MINKOWSKI ERA IN DIABETES
This year marks the 100th anniversary of the publication by von Mering and O. Minkowski entitled "Diabetes Mellitus After Extirpation of the Pancreas."

It occupied only about three-fourths of a page, but in this small space the authors were able to record the following results of pancreatectomy in the dog: glycosuria, polyuria, intense thirst, ravenous hunger, and loss of weight despite good food intake. Glycosuria persisted despite a fast of 48 h or the exclusive intake of a meat diet. The urine contained significant amounts of acetone, the blood glucose was 0.3–0.46 g/dl. Glycogen practically disappeared from both the liver and skeletal muscle. The solar plexus showed no evident structural changes; hence, the diabetic state had to be attributed to the removal of the pancreas rather than to nervous system influences. The transfusion of blood from a diabetic animal into the venous system of a healthy dog did not result in glycosuria.

By 1893, Minkowski, followed by Hedon and by Laguesse, had established by means of transplantation that this form of diabetes was due to the deficiency of an internal secretion of the pancreas. It was probably produced by the special glandular cells which Laguesse then named the islets of Langerhans, in honor of their original discoverer.

Diabetology owes much to the Franco-Prussian War and its sequelae. In 1870, during the siege of Paris, it was noted by French clinicians that the widespread famine in the besieged city had a salutary influence on diabetic patients. The glycosuria and ketonuria decreased or disappeared, and so did the cardinal symptoms and signs. These observations supported the view of clinicians who had previously prescribed calorie restriction, periods of fasting, and increased muscular work as the rational therapy for the overweight diabetic individual.

Another important "diabetic dividend" of the Franco-Prussian War of 1870 emerged because Germany thereby acquired Alsace-Lorraine from France. The German Imperial Government invested large amounts of money in the development of the University of Strassburg (the germanc version of Strasbourg). The University was strengthened by importing first-rate faculty from across the country. Bernard Naunyn, Europe's premier diabetologist of that period, held the Chair of Medicine, and he brought a young assistant with him from Königsberg, Oscar Minkowski. Physiological chemistry was taught by Hoppe-Seyler and von Mering was a member of that department. The Head of Pharmacology was Schmiedeberg, who edited the German Archives of Pharmacology. This journal published many of the important papers from the laboratories of Naunyn, Minkowski, von Mering, and others.

In 1929, 40 yr after the discovery and 2 yr before his death, Minkowski published a masterly analysis of the historical background to the epochal paper. The publication in English of this important clarifying contribution sets the historical record straight and provides valuable material for reflections concerning the logic of discovery and means of fostering scientific creativity.

Minkowski's story certainly bolsters the view that problems should be approached with an open, uncluttered mind not afraid of established and eminent "authority." The "gray-beards" of the 1860s and 1870s had reported that 1) survival could not be expected after pancreatectomy in the dog, and 2) the pancreas played no role in diabetes. Bernard, as well as Schiff, showed that "almost total atrophy" of the gland could be produced by the chronic obstruction of the pancreatic ducts without the appearance of glycosuria and/or hyperglycemia, hence suggesting that resection of the gland would not be followed by diabetes. Minkowski respected authority and was therefore not expecting the results he stumbled on. However, he quickly drew the correct conclusion and pursued the finding in an exemplary fashion.
By all accounts, Minkowski was a very talented young man with considerable intellectual powers. He made a major medical discovery at age 31. It is therefore not surprising that this outspoken young investigator did not have an easy time for several years. Some of the critics refused to believe the simple and logical interpretation Minkowski gave his findings. Officially, endocrine physiology had not yet been born (this was before Starling’s lecture). Others insinuated that perhaps the work was not even original. However, time has long ago judged the 1889 paper by von Mering and Minkowski to be one of the classic and glorious achievements of experimental medicine.

Rachmiel Levine, MD

For the convenience of the reader:

3. Naunyn B. Der Diabetes Mellitus. Vienna. Holder, 1898 (classic textbook that sums up the knowledge of the period. Naunyn supported Minkowski’s work and provided space, facilities, and sincere encouragement)

I was very pleased to accept the Chairman’s invitation to speak on this festive occasion about the historical development of our concepts concerning pancreatic diabetes. It is particularly pleasing to return to the City of Koln where I worked and helped found this medical society 25 years ago. The theme of the lecture provides me with the opportunity to state that the hopes and expectations I once voiced to this group have been realized in a most happy fashion. On 28 October 1901, our colleague Hochhaus, whose premature death we all mourn, reported to this medical society a case of hemorrhagic necrosis of the pancreas. In the discussion I had the opportunity to state my views on the relationship between diabetes and the pancreas. I quote here the closing sentence of my remarks:

We may hope that the recognition of the etiology of diabetes as deriving from a functional disturbance of the pancreas will some day lead to a successful therapy; just as happened with myxedema, once it was established that the disorder is associated with loss of thyroid function.

This comparison between the effects of the thyroid hormone and that of the pancreas is obviously justified and need not be stressed. The practical importance of insulin in treatment is more important than that of thyroid because the total number of diabetic patients is so much larger than that of patients with myxedema.

It seems odd that I should be asked to talk about the historical development of our knowledge of pancreatic diabetes. I do not underestimate the significance of historical research for every science, especially not for medicine. However, the discovery of pancreatic diabetes tends to validate the view that a piece of scientific research may actually profit from the total ignorance on the part of the investigators of any prior attempts and results. I must admit here and now that von Mering and I did our experiments on the consequences of pancreatectomy without the benefit of the knowledge of the relevant scientific literature. Looking back convinces me that this ignorance was the real source of our success! Had we realized that all previous attempts at pancreatectomy had led to nothing of note and that no less a person than Claude Bernard had stated that it was impossible for dogs to survive the total surgical removal of the pancreas, we would have certainly not dared to make a new attempt at this procedure. Had we been cognizant of the ideas of previous workers concerning the relations of diabetes to changes observed in the pancreas, we would probably have been satisfied to agree with their opinions and would not have attempted to delve into this subject with new techniques. Because of our ignorance, we followed our initial finding in all innocence. We made our first observations by pure accident. Let me tell you about it in detail.

We undertook our investigation for purposes other than to study the regulation of carbohydrate metabolism. Von Mering and I met one day by chance, and he asked me whether our clinic used Lipanin, a preparation he recommended as a substitute for cod liver oil. Lipanin was an oil to which 6% free olate was added. I jokingly replied, "Why should we give our patients an artificially rancid product?" "Don’t you laugh," he said, "the splitting of fat into fatty acids is of paramount importance for the emulsion and absorption of a fat meal. When pancreatic function is not optimal, esterified fat is poorly utilized. The favorable actions of liver oils depends on their content of fatty acids." "Did you prove this hypothesis?" I asked. "I tried to tie all the ducts of the pancreas in order to show that neutral fat is absorbed more slowly than fatty acids, but I could not totally prevent the appearance of pancreatic juice in the lumen of the intestine," said von Mering. "Why didn’t you extirpate the gland?" I asked. He did not think this was a feasible operation from which a dog could survive. I had by that time done some successful hepatectomies and considered myself a good experimental surgeon. With youthful abandon I told him, "Please give me a dog and I will try to do a total extirpation of the pancreas." The same day von Mering transferred a dog to me from the kennels of the Hoppe-Seyler Institute (biochemistry) to the laboratory of Albert Naunyn where I worked. Von Mering and I removed the gland in toto; I endeavored to do this under meticulously clean surgical conditions. The animal withstood the operation surprisingly well, and we thought we would use it for the absorption experiments as soon as the wound healed. We did not think of diabetes; hence, we did not test the urine for glucose.

It so happened that von Mering went out of town for 8 days because of a serious illness in his family. Meanwhile, the operated animal had the freedom of the laboratory. It was housebroken and was supposed to get used to its surroundings to learn to urinate and defecate on demand into lab receptacles. However, on several occasions the dog emptied its bladder spontaneously on the floor, and I reproached the lab assistant that the animal was not properly trained. "I did train him," he stated, "but this animal is quite peculiar. No sooner does he empty his bladder completely when he has to urinate again and again."
I followed a subconscious hunch. I gathered a few drops of urine off the floor into a pipette and tested it for glucose. It produced a strong reduction signify¿g more than 10% sugar content. My first thought was that this particular dog must have received a great amount of phloridzin. (Note: v. Mering had previously discovered the glycosuric action of phloridzin and worked with this substance.) However, the supposed action of the drug had continued for too long. Therefore, I operated on several dogs that were tested pre-operatively for urinary glucose. All of them became heavily glycosuric; this happened in all cases in which the pancreas was completely removed. When von Mering returned from his trip I could report to him that total pancreatectomy regularly produced the diabetic state. We agreed to postpone the planned experiments on fat absorption (these were later done by Abelmann in dogs that I prepared for him) and to study this form of diabetes more closely. Because we began this work jointly and followed it up with discussion of the data, we published the first reports under joint authorship. Von Mering never mastered the technique of pancreatectomy and was not interested in the import of these investigations. He left the further pursuit of this subject to me and did not concern himself to any extent with pancreatic diabetes. I presented an oral report about this work to the local medical society in Strassburg (May 1889) and to the International Congress on Physiology in Basel. In a lecture to the Society of Naturalists in Heidelberg in September 1889, concerning the relationship of pancreatic lesions to cases of diabetes in humans, I came to the conclusion at an early stage of the research that many if not all cases of diabetes in humans were related to disturbances of pancreatic function.

As stated before, the discovery of pancreatic diabetes was in itself accidental, but it was a lucky accident that it was von Mering and I who stumbled on it, because both of us had been concerned with problems of diabetes and were thus in a position to explore this finding more deeply. A colleague of ours who was not well disposed toward me expressed himself some years ago that the technician in my lab was really entitled to be considered as the man who discovered the phenomenon of pancreatic diabetes. However, it has also been said that the discovery of X rays was really due to the cleaning woman in Roentgen's lab who accidentally left a cloth on the cathode ray tube. It was also fortunate that Roentgen drew the proper conclusions from this occurrence.

Of course we read the available literature before we published our first data. We could thus establish that the many attempts to nullify the function of the pancreas by experimental excision were imperfect and uncontrolled. The viewpoint that the pancreas was a dispensable organ prevailed; there were no evident consequences of its removal.

The first attempts at pancreatectomy occurred over 200 years ago. In 1682, Conrad Brunner performed the operation to show that the duodenal glands, named after him, had identical functions to those of the pancreas. Again, I must relate a peculiar coincidence that 200 years later I found myself in the Strassburg flea market and noticed out of the corner of my eye a small book lying on the table of a used-book dealer. The title page showed in an allegoric manner an operation on the pancreas. The book was Brunner's "Experimentera Nova Circa Pancreas (1683). Brunner's animals withstood the operation and survived it for a long time. From the text it appears that only a portion of the gland was removed, leaving the whole horizontal section intact. As mentioned by Bouchardat, Haller reported later that dogs from whom he excised the pancreas succumbed to extreme emaciation in a state of great hunger and thirst. Bouchardat remarked, in 1846, that all dogs on whom he attempted pancreatectomy succumbed to the immediate complications of the operation. He does mention one incident of glycosuria after the tying of one of the ducts.

Later authors (Frenich, 1849; Bidder and Schmidt, 1852) were satisfied to tie the secretary outlet of the gland. However, they often overlooked the fact that the pancreas had more than one excretory duct, so that very often they could not reach their goal of keeping the pancreatic juice from reaching the intestine. However, authors who knew the anatomic relationships looked for digestive disturbances only and did not think of the possibility of other metabolic functions of the pancreas. Claude Bernard, as stated earlier, believed that survival after complete surgical extirpation of the pancreas was impossible. He sought to cause glandular destruction by injecting masses of fat into the ducts. The expected digestive disturbances did not occur when Schiff injected paraffin in similar experiments. Schiff especially stressed the fact that the animals behaved normally in all respects despite total atrophy of the pancreas. Many authors who had extirpated the pancreas before our experiments had evidently not done a total removal (Berard and Colin, 1857; Martinotti, 1888). The American surgeon Senn, who worked more thoroughly, lost his animals under circumstances that were similar to diabetes, but the animals were not examined for urinary glucose. In addition to Bouchardat, only Klebs and Munk (1869) operated on the pancreas for the express purpose of trying to elucidate the relationship of pancreatic lesions to diabetes. They had uniformly negative results, which persuaded them to attribute the occurrence of diabetes in pancreatic disease to possible lesions in the nerves of the solar plexus. Finkler (1886) mentioned that he also could not produce diabetes by eliminating the pancreas. There are no further details available concerning his work.

The older experimental data on anatomic findings in the pancreas of known diabetic individuals were more impressive. If the meager findings in diabetes at autopsy are considered—I well remember the statement by Naunyn when two diabetic patients died on the ward the same day. "There is nothing more boring than an autopsy of a diabetic unless it be two diabetic autopsies on the same day." However, slowly over the years there had accumulated descriptions of a set of pathological changes in the pancreas of individuals who were known to have diabetes.

In 1788, Cawley published a case with anatomic pancreatic changes. Later, Chopart, Bright, Bouchardat, Griesinger, Recklinghausen, Klebs, Lancereux, and others published numerous cases. Frenich reported an incidence of 12 pancreatic lesions in 40 autopsies; Seegen saw the pancreas affected in 13 of 30 cases; Senator even reported that in fully one-half of diabetic patients, lesions of the pancreas could be found.

Bouchardat was the first worker who (in 1866) proposed
a theory of the pancreatic origin of diabetes. He felt that when the digestive functions of the pancreas were disturbed, the diastatic (starch-splitting) enzymes were then secreted by the mucosa of the stomach. This allegedly resulted in an increased transformation of starchy materials into sugar and thus (secondarily) glycosuria was produced. This rather poorly supported theory found no echo until Lancereux (1877) put forward his ideas concerning the various forms of diabetes—diabetes gravis and diabete maigre. Diabetes (according to this concept) was not a unitary disease; it was a collective noun for many conditions, and one of them was related to pancreatic lesions. *Diabete pancreatique* was characterized by rapid onset, unusually rapid development of bodily weakness, digestive difficulties, and relentless progression. Because of the lack of correspondence between the degree of clinical symptomatology and the extent of the pancreatic lesion, many observers did not accept the proposed etiologic relationship. Some even concluded that the observed anatomical changes were not related to causation of the disorder but were the result of the clinical state or that the diabetic state and the pancreatic lesion were both due to one unknown common cause. On the other hand, Baumel (in Montpelier) concluded that all cases of clinical diabetes were due to pancreatic disturbances. He felt that in all cases of diabetes, anatomical changes could be found, microscopic in milder instances and macroscopic in severe cases.

Baumel's voice found no further echo, and when von Mer- ing and I published our initial results, the concept of pancreatic diabetes was scarcely heard.

Our findings were not readily accepted as given. The consistancy of the results was questioned. The workers who wanted to test our data were not always aware of the technical difficulties associated with total removal of the pancreas; for example, see the work of de Dominicis, Reale, and de Renzi in Italy and that of Thiroloix in France.

It seems odd that especially German workers attributed equal value to the findings of our laboratory and that of de Dominicis. I would like to point out that his first publication appeared in December 1889, but, as early as May of that year, many journals here and abroad carried notices of our chief findings. His results were indeed different from ours. He, as well as others mentioned above, did not obtain glycosuria regularly after pancreatectomy. That is why he did not accept the view that the gland exerted a direct influence on carbohydrate metabolism. He thought that the glycosuria was produced by the digestive problems that follow exclusion of the external secretion of the pancreas. The digestive difficulties could, in his view, be the result of abnormal modes of breakdown of nutrients whereby toxins were produced that would, when absorbed, lead to glycosuria. Other authors thought that the glycosuria was a side effect due to lesions of nerves during the operation on the pancreas. The last suggestion had been previously voiced. However, von Mering and I thought that we had negated it in our first group of experiments. We believed that we had very carefully avoided injury to neighboring tissues and to the process of external secretion. We were convinced that we were dealing with the loss of a specific metabolic function. We endeavored to show that this was not due to the retention of a glycosuric substance but was entirely the result of lack of pancreatic material acting positively on glucose utilization in the body. Lepine pointed out that he was the first one to label the pancreas as an organ of "internal secretion." It is true that we did not use that term in our first communication. This was published early in 1889, when Brown-Sequard coined the term. However, it is clearly apparent from our experimental procedures and the derived conclusions that the concept was always in our thoughts. Lepine supposed that I associated myself with his concept only when I did the implantation of pancreatic pieces under the skin. He overlooked the fact that the transplant procedure was devised to show that the pancreas operated in a fashion similar to other endocrine glands.

The results of the experiments with pancreatic transplants were confirmed by Hedon (Montpelier), who performed them independently and simultaneously. Hedon produced many other valuable additions to our knowledge of pancreatic diabetes. The ability of subcutaneous implants of pancreatic tissue to prevent the appearance of diabetes, which promptly reappeared on their surgical removal, was considered proof of an internal secretion until Pflüger, in 1905, began to participate in studies concerning pancreatic diabetes. Many of you in this audience may remember the spirited battles I waged with this temperamental worker. He was not above the use of personal insults. This matter has its own prehistory that I shall mention very briefly. When I moved to Köl, I made a courtesy visit to his office and was received by him most courteously. He gave me a copy of his monograph on glycogen, which I studied with great interest. Several of his conclusions concerning the sequelae of pancreatectomy seemed to me due to misunderstandings that could only be explained by Pflüger not having personally seen and studied animals after pancreatectomy. I mentioned this during conversation with one of his co-workers, and I offered to come to Bonn and to operate on several dogs that he would then be able to observe. Pflüger, however, considered my suggestion as demeaning to him. Witzel did the surgery, and Pflüger began to attack me more forcefully than before.

Finally, Pflüger expressed grave doubt as to the very existence of pancreatic diabetes. He believed that the consequences of pancreatectomy were due to lesions of an antidiabetic nerve center located in the duodenum, a center that he compared to the peripheral neural nodes connected with cardiac function.

On the other hand, I was able to show that removal of the pancreas after gastroenterostomy and choledochojejunostomy and the total removal of the duodenum, plus all pancreatic remnants, was not followed by glycosuria as long as a small piece of transplanted pancreas was still viable. Only removal of this glandular remnant induced glycosuria. These experiments and those with parabiotic pairs of dogs that Forschbach and I prepared (according to the method of Sauerbruch and Heyde) showed that removal of the pancreas of a dog that was in parabiotic union with another animal did not lead to hyperglycemia. These data strengthened the concept of a pancreatic internal secretion.

At this time, too, the idea of a pancreatic form of diabetes was measurably strengthened by anatomical observations on the glandular changes in the pancreas of diabetic individuals. However, in this area, "negative" findings were still more commonly encountered. Slowly, attention began to be
paid to the areas of the pancreas in which groups of cells lived in islandlike fashion within the body of the gland were aggregated. These were known as the islands of Langerhans. He had detected these cell "heaps" in 1869 but had no particular notion of their function. Others subsequently thought that they were lymph follicles, as seen in many organs. It was, however, pointed out that unlike the follicles in other organs, these pancreatic cells did not proliferate during the development of a leukemia in the same patient. More detailed investigation showed that the cells of these islets were of epithelial origin, glandular in character even though their appearance differed greatly from the externally secreting pancreatic cells. There followed arguments as to whether these cells had secretory channels; were they atavistic remnants of a glandular apparatus; did they take part in the formation of particular constituents of pancreatic juice such as diastase or trypsin? Some authors maintained that the islets and the acini appeared structurally different but fulfilled the same functions. Levachev felt that the islets were acini in a state of functional exhaustion that, after a period of rest, would resume their function as part of the gland of external secretion.

Laguesse (in 1893) voiced for the first time the opinion that the cells of the islets were the seat of production of the internal secretion that served a regulatory function in carbohydrate metabolism. The acinar cells, on the other hand, were active in preparing the external pancreatic secretion. Diamare and Schäfer agreed with this concept. Yet, Laguesse also supported the view that transitional forms between acini and islets could be found and that there probably was a continual process of transformation of one form into the other depending on the need for the external versus the internal secretion. Diamare, Sobolev, and Opie regarded the islet tissue as an independent endocrine organ having only spatial relations to the gland of external secretion, as, for example, the epithelial parathyroid and the thyroid, the cortex and medulla of the adrenal, and the anterior and posterior pituitaries. In addition, one could point to changes in the size of the islets and details of their structure induced by the administration of glucose, of phloridzin and/or epinephrine. Anatomical changes in the glands of diabetic patients were being described more and more frequently. Atrophy and complete loss of islets, hyaline and hydropic degeneration, vacuole formation, calcification, and sclerotic changes have all been demonstrated. Heiberg from Denmark worked out a technique for the exact determination of islet size and number and found these regularly diminished in the diabetic population. Particularly convincing were the findings that ligation of the pancreatic ducts produced severe atrophy of the parenchyma without affecting the appearance of the islets and that, in such instances, diabetes did not appear until the glandular remnants were removed. He also published such data. The view prevailed that the islets were the seat of production of the pancreatic hormone that affected carbohydrate metabolism. The name insulin was suggested for this substance long before its existence was clearly demonstrable. MacLeod states that the English physiologist Schäfer proposed this term in 1916; however, the name insulin appears earlier in a paper by de Meyer from Brussels published in 1910.

There remained some workers who did not agree with the notion of a functional difference between the islets and the pancreatic acini. In 1920, Seyfarth (Leipzig) concluded on the basis of developmental and anatomical studies that the islets of Langerhans did not constitute a separate organ but represented only a special type of secretory parenchyma. "They are the foci of origin of the glandular parenchyma responsible for the major portion of its development. They are the predecessors in the development of the parenchyma or its regeneration." The internal secretion, in this view, originated from both the islets and the acini.

Absolute proof that the islets were the most important site of formation of the pancreatic hormone came after the Toronto group of MacLeod and co-workers succeeded in isolating the hormone to a point at which it was possible to do a quantitative assay even though only in relation to its biological action on the blood glucose level. It was shown that the atrophied remnants of the pancreas, in which the acinar cells were completely destroyed by tying the ducts of the gland, exhibited much greater hormonal activity than the same amount of normal pancreas. It could also be shown that certain species of fish exhibited a small separate organ in the immediate vicinity of the pancreas. This contained primarily islet tissue without acini and had five to seven times the amount of insulin as did an equal weight of normal pancreas. As early as 1846, Stannius described these small organs in teleost fish, and he regarded them as "blood glands." Diamare (ca. 1900) spoke of them as corresponding to the islets of Langerhans and serving in the regulation of carbohydrate metabolism.

I stress that the various anatomical and embryological studies in favor of a common origin for the islet and the acinar cells were not negated by showing the quantitative differences in insulin content. MacLeod admits this as well as the possibility that a new formation of islets could perhaps occur in the course of a disturbance in pancreatic function by disease. Islets could then arise from acinar cells at certain stages. Such a view holds out the hope that healing and restoration of function could occur in severe cases with profound loss of islet cells.

The observation that only the pancreatic acinar cells atrophied after ligation of the ducts but that the islet cells were preserved was an important initial step in the work of the Toronto group in isolating insulin. Banting and Best as well as others assumed that the prior unsuccessful efforts in preparing potent pancreatic extracts were due largely to the actions of pancreatic enzymes that could destroy the active material during the initial working up of the glands. They therefore tried to get a better preparation by using glands first made atrophic by tying off the ducts. They did succeed in doing so, and they also succeeded in making an active preparation from the pancreases of fetal calves who have an inactive acinar pancreas while the internal secretory portions are intact. It was known that pregnant animals did not become diabetic after pancreatectomy because the fetal pancreas supplied insulin to the mother. After the Toronto group succeeded in their search for the active material by these roundabout methods, they overcame the tryptic action of the normal pancreas in a much simpler way, namely by adding freshly chopped-up glands to a cold alcohol-HCl mixture, a procedure that allowed the commercial preparation of insulin in rather large yields.
Some people thought that physiologists and physicians should be somewhat ashamed that it took over 32 yr from the time of the discovery of pancreatic diabetes to the first practical therapeutic consequences, but this is understandable and excusable if the causes of the delay are considered. The use of a pancreatic preparation suggested itself very early. I, myself, did such trials after the discovery of pancreatic diabetes. However, the feeding of pancreas to patients and/or diabetic animals did not lower the level of glycosuria. Rather, it seemed to raise urinary glucose, perhaps because there was better breakdown of starch and absorption of glucose by the introduction of pancreatic enzymes. I then tried the effects of the subcutaneous injection of pancreatic extracts. Such a procedure did lead to a lowering of urinary glucose excretion; however, it also led to evident widespread tissue damage in the animals. Nothing useful was achieved, and the results could not be properly evaluated. Isolation of an active ingredient and its separation from protein materials and enzymes did not appear feasible. At that stage in our knowledge it could only by surmised that the sought-after substances belonged to the group of proteins and ferments. Later, workers who endeavored to separate the active ingredients from damaging admixtures used in part techniques similar to those that finally proved successful. Thus, Macleod mentions that in France, Gey had deposited a sealed letter with the Societe de Biologie in Paris around 1905. In it he claimed that he had prepared an extract with the atrophic remnants of a pancreas with ductal ligation, which lowered the glycosuria of a diabetic dog.

Alcohol was used to isolate the active substance even at that time. Blumenthal (1898) used alcohol to extract pancreas, but the resulting preparation was so toxic it could not be used. In 1908, Zuelzer, using alcohol, was able to make an extract that abolished epinephrine glycosuria in experimental animals and lowered glucose excretion in diabetic humans. Experiments done by Forschbach, of my medical staff, according to Zuelzer's technique, resulted in very unpleasant side effects and had to be abandoned. I have often chided myself for not pursuing the causes of these side reactions, because the preparations undoubtedly had some effect on the degree of glycosuria. We were satisfied with establishing the unacceptability of the extract for human use.

A few years after Zuelzer's work, the American physiologist Scott prepared a pancreatic extract that could lower the glycosuria of diabetic dogs; he doubted, however, whether the effect was due to a pancreatic hormone.

Evidently, the time had not yet sufficiently ripened. Several steps in the reasoning process had yet to be established. The success of the Canadian scientists was due primarily to the advent of modern microanalytic techniques of blood constituents with small quantities of blood. These enabled them to repeat the determinations at will and to verify their results more effectively than by using the method of urinary glucose estimations.

In addition, the work since the beginning of the 20th century on the physiology of endocrine organs (especially the thyroid, adrenals, and pituitary) had taught us some of the characteristics of hormonal materials that could be usefully applied to procedures for the isolation of a new substance. Also, it must be remembered that the American (Canadian) workers had access to better equipment and an almost unlimited supply of the needed raw material. The most important advantage these research workers enjoyed was that they were not frightened away by the toxic properties of their extracts. They took into account the possibility that these could be due not only to the actual presence of toxic materials, but also to the effects of overdosage by the active ingredient they were seeking. Finally, their biggest achievement was their correct persistence in the investigation to the point of success.

The preparation of insulin finally removed the major objection to the concept of a pancreatic internal secretion and its important functional significance in carbohydrate turnover. Thus, the possible existence of a pancreatic diabetes could be affirmed in a positive sense. However, as is evident in other areas of the natural sciences, each new solution of a puzzle suggests more questions and presents more puzzles. It would take me far afield were I to include within this one lecture all of the problems that the discovery of insulin has posed for both the experimental and clinical aspects of diabetes. The literature that has accumulated over the last few years on the subject has become impossible even to enumerate. We still do not understand the chemical nature of the insulin molecule, how it is formed and in what manner its activities are expressed. Why does the hormone in some cases not exert its activity? Which tissues and organs are affected by it? Does it regulate carbohydrate metabolism in normal individuals or does it only decrease the increased formation of glucose in diabetes? Are all cases of diabetes due to functional alterations in the pancreas, or could lack of insulin activity in tissues point to another etiology? Barger recently confirmed Abel's work on the preparation of insulin crystals. Can we now expect a more accurate picture of pancreatic hormone action? New problems will undoubtedly arise, and their final solution will always remain unattainable. However, we should not undervalue our progress. Diabetes has lost much of its previous dread aspect; many, many people with the disease are healthy and active only because insulin has become available.

Nowadays, when scientific investigation is not highly prized by the general public, it should be pointed out how the discovery of insulin demonstrates that research, even though not directly guided by purely practical aims, will sooner or later result in findings that become useful in medical practice. It is not necessary to know all the answers concerning the forces of nature for them to become useful to human needs. It suffices to understand the laws by which the forces act to master them. When movements of a dirigible are followed on the radio, one can do so with feelings of joy and amazement even though we still do not understand the essential nature of the electrical forces involved in the wireless signal systems. We should not speak of scientific bankruptcy in the field of medicine at a time when we can point to the many valuable remedies scientific research has provided in recent years to the pharmaceutical and medical areas.