. "To observe how such efforts can delay or prevent diabetic complications was an incentive. To have enjoyed 50 years of those adventures has been an unexpected bonus." Here, Dr. Krosnick looks back on his long career in diabetes and endocrinology, noting the many advances he witnessed and participated in along the way.

Two other tutors and friends were Dr. Garfield Duncan and Dr. Harold Rifkin. Dr. Rifkin, who was president of the ADA and the International Diabetes Federation and an elegant teacher, appointed me to follow in his path as editor-in-chief of *Diabetes Forecast*.

Our clinical team—a full-time nurse, a dietitian, and I—emulated the Joslin/Beardwood/Duncan clinical and educational programs. It wasn't long before primary care physicians generously referred diabetic patients for both clinical care and diabetes education.

We taught meal planning based on the ADA and American Dietetic Association Exchange System,[3] and, in the spirit of Dr. Best, we served as translators for physicians, nurses, pharmacists, and dietitians about new developments in diabetes. This led many of them to become active ADA members.

My nurse taught our patients to measure glycosuria with Benedict's Qualitative Test and Clinitest, as well as qualitative tests for acetone ("Acetest") and diacetic acid. Though time-consuming and of limited use, they were all we had.

Glycemic levels required venous or capillary blood samples with the Somogyi or Folin-Malmros methods. Suddenly, however, we had a spectacular breakthrough in 1970: the Ames reflectance meter! This was our first "solid phase" system, utilizing a drop of blood and a reagent strip to measure blood glucose levels. By comparison, today's relatively inexpensive, sophisticated, computer-based glucose meters are ultra-scientific.

The new continuous subcutaneous glucose monitoring device is interesting,

but patients now hope for a truly noninvasive glucose-measuring device. Of course, our present test materials for urine glucose and ketones are simple, inexpensive, and accurate.

Insulin in the Early Days

In the 1930s and beyond, supplies of beef and pork insulin became plentiful, and purity improved, especially in the 1960s and 1970s. Available insulins were regular (short acting); NPH, lente, semi-lente, and globin insulin (intermediate acting); and ultralente and protamine zinc insulin (PZI) (long acting).

Initially, I prescribed NPH and regular insulin twice daily in type 1 diabetes, but I soon found that regular insulin three or four times daily, plus intermediate- or long-acting insulin twice daily, provided a higher quality of control. I was never fond of PZI because its time action was unpredictable. Our goal was to have a true basal insulin, which today's glargine (Lantus) insulin appears to be.

Involvement in Diabetes Research

In 1965, Dr. Donald F. Steiner's research led to synthetic proinsulin, which consisted of A-, B-, and C-peptide chains and was the precursor to insulin.[4] In 1981, I was the principal investigator in the Eli Lilly recombinant DNA (rDNA) human insulin research protocols, which required C-peptide measurements to ensure that subjects had type 1 diabetes. Endogenous insulin, after C-peptide is physiologically cleaved off and discarded in the urine, consists of the 21-amino-acid A chain and the 30-amino-acid B chain.

C-peptide has been a valuable measure of pancreatic insulinogenic capacity, but new research suggests it may have therapeutic possibilities: *1*) residual C-peptide in those with type 1 diabetes may be useful in protecting or restoring β-cell function;[5] *2*) C-peptide replacement may improve coronary flow reserve in those with type 1 diabetes;[6] and, *3*) C-peptide may ameliorate early signs of sensory nerve dysfunction in type 1 diabetes.[7]

The pharmacological research carried out by my team in Princeton, N.J., which included three nurses/diabetes educators, two registered dietitians/diabetes educators, and three endocrinologists, consisted of about 90 protocols for many of the large pharmaceutical companies.

Development of Synthetic Human Insulin

In 1978, an ADA policy statement on rDNA research addressed the question of a possible shortage of pancreatic insulin due to increased demand in developed and developing countries and the relative shortage of animal pancreases as the main source of insulin. After a momentary brouhaha in Cambridge, Mass., about the potential dangers of genetic and DNA technology, scientists from Harvard and the Massachusetts Institute of Technology synthesized rat insulin by that method.[8] This was followed by a stupendous effort to develop synthetic human insulin to meet the world's needs for diabetes treatment.

In 1980, Eli Lilly produced rDNA human insulin, humulin R. By 1996, they had designed an rDNA human insulin analog, insulin lispro (Humalog), by transposing the amino acids lysine and proline near the end of the B chain. Lispro is a rapid-acting premeal insulin whose forte is improvement of postprandial glucose levels. Indeed, these were monumental developments in the diabetes timeline. Table 1 lists our present excellent insulin preparations.

Improvements in Insulin Syringes

Life was not easy in the early days for those with diabetes. Insulin syringes were glass, and large-bore needles were painful. Syringes had to be sterilized daily, and needles had to be sharpened and sterilized after each use.

Insulin syringes were 1 cc and graduated in units for insulin concentrations of U10, U20, U40, and U80. Two-cc syringes were graduated to 80 units for use with U40 PZI and to 80 and 160 units for use with U40 and U80 PZI. Tuberculin-type 1-cc syringes were graduated in tenths or hundredths of a cubic centimeter. At best, the system was complicated for doctors, patients, and pharmacists and fraught with measurement errors because of the complexity of the syringe markings and the variety of insulin types and strengths used.

The goal of the ADA Committee on Materials and Therapeutic Agents was to eliminate U40 and U80 insulin and the corresponding syringes. In 1972, insulin manufacturers in the United States and Canada announced the forthcoming U100 concentration of insulin.[9] Actually, the Food and Drug Administration

Table 1. Current Insulin Preparations

Product	Trade name, available forms	Type
Human insulin	Humulin, regular, NPH, lente, ultralente, 70/30, 50/50	Recombinant human insulin
	Novolin, regular, NPH, lente 70/30	Recombinant human insulin
Insulin aspart	Novolog	Recombinant human insulin analog
Insulin lispro	Humalog, 75/25	Recombinant human insulin analog
Pork insulin	Iletin II, regular, NPH, lente	Pork insulin
Glargine	Lantus	Recombinant human insulin analog

(FDA) did not decertify U80 insulin until 1980.

Present-day insulin syringes are compatible with the metric system, disposable, and accurate. They feature micro-fine needles with gentle, almost painless penetration and pose minimal problems related to air bubbles or loss of insulin. They are beyond compare with the syringes of the "old days."

Diabetes Epidemiology: Case Finding, Education, and Insulin Shock Therapy

From 1954 to 1977, I served as senior public health physician and coordinator of the New Jersey State Department of Health Diabetes Control Program (DCP) and consultant to the United States Public Health Service (USPHS) DCP from 1962 to 1970. Our programs (case finding and patient, professional, and public education) had major impacts on diabetes in New Jersey and elsewhere in the United States.

The classic Oxford [Massachusetts] Study by Dr. Hugh Wilkerson at USPHS and Dr. Krall at the Joslin Clinic was the first comprehensive diabetes prevalence study in the United States.[10] In 1947, they tested 3,516 of the 4,983 Oxford inhabitants for diabetes. Forty subjects were known to have diabetes, 30 more were diagnosed, and the diabetes prevalence was 1.7%. Follow-up studies 10 years later suggested a national diabetes prevalence of 3 million, half of which were undiagnosed. We now estimate diabetes prevalence to be 16–18 million in the United States and predict an increase to 50 million in the next three decades.

These studies led to statewide diabetes detection programs. Initially, we distributed hundreds of thousands of Dreypaks, which were identification cards with an attached filter paper that could be moistened with urine and mailed to the DCP for testing. Although relatively insensitive, these led to new diagnoses of many patients, who were then referred to physicians for care. Later, large-scale venous blood glucose sampling followed, but that was replaced by fingerstick capillary blood testing using the newly invented Japanese glucose meters. Each new method increased the sensitivity and specificity of the tests and detected more cases of undiagnosed diabetes.

From 1962 to 1970, we were active in patient, professional, and public education by way of films, pamphlets on foot care, publications, and telephone presentations for patients, physicians, and the public. One film, *Diabetes and Its Long-Range Control*, included Drs. Best, Duncan, Wilkerson, and Krosnick.

At the request of the USPHS diabetes program, we trained their representatives for assignment to state diabetes detection and education programs. A unique experience for our trainees was observing insulin shock (coma) therapy at the Trenton Psychiatric Hospital (TPH) in West Trenton, N.J., in 1962.

Dr. Manfred Sakel, a Viennese psychiatrist, developed the technique in 1928 and introduced it to the United States in 1936. Nondiabetic patients with schizophrenia and major depression were treated with insulin coma therapy 5 days a week for 6 weeks.

The insulin unit at TPH treated 24 males and 24 females daily in separate wards. The initial dose of regular insulin was 10–20 units administered intramuscularly at 7:00 a.m. in the unit; the dose was increased by about 10 units per day to about 90–100 units until hypoglycemic coma developed. A team of trained nurses and physicians supervised the care of the patients, who rested on litters. In some patients, more than 100 units of insulin were needed to produce coma.

After 30–60 minutes of hypoglycemic coma, nurses reversed the condition by intragastric glucose solution or Karo syrup. Patients were carefully observed until cognitive, returned to their room, and then provided meals and snacks.

The most notable of the schizophrenic patients treated in the TPH insulin coma unit was Prof. John Forbes Nash, Jr., 1994 recipient of the Nobel Prize in Economics and subject of the recent film *A Beautiful Mind*.[11–13] He, like many others, went into remission lasting months. He is presently doing research and lecturing.

When exacerbations occurred and insulin coma treatment was repeated, physicians noted a troublesome phenomenon, insulin resistance, in patients who were retreated with insulin coma months later. The doctors found that insulin doses had to be doubled and redoubled to cause coma and convulsions; some patients required up to 1,000 units daily (M. Epstein, unpublished observations). The cause became clear after 1959, when Solomon A. Berson, MD, and Rosalyn S. Yalow, PhD, developed a radioimmunoassay test for measuring blood insulin levels. Berson received the first ADA Lilly Award and Yalow was awarded the Nobel Prize. Their work taught us that animal insulin antibodies were the source of insulin resistance in those nondiabetic individuals.[14]

Advances in Diabetic Pharmacotherapy

Glucagon

Glucagon, a polypeptide hormone in the α-cells of the pancreas, was discovered in 1923. One of the first such hormones to be synthesized in 1961, glucagon was the second such hormone to be measurable by radioimmunoassay, shortly after insulin.[15]

Although it has many physiological effects, glucagon is an emergency treatment for severe hypoglycemia. A recombinant, antihypoglycemic hormone, glucagon raises the blood glucose by mobilizing hepatic glycogen. The lyophilized product is contained in a sterile vial and the diluent in a syringe. When reconstituted and injected, it rapidly elevates the blood glucose level. Glucagon has been a lifesaver for diabetic children.

Oral Antidiabetic Agents

Sulfonylureas. In the 1940s, serendipity during sulfonamide research in Europe led to the recognition that certain sulfonamide antibacterial compounds were

capable of lowering blood glucose levels.[16] I wrote my first prescription for a sulfonylurea drug for a patient with type 2 diabetes in 1955, and that was an exciting moment.

Most such patients were obese and had been treated with insulin. Although we were not yet aware of insulin resistance, type 2 patients required large insulin doses compared to type 1 patients. Where possible, I discontinued insulin and prescribed the new oral agents. However, some patients failed to respond to the oral drugs (primary failure), while 20% developed secondary failure to respond.

In 1970 and 1971, a study by the University Group Diabetes Program (UGDP)[17] questioned the cardiovascular safety of sulfonylureas. Many patients discontinued the tablets and returned to insulin, but further studies refuted the UGDP findings. In my experience, no cardiovascular adverse events occurred, but the FDA placed a generic warning in the package inserts at that time, and it still remains in the 2002 *Physicians' Desk Reference*.[18]

The sulfonylurea family—tolbutamide (Orinase), acetohexamide (Dymelor), tolazamide (Tolinase), glipizide (Glucotrol), glyburide (Micronase), and chlorpropamide (Diabinese)—were very important therapeutic players. At present, glyburide, chlorpropamide, glipizide, and glimepiride (Amaryl) are safe and effective and regularly prescribed. Like the sulfonylureas, the newer nateglinide (Starlix) and repaglinide (Prandin) are also insulin secretagogues.

Biguanides. It is interesting that Elliott P. Joslin, in the 1959 10th edition of his famous textbook, was a bit wary of both the sulfonylureas and biguanides, stating, "It is too early to make any more than a preliminary evaluation of the place of the sulfonylureas or the biguanides in the management of diabetes."[19]

I began to prescribe phenformin in 1959, although its mechanism of action was not clear. In my hands, it was very useful in obese type 2 diabetic patients because it lowered blood glucose, produced anorexia, and aided with weight loss. Despite its good features, the FDA withdrew phenformin from the market in 1977 because it caused lactic acidosis in some patients. Fortunately, none of my patients had that complication.

Phenformin's removal left a therapeutic void. Metformin (Glucophage) was introduced in France in 1959 and had wide use in Europe, but it was not approved for the U.S. market until 1994. Metformin was and is an extremely effective antidiabetic agent, which I prescribed for most of my type 2 diabetic patients. It works as monotherapy, but works even better when combined with other drugs. Metformin has been a potent agent and a great addition to our therapeutic armamentarium.

α-Glucosidase inhibitors. We did a number of clinical trials with acarbose (Precose) and miglitol (Glyset), and both research subjects and private patients were unhappy with their major side effect—flatulence. Doses were to be taken before meals, but patients tended to be noncompliant.

In our trials, the best postprandial effects with monotherapy were disappointing; hemoglobin A_{1c} (A1C) and postprandial glucose levels were better, however, when these drugs were combined with other antidiabetic drugs. I have found that, since the insulin sensitizers have become available, these drugs are rarely necessary.

Insulin sensitizers: thiazolidinediones. This class of drugs appeared to offer a great opportunity to fill a needed treatment slot. When troglitazone (Rezulin) became available, I prescribed it to many of my eligible type 2 diabetic patients and monitored patients' liver function studies carefully.

However, the company recognized severe liver toxicity in a group of patients and notified the FDA in 1997. In June 1998, the National Institutes of Health–sponsored Diabetes Prevention Program (DPP) discontinued the troglitazone-therapy arm of its study because of safety concerns. In March 1999, the FDA reviewed the status of troglitazone as compared to two newer thiazolidinediones, rosiglitazone (Avandia) and pioglitazone (Actos). And, on March 21, 2000, the FDA asked Parke-Davis/Warner-Lambert to remove troglitazone from the U.S. market.

At my request, Parke-Davis/Warner-Lambert sponsored a retrospective chart review protocol of 100 diabetic patients from our St. Barnabas Joslin Centers for Diabetes at Princeton and Livingstone, N.J. Data from 97 of the patients could be evaluated. The review found two cases of concern: a 67-year-old man on troglitazone monotherapy developed abnormal serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), which became normal without stopping the drug, and a 77-year-old man taking troglitazone plus insulin developed abnormal SGOT and SGPT, which became normal when the troglitazone was discontinued. No other serious adverse events occurred.

As principal investigator on a 2-year clinical trial involving pioglitazone, I saw no adverse events regarding liver function. When they became available, I regularly prescribed both pioglitazone and rosiglitazone.

In our practice, we were thrilled with the improved glycemic control, especially when combined with metformin or sulfonylureas. These drugs have made it possible for patients with chronically poor control of type 2 diabetes to attain A1C results of <7% for the first time in their lives with diabetes.

Conclusion

Preparing this review of 47 years as a diabetologist has been a humbling experience. Observing and participating in so much that has occurred in diabetes during this time period has been breathtaking.

I would like to see the wonders that will occur in another 3 years. Is there a cure for diabetes in the future?

The first time I spoke to the parents of a child with newly diagnosed type 1 diabetes, I promised them a cure. I didn't

know when, and I still don't. My message was and is: "Take the best care possible of the diabetes, and I'll let you know when we have a cure."

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