

2002 Presidential Address: A Tide in the Affairs of Medicine

*There is a tide in the affairs of men
Which taken at the flood, leads on to fortune;
Omitted, all the voyage of their life
Is bound in shallows and in miseries.*

—Shakespeare, *Julius Caesar*, act iv, scene 3

I am convinced that at this moment, we are riding a great tide of scientific progress. There are opportunities that have never existed in the history of humankind—opportunities to advance our understanding of diabetes and its treatment, opportunities even to cure diabetes. The American Diabetes Association (ADA), our community of scientists and clinicians throughout the world, and society as a whole must seize these opportunities, or all our lives will, indeed, be bound in the shallows and miseries of unfulfilled possibility.

I would propose that we have reached this moment of scientific opportunity in a relatively short period of time, about 100 years, and that the credit for progress over this past century is due more to the painstaking work of many scientists and clinicians than to the triumphs of a few brilliant discoveries.

Diabetes itself, of course, has been recognized for a long, long time—at least 3,500 years. The ancient Egyptians knew it very well, as documented in the so-called Ebers Papyrus (1). Fifteen hundred years later, Aretaeus (130–200 CE) not only used the term diabetes (from the Greek for siphon), but accurately described the signs and symptoms:

It is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patient never stops making water, and the flow is incessant, like the opening of aqueducts. (2)

Several millennia passed without significant progress in the understanding or management of diabetes. Through the entire span of human history, in fact, from ancient Egypt, the Greek and Roman empires, through the dark ages, middle ages, and the Asian dynasties, even through the Renaissance and the Age of Enlighten-

ment, very little progress was made in treating diabetes. It is fair to say that almost everything we now know about its causes and treatment has been learned just over the last hundred years or so.

What, then, was understood, and what was done about diabetes just 100 years ago, in 1902? The answer, quite simply, is not much, particularly in the realm of therapeutics. Through the last half of the 19th century, the best minds in medicine were most busy naming diseases, classifying them, describing their natural history and prognosis. Some startling advances were made, such as the discovery of bacteria as pathogenic, the importance of antiseptics, anesthesia, and vaccination. And the description of diabetes was being refined, with a hint at the distinction between what we now call type 1 and type 2:

The most prominent clinical feature of diabetes is the manifold differences that exist between different cases of the disease, so that the conclusion is reached that these distinct types of the disease must have dissimilar pathological basis. . . .

. . . It has always been debatable whether mild forms of diabetes ever progressed so as to become severe forms. (3)

On the whole, physicians 100 years ago were confined to making a diagnosis and a prognosis and providing pain relief and human comfort. There was very little specific therapy available. In 1913, the most famous diabetes expert at the time, Frederick Allen, agreed with Josef von Mering's opinion that he had "never seen a genuinely cured diabetic" (4). This era of medicine is beautifully described in a new biography by Professor Michael Bliss, *William Osler: A Life in Medicine* (5). Osler was the preeminent clinician and physician of the late 19th and early 20th centuries. He was international—born, raised, and educated in Canada; trained in the best clinics in Europe; and holding major teaching positions at the University of Toronto, the University of Pennsylvania, the nascent Johns Hopkins Univer-

sity, and Oxford University, where he was knighted and was the Regius Professor of Medicine. Osler was, and remains, the most revered of all clinicians and the quintessential academic physician, idolized not only in his time but ever since, particularly at Johns Hopkins.

What did Osler do to treat diabetes on the wards? He did use medical nutrition therapy, prescribing a "von Noorden" diet that contained 65% fat, 32% protein, and 3% carbohydrate. In his famous textbook of medicine (6), Osler also carefully prescribed "20 cc whiskey in 400 cc water" with black coffee for lunch. But in the end, his therapy was nonspecific at best. His discussion of treating diabetes concluded with the depressing thought that "opium alone stands the test of experience as a remedy capable of limiting the progress of the disease" (7).

So 100 years ago, medical therapeutics was on the whole a mixed bag of polypharmacy, home remedies, crude surgery, and pain management. The age of scientifically proven therapeutics, of evidence-based medicine, had simply not arrived.

Throughout the later 19th century and into the early 20th, however, the scientific tide was beginning to gather. Nowhere was this better illustrated than in the events leading to the first therapeutic use of insulin in 1921. Indeed, while the "discovery of insulin" in Toronto was an enormous therapeutic advance, it is a mistake, in my view, to consider it a miracle, a stroke of genius. Bliss's classic book, *The Discovery of Insulin* (8), describes the series of steps that led up to the use of insulin, occurring over the prior 50 years or so.

In 1869, Paul Langerhans, a German medical student, had used the newly improved microscope to note the clusters of cells that would bear his name, but the "nature of the cells, author (Langerhans) confesse[d] himself ignorant completely" (9). They were cells without known purpose, like the many genes without known purpose today.

In 1889, 20 years after Langerhans' descriptions of the mysterious islets, a renowned professor in Strasbourg, Oskar Minkowski, was studying digestion. On a challenge from Josef von Mering, Minkowski demonstrated that he could perform a surgical pancreatectomy in a dog. As described by the Argentinean Nobel Laureate Bernardo Houssay (10), Minkowski's animal caretaker found that the dog had become uncontrollably polyuric and polydipsic. Minkowski, after thoroughly scolding the poor man for not cleaning the cages, realized that these were symptoms of diabetes and proved it by demonstrating glucose in the urine. He proceeded to confirm that pancreatectomy causes diabetes and rightly concluded that there is some necessary antidiabetic factor in the pancreas. He had no idea what it was within the pancreas that protects against diabetes.

Enter a young pathologist, Eugene Opie, in 1901. A recent graduate in the first class at the new Johns Hopkins Medical School, Opie was riding the scientific flood tide, as we all try to do. He knew the literature about diabetes and knew how to make careful observations of pancreatic histology. And the tide of information had risen to the point where Opie could make a crucial discovery. Writing in small spiral-bound notebooks with a fine, precise handwriting that I have been privileged to see, he defined the purpose of the islets of Langerhans and the source of what was to become known as insulin:

I have described two types of chronic pancreatitis. . . . Where diabetes was absent, the islands of Langerhans persisted unaltered. . . . In the present case, however, diabetes followed a lesion affecting only the islands of Langerhans. . . . Diabetes mellitus. . . is caused by destruction of the islands of Langerhans and occurs only when these bodies are in part or wholly destroyed. (11)

With this and subsequent publications by Opie (12,13), the process of discovery had progressed from a simple description of these cells, without known function, to the understanding that diabetes was caused by *something* in the pancreas, to the observation that the islets of Langerhans did in fact contain the antidiabetic factor missing in diabetes. Each scientist was building on what was already known, each aware of the relevant literature.

From 1902 on, the scientific issue became how to successfully isolate this substance from the islets and how to use it to treat diabetes. There is no doubt that the goal was to find a treatment for diabetes. To quote from another passage from that time reprinted recently in the *Journal of the American Medical Association*: "And it may not be too far-fetched to suggest that eventually some form of organotherapy of diabetes may develop. . ." (3).

So I am asserting that the advances were steady, inexorable, with a series of contributors. The tide was on the rise.

In *The Discovery of Insulin* (14), Bliss summarizes the work of other scientists who were also extracting insulin even before the Toronto group: Georg Ludwig Zuelzer in Berlin in 1906; E.L. Scott at the University of Chicago in 1911–1912; Israel Kleiner at the Rockefeller University in 1919; and of course Nicolas Paulesco, professor of physiology in the Romanian School of Medicine.

Each of these investigators was more or less successful at showing a hypoglycemic effect of pancreas extract. But Zuelzer was never encouraged to pursue his work, apparently because he was Jewish and lacked social status. Scott gave aqueous extracts of pancreas intravenously to pancreatectomized dogs and reported "a slight diminution of glycosuria" according to Allen, but Allen dismissed his findings as "doubtless explained by renal or other nonspecific changes" (15). Kleiner's work was interrupted by World War I, and he never returned to it (14). The Romanians still feel strongly that Paulesco should receive credit for first discovering insulin.

Bliss also emphasizes that small, seemingly technical advances were crucial. For example, the ability to measure glucose quickly, without waiting for days or weeks of analytic time, was credited to Lewis and Benedict. As a technique, it was just as important to the discovery of insulin in 1921 as was PCR to the sequencing of the human genome in our own time.

Although frequently on the verge, none of these investigators in the first two decades of the 20th century reached the point of using pancreas extracts in humans, however. Until 1920, consummation was denied for one reason or another. The glory was left for the Toronto group.

In October of 1920, Frederick Banting jotted his famous note to himself, what he later repeatedly referred to as

"The Idea." Preparing for a lecture on diabetes to a small medical school in London, Ontario, Banting browsed the current edition of *Surgery, Gynecology and Obstetrics*, which had a relevant article describing the ligation of pancreatic ducts (16). A photomicrograph showed preservation of the islets of Langerhans as the pancreatic acinar tissue degenerated. Banting thought this procedure could be used to isolate the contents of the islets:

Oct 30/1920. Diabetus [sic]: Ligate pancreatic ducts of the dog. Keep dogs alive till acini degenerate leaving islets. Try to isolate internal secretion of these and relieve glycosuria [sic]. (17)

It was a startling idea, with all the hallmarks of genius, especially, I expect, to Banting, who was not trained in science and had little up-to-date understanding of diabetes. So the young, ambitious surgeon acted upon his idea, marching into the office of one of the most knowledgeable carbohydrate physiologists of the time, J.J.R. Macleod. Macleod was not so immediately struck by the merits of duct ligation. He knew very well that the islets contained the antidiabetic factor and knew that its isolation could treat diabetes; after all, that concept had been common knowledge for almost 20 years. Perhaps Macleod did not take full account of the fact that the tide of science had risen and advances in laboratory technique might now allow the successful extraction of the internal secretion. At any rate, he could hardly have missed the personal drive of Frederick Banting, and he did ultimately support Banting's work, even steering a bright young student, Charles Best, in his direction for the summer.

The rest, as they say, is history. Insulin was "discovered," Banting (and Macleod) received their Nobel Prizes, and the story quickly reached mythical proportions (albeit while quickly turning acrimonious on a personal level, almost to the point of within-lab fist fights). Looking back at this sequence, we see that Banting, whatever personal strengths and persistence he had, was not a genius, and this triumph did not result from his Idea. It resulted from the gradual accumulation of knowledge and technical progress, from the rising tide (18) and the efforts of many. Specifically, as it turns out, Banting's triumph was probably not at all related to his duct-ligation idea, but to the

fact that scientists in 1920 knew enough to keep the tissue on ice (19) and that their chemist, J.B. Collip, knew how to purify a crude alcohol extract.

I should also add that as honors were showered on Banting—and to a lesser extent Best, Macleod, and Collip—industry was the unsung hero of the time. Connaught Laboratories, Eli Lilly and Company, and Nordisk Insulin Laboratory each made enormous contributions by ramping up production and making commercial-grade insulin widely available within a matter of months.

But to summarize, when I see the number of people about to successfully extract insulin, as well as the sequence of events that was ultimately successful, from Langerhans through Minkowski and Opie to the Toronto group, I have to conclude that the discovery of insulin was inevitable. It was going to happen somewhere, if not within months then certainly within a few years. (And I know that in drawing this revisionist historical conclusion, I risk the ire of at least some of my Canadian friends.)

Now, is this a new idea of mine, that progress in science is inevitable, dependent less on individual genius than on time? Hardly. It turns out that the theory of the inevitability of scientific discovery dates back at least to the early 17th century, actually to a contemporary of Shakespeare (assuming he was not actually Shakespeare), Sir Francis Bacon:

The path of science is not . . . such that only one man can tread it at a time. (20)

. . . all innovations [social or scientific] . . . are the births of time. . . . Time is the greatest innovator. (21)

Bacon, who is acknowledged as one of the greatest geniuses of all time, even conceded that “the course I propose for discovery of sciences is such as leaves but little to the acuteness and strength of wits, but places all wits and understandings nearly on a level” (22). The promise of science, he suggests, is to be realized by “[scientists] working in association with one another, generation after generation” (20).

Bacon, then, was emphasizing the central importance of social and professional interaction among scientists, of communication, sharing knowledge and discoveries. He seemed to anticipate, almost 400 years ago, exactly the sort of

scientific life we now have through our publications and major scientific meetings.

Not that these early sociologists of science were perfect. In another passage from the 17th century, the first historian of the Royal Society, “fat Tom Sprat,” recommended,

. . . even joyning [*sic*] [scientists] into committees, if we may use that word in a Philosophical sence [*sic*], and so in some measure purge it from the ill sound, which it formerly had. (23)

And some of us may disagree when Bacon characterized scientists as “men abounding in leisure time” (20).

It is remarkable, however, how fully we have realized Bacon’s prediction that we would be meeting to share the labors of many. This is exactly how I see the ADA Scientific Sessions. We share results, ideas, and opinions. We share at the podiums and in the lobbies, the restaurants, the bars, and the airports. And we have certainly realized Sprat’s recommendation that we all form committees!

But there is another part of Bacon’s theory that struck me: the notion that science “leaves little to the acuteness and strength of wits, but places all wits and understandings nearly on a level.” This concept suggests that various people might have the same ideas and make the same advances simultaneously and independently.

I was fascinated to find this confirmed in the *Journal of the American Medical Association’s* theme edition on diabetes in May 2002, with the mention of a new name and a story that was new to me at least. The name is Leonid V. Ssobolew, a Russian scientist working at the turn of the century in St. Petersburg—as it turns out, in the laboratory of Professor Pavlov (24). Ssobolew was reaching exactly the same conclusions, at the same time, as was Eugene Opie:

In fifteen cases of diabetes, Ssobolew found more or less well-marked changes in the Langerhans islands in practically all the cases. . . . Unfortunately Ssobolew, in his review of the literature, omits entirely references to the American literature. (25)

This is a striking coincidence: the same discovery being made at the same time, independently, in Baltimore and in St. Petersburg. Or was it coincidence? In

1961, a professor of sociology at Columbia University named Robert K. Merton cited a compilation of 150 cases of scientific discovery (26). He concluded that it is the rule, not the exception, for discoveries to occur in multiple places almost simultaneously:

. . . far from being odd or curious or remarkable, the pattern of independent multiple discoveries in science is the dominant pattern. . . . It is the singletons—discoveries made only once in the history of science—that require special explanation. . . . Put even more sharply, the hypothesis states that all scientific discoveries are in principle multiples. (27)

The best evidence for this may be our everyday behavior as we practice science: Why do we rush to get our papers submitted and into print? Because if we don’t do it first, someone else will, and soon. Why was sequencing the human genome such a personal race between Craig Venter and Francis Collins? Because two groups, two methods, were each capable of doing it. The tools were there last year for cloning the human genome, just as the tools were there in 1921 for extracting insulin.

Why did Banting spend the rest of his life, well documented in other works by Bliss (28,29), futilely trying to make another major discovery, trying to cure cancer or treat sepsis, when for most of us discovering insulin would have been plenty for one career? Because he too was trying, in effect, to disprove Bacon, trying to show that he was better than, not just “nearly on a level” with, other scientists. He was trying to work well in advance of the rising tide of science (as he had done also in the fall of 1920 in proposing to “graft,” or transplant, pancreases).

The question then becomes: Are these academic/scientific rivalries nothing more than minor ego trips, little ripples on the rising tide? Does it really matter who reaches a goal first, who publishes the first report and claims primacy?

I would answer that yes, it matters. Let the competition go on. I believe that competition does spur advances, whether it is capitalism or the World Cup. Competition speeds the process, catalyzes the reaction. And it is important for scientific advances to move to the clinic just as quickly as possible. It makes a difference.

For one thing, there are individual lives at stake, as people with diabetes

await a scientific, therapeutic, or clinical practice advance. Bliss dramatically describes the condition of children on the diabetes ward at Toronto General Hospital in January of 1922 (30). They were on the verge of death from ketoacidosis, undergoing the torture of therapeutic starvation diets, and would never have survived had not the so-called Banting Extract been injected.

As it turned out, the first child to receive insulin, Leonard Thompson, lived 13 years longer, thanks to insulin, before dying of bronchopneumonia (31). The first American to receive insulin, Jim Havens, lived 49 years thereafter, ultimately dying of cancer. And a third, Elizabeth Hughes, lived a remarkably productive life on insulin therapy until 1981, 59 years after her first injection of the crude extract. (Elizabeth Hughes' father, Charles Evans Hughes, incidentally, was a U.S. Supreme Court justice memorialized in John F. Kennedy's *Profiles in Courage* for a courageous stand taken in 1920, defending a group of Socialists.) I personally happen to have seen a patient recently whose father was saved by insulin in Brooklyn, New York, in 1922. Those were dramatic days in the treatment of diabetes.

So advances in clinical research do save lives, and this can never be discounted.

Nor does this theory that science "places all wits and understandings nearly on a level" minimize the importance of individual leaders. There are always standouts, people leading the way in American science and around the world. They receive credit, and they deserve credit. But you will have noticed that virtually every time an honorary lectureship is delivered, the lecturer ends by thanking a long list of collaborators. Surely, medical science is in fact a "joint labor of many."

Nor should crediting science as a whole be an abstract, impersonal concept. In fact, we are crediting individual accomplishment: the many, many individual scientists from around the world who over the years have contributed to the rising tide of medicine. In crediting the whole scientific community, we are in effect paying homage to each of you, scientists and clinicians, as you congregate at this ADA meeting. Each of you plays a part, when writing up a new contribution to the literature, figuring out a better way

to help your patients, consulting with a colleague, sharing your own expertise, or enhancing that expertise by reading or by listening to reports at a scientific meeting. Each individual effort moves the science and the practice of diabetes to a new, higher level, taking part in the rising tide of science and medicine, and the ADA brings together as fine a group of scientists and clinicians as can be found anywhere.

It is worth asking, then, how did this ADA Professional Section meeting begin? Bacon could hardly have anticipated the present-day Scientific Sessions, with its enormous aggregation of brains, commitment, professional accomplishment, and altruism. I doubt that even the founders of the ADA could have imagined it as they met over lunch at a Schraft's Restaurant in New York City in 1941 to formalize a new professional association.

When the ADA was founded, it all looked small and, to current sensibilities, embarrassingly conventional. A group of distinguished physicians, all white, all male, most probably all with significant visceral adiposity, and all wearing bow ties for their inaugural photograph. But to their credit, they were actively, devotedly treating diabetes and asking the important questions of their time: How do we use the new insulin formulations? What is the proper role for these new diabetes pills? How tightly should we control blood glucose? How can we preserve limbs and eyes and kidneys? Familiar sounding questions.

A hallmark of the ADA has been its embrace of growth and change, its acceptance of cross-fertilization. It did not stay all middle-aged white men for long. To begin with, strong and accomplished women excelled in the field of diabetes, women like Priscilla White at Joslin, Nobel Laureates Dorothy Hodgkin of Oxford and Roslyn Yalow in the Bronx, Banting Award winner Ora Rosen of Albert Einstein, and more recently, Kathleen Wishner, our first female president, and Francine Kaufman, my successor.

Almost from the start, the ADA brought clinicians and scientists together, rejecting the restrictions imposed by being either a clinical or a research society. We now have a membership and a balanced program of basic and clinical science, research, education, and practice. We believe that clinicians enjoy the intellectual "fix" of hearing the latest science.

Scientists learn to focus their research questions by exposure to the clinical issues facing practitioners and the clinical problems facing people with diabetes. Recently, I talked with a basic scientist on his way to a diabetes congress specifically in order to learn more about clinical diabetes. The ADA brings these worlds together.

We also bring people together, literally, from all over the world. International attendees now make up close to half of the registrants at the ADA Scientific Sessions, about 6,000 people. We are enormously happy and honored to have them come and share their research, their expertise, and their perspective at what has become a truly international meeting.

Another great and distinguishing feature of the ADA is the inclusion of all health care professionals. In the ADA Professional Section, we equally seek, respect, promote, and value members of all the health care professions. We have major representation of nurses, nutritionists, podiatrists, pharmacists, behaviorists, and health policy makers. Our top leadership posts reflect this emphasis in the position of President, Health Care and Education, held by my colleague, Anne Daly.

One of the ADA's very proudest achievements has been to promote diabetes education and to nurture a whole new profession—the Certified Diabetes Educator—as well as to recognize excellence in diabetes education programs. I have said many times that diabetes education is the single greatest advance in diabetes care—ever.

But surely we can improve. We have to learn to better meet the needs of each professional group. We have to get to know each other better and respect each other more. We need to learn the right balance between thoroughness and bureaucracy, between high standards and excessive burdens.

In 1970, the ADA took yet another radical next step. We expanded beyond the notion of a professionals-only association, welcoming as equal partners non-health care professionals. The so-called lay section is now in full partnership with the professional section and led by the Chairman of the Board of Directors, my colleague Stephen Smith, in our year. Under Steve, non-health care professionals led many of the committees and task forces of the ADA.

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