Contributions of the American Journal of Physiology to the discovery of insulin

IRA D. GOLDFINE AND JACK F. YOUNGREN
Division of Diabetes and Endocrine Research, Department of Medicine, Mount Zion Medical Center, University of California, San Francisco, California 94143-1616

Goldfine, Ira D., and Jack F. Youngren
Contributions of the American Journal of Physiology to the discovery of insulin. Am. J. Physiol. 274 (Endocrinol. Metab. 37): E207–E209, 1998.—Since its inception in 1898 the American Journal of Physiology has been a leader in diabetes research and has published many key articles on the subject. The Journal first published studies of phlorhizin-induced diabetes in 1898, and after many other contributions went on to publish the first reports of Banting, Best, Macleod, and Collip in 1922 concerning the isolation and purification of insulin (5–8, 13). This review highlights some of these key contributions of the Journal.

DIABETES MELLITUS is an ancient disease whose symptoms were described over 3,500 years ago in a compendium of medical diseases acquired in Luxor by the Egyptologist George Ebers (28) in 1872 and given the name the Papyrus Ebers. The Roman physician Celsus in 10 AD first described diabetes mellitus as a disease of excess urination and wasting (16). Diabetes is derived from a Greek word meaning “going through” or “siphon.” Mellitus is the Latin word for honey or sweet. Other Greco-Roman ancients, including Galen, Areteaus the Cappadocian, and Demetius of Apamea, mentioned the disease (4, 22, 28). Diabetes mellitus was also described by Indian physicians Charak and Sushrut two millennia ago (22). Avicenna in Baghdad one millennium ago wrote about diabetes mellitus and emphasized the sweetish taste of the urine (22). For more than two thousand years diabetes mellitus was believed to be a disease of the kidneys and bladder. This view was supported and extended by the studies of Matthew Dobson, who in 1776 evaporated urine from a patient with diabetes mellitus and found that the residue contained sugar (15).

Early Search for the Etiology and Cure

The source of glucose appearing in the urine was not known. In 1857 Claude Bernard described glycogen as a product of glucose metabolism in liver and set forward the concept that altered glucose metabolism is the cause of diabetes (9). In 1869 Paul Langerhans discovered the Islets of Langerhans (17, 24). Others then observed pancreatic and islet abnormalities in necropsies of patients with diabetes mellitus. A major conceptual breakthrough came with Minkowski (32), whose studies clearly demonstrating that removal of the pancreas led to diabetes mellitus led to the concept that the internal secretions of the pancreas were involved in the etiology of the disease (32). Whether these secretions regulated the blood glucose or the kidney was uncertain. In the first year of publication of the American Journal of Physiology, Lusk and colleagues (27, 31) began to report a series of investigations demonstrating that the agent phlorhizin induced polyuria and glycosuria. Although it was subsequently discovered that the kidney was not the primary pathological site in diabetes, nonetheless these investigators made major progress in understanding renal pathophysiology.

The investigation of diabetes was a rapidly growing area of research in the early 1900s. In fact, diabetologist Eugene Opie (26) complained that the literature on diabetes was voluminous. The nature and focus of that research were to be changed forever with the discovery of insulin in 1921. The American Journal of Physiology played a major role in publishing preliminary studies leading to the breakthrough by Banting, Best, and co-workers and also published much of the celebrated early reports from the Toronto laboratory.

The head of the Toronto laboratory, J. J. R. Macleod, who would be awarded the Nobel prize along with Frederick Banting, published early studies in the American Journal of Physiology on the mechanisms of experimental glycosuria (18–21). At this time Macleod believed that experimental diabetes was, at least at the early stages, due to elevated glucose output by the liver. His theory that the internal secretion of the pancreas mainly affected the liver, and not tissue combustion of glucose, resulted from reports of previous researchers that ligating the hepatic artery could prevent hyperglycemia after pancreatectomy. Although he underestimated the role of the internal secretion on peripheral glucose utilization, his studies provided important infor-
mation on the regulation of glucose metabolism in the liver and the nature of the "glycogenase" activity of hepatic tissue.

Macleod published regularly in the American Journal of Physiology, testing his theories on the role of the liver and muscles in sugar consumption. Macleod employed depancreatized and eviscerated dogs to test whether an internal secretion of the pancreas might affect glucose utilization in muscle (21). This procedure was analogous to the subsequent hindlimb perfusion technique and was employed as a more physiological model than perfused hearts, which had previously been used to generate initial evidence for an effect of a pancreatic hormone on muscle glucose utilization.

Although Macleod's successful involvement in the search for the mysterious internal secretion of the pancreas would not begin until 1920, several investigators had attempted to isolate the theoretical hormone. E. L. Scott worked to obtain the internal secretion as the research project for his master's degree at Columbia University. Scott's series of experiments was published in the American Journal of Physiology in 1912 (29) and represented compelling evidence that an extract of the pancreas could diminish glycosuria in depancreatized dogs. Scott's plan of attack was to ligate the pancreatic ducts. This ligation would cause atrophy of the glands producing the digestive enzymes that he believed responsible for both the destruction of the internal secretion and the consistently toxic reactions to pancreatic extracts that previous insulin researchers had encountered. It was a strategy copied by Banting in his initial work. However, Scott reported his abandonment of the ligation technique as being too difficult to fully accomplish. Alcohol extraction of whole pancreas produced positive results for Scott, and it was this basic procedure that was eventually adapted by the Toronto group, who had experienced greater success with the ligation technique. Scott's 1912 article reported impressive decrements in sugar and total urine output after the injection of extract in depancreatized dogs. The experiments convinced Scott that he had discovered the internal secretion, but readers of the American Journal of Physiology were presented with a highly cautious summary of the results. Scott wrote, "It does not follow that these effects are due to the internal secretion of the pancreas in the extract." He offered the alternative hypothesis that the decreased glycosuria could result from a nonspecific toxic or depressor action, and he cited the slight rise in body temperature after injection as a possible factor confounding the results. Unfortunately, a subsequent experiment produced the surprising result of elevated blood sugar in cats after injection of his pancreatic extract (30) and apparently led Scott to abandon his work on what would become known as insulin.

Much of the early work involving measurement of glucose levels in the blood was questionable because of the lack of accurate assay techniques. Results were not highly reproducible, and the assays required a large volume (25 ml) of blood for analysis. This circumstance contributed to the fact that, whereas diabetes was known to involve elevated blood glucose levels, the relationship between hyperglycemia and glycosuria was not clearly understood. Thus glycosuria was often used as the end-point marker in studies on experimental diabetes. However, blood glucose testing procedures improved greatly between 1910 and 1920, which allowed for a greater emphasis on hyperglycemia in diabetes (25). In 1917, the American Journal of Physiology published a report by D. M. Davis (14) that examined the relationship between experimental elevations in blood glucose and appearance of glucose in the urine, increasing the understanding of the mechanisms of glycosuria in diabetes.

An article in the American Journal of Physiology by Carlson and Ginsburg (12) attempted to finally establish that the pancreas functions as a secretory organ rather than a detoxifier. Previous work involving para-biosis or cross circulation of diabetic and normal dogs and a study of depancreatized pregnant dogs published in the American Journal of Physiology could all be interpreted as supporting either model. Although most researchers believed that a hormone released from the pancreas was the necessary agent for maintaining glucose homeostasis, it had not been firmly established that it was not the ability of the pancreas to scrub some inhibitory agent from the blood that would permit the tissues to combust glucose. Carlson and Ginsburg found that infusing blood from normal dogs into depancreatized dogs produced a marked diminution of hyperglycemia and glycosuria, even when the total volume infused amounted to only one-tenth of the total blood volume. This procedure eliminated the need for large prior bleedings, as in previous studies in which much larger volumes had been transfused.

The noted clinical diabetologist Frederick Allen published several articles in the "Experimental Studies in Diabetes" series in the American Journal of Physiology (1–3). At the time, Allen was the acknowledged expert in clinically treating diabetic patients through his radical hypocaloric diet therapy (11). In his clinics, incoming patients fasted until glycosuria disappeared, and then caloric intake was slowly increased until the sugar again appeared in the urine. A maximum caloric intake was thus titrated for each patient, with the end result normally being severe weight loss and weakness, but prolonged survival (11). His experimental studies were conducted in partially depancreatized dogs, a more appropriate model, he thought, for human diabetes. In these dogs Allen carefully recorded the effects of such perturbations as fever, infection, cold, and intoxication to more fully understand how these conditions might affect clinical diabetes.

Discovery in Toronto

The work being done in Toronto to isolate the internal secretion of the pancreas would render Allen's harsh dietary treatment regimen obsolete. In 1921, Banting and Best succeeded in producing a pancreatic extract through the duct ligation technique that was pure enough to consistently lower blood glucose and reduce glucose loss in the urine. Before these findings
were published, their data were first presented by Banting (with Macleod) at the American Physiological Society’s 34th Annual Meeting in December of 1921. The abstract of this presentation was published in the American Journal of Physiology in 1922 (6). The investigators presented data discussing their technique to isolate extract from pancreas in which the acinous but not the islet cells had degenerated after ligation of the pancreatic ducts. They demonstrated that their extract could improve the clinical condition of depancreatized dogs and provided information on the potential for different modes of administration (i.e., subcutaneous injections were effective, whereas those via rectal administration were not).

Work on the pancreatic extract continued in Toronto in 1922, as the alcohol extraction technique was employed to improve and streamline the purification procedure. James Collip was brought in to perfect the isolation protocol as tests on the effects of insulin in models of disease went forward. Eventually, the large-scale production of insulin by the Connaught Antitoxin Laboratories and subsequently the Eli Lilly Company allowed for numerous laboratory and clinical experiments to be conducted. Banting and co-workers (7, 8) published two articles in The American Journal of Physiology in 1922 concerning the effects of insulin on both normal and hyperglycemic rabbits.

At the American Physiological Society Annual Meeting that year, the Toronto team presented several separate papers on different aspects of the effects of insulin (5, 10, 13, 23). One paper outlined the rate of decline of blood glucose levels after insulin injection, as well as the changes in respiratory quotient that accompany insulin treatment (23). Best presented a paper [see Best and Macleod (10)] on basic chemical properties of insulin, including the effects of heat and pH on the potency of the extract. Banting reported the results of treatments of human patients as well as dogs and rabbits (5). Collip (13) presented data on variabilities in the potency of different preparations of extract. Proceedings from this meeting were published in the American Journal of Physiology in February 1923 (5, 10, 13, 23). In October of that year The Nobel Prize for Medicine was awarded to Banting and Macleod, who subsequently announced that they would, respectively, share their awards with co-workers Best and Collip.

Address for reprint requests: I. D. Goldfine, Division of Diabetes and Endocrine Research, UCSF/Mt. Zion Med. Center, Box 1616, San Francisco, CA 94143–1616.

REFERENCES