Toying with the Truth to Win a Nobel

Amid a priority dispute, J. J. R. Macleod in 1922 disclaimed credit for the discovery of insulin; 2 months later he told a different story to a Nobel emissary and thereby won the call to Stockholm

Right from the start, the 1923 Nobel Prize for Physiology or Medicine has been mired in controversy. The award went to John J. R. Macleod, 47, a distinguished physiologist at the University of Toronto, and Frederick G. Banting, 32, a small-town surgeon who had a "bright idea" on how to isolate the internal secretions of the pancreas and came to Macleod's lab in Toronto to try it out. Macleod was on vacation in Scotland in 1921 when Banting and his student assistant, Charles Best, unraveled a major part of the insulin mystery, and a fight over credit for the discovery soon broke out.

Half a century later, the sentiment in Stockholm was that Banting and Best should have shared the prize, and that Macleod was guilty of interloping on the glory of his subordinates (*Science*, 27 March 1981, p. 1404). Rolf Luft, past chairman of the Nobel Committee for Physiology or Medicine, considered the episode one of the worst errors of commission in the history of the prize.

Despite the prevailing wisdom, the insulin story has always been long on rhetoric and short on facts. Now, a meticulously researched and subtle look at the controversy, *The Discovery of Insulin*, to be released in Canada in September and the United States in October,* reveals a wealth of fascinating detail. In researching the tale, historian Michael Bliss of the University of Toronto had the good fortune to find the Nobel archives on the subject recently opened.

The portrait of Macleod that emerges is both compelling and complex. In places it counters the conventional wisdom and reveals the importance of Macleod's ideas for the successful first use of insulin on human diabetics. In other places, it reveals a subtle disinclination to modesty on Macleod's part.

Not the least riveting detail in the book is how Macleod privately changed his appraisal of the work when it became clear that a Nobel Prize was in the offing. In an unpublished account of the discovery, written in September 1922, Macleod said that Banting and Best deserved complete credit for the initial work. Two months later, however, he told a Nobel emissary that they would have been lost without his guidance.

Macleod's surprising earlier account lay buried in the University of Toronto archives for more than 50 years. Notes Bliss: "Fearful of reopening a controversy that might do no one any good, the president of the University of Toronto in the mid-1950s had quite improperly used his influence to prevent its publication."

Hailed as one of the most dramatic events in the history of medicine, the discovery of insulin in the 1920's aroused much interest because it immediately extended the life-span of diabetic patients. After diagnosis, untreated juvenile diabetics usually died in less than a year. Insulin, as Bliss puts it, quickly became "the elixir of life for millions of human beings around the world."

In 1920, prior to the discovery, physiologists were in search of the internal secretion of the pancreas. It was already known that experimental animals, after the removal of the pancreas, immediately lost the ability to use carbohydrates, experienced a rise in the sugar content of their blood, and soon died of severe diabetes.

In the autumn of 1920, Banting, a surgeon in London, Ontario, read an article on the pancreas and late one night jotted down a procedure for isolating its life-promoting product. He proposed to tie off the pancreatic ducts, allow pancreatic fluid to accumulate, and then isolate the substance. He took his idea to Macleod at his alma mater, Toronto. Macleod, chairman of the department of physiology, was skeptical. In the most recent edition of his textbook of physiology, Macleod had asserted that there was as yet no proof of the existence of a pancreatic secretion, nor any way of disproving the theory that the critical cells in the pancreas were centers of detoxification, rather than secretion. Macleod reluctantly gave Banting eight dogs, an undergraduate assistant, and a place to work. The medical odyssey began on 17 May 1921. Macleod made significant suggestions and helped get the experiments rolling, but by the end of June he left Toronto for his summer vacation in Scotland.

University of Toronto Archives

J. J. R. Macleod

After 2 months of incessant labor, the Toronto experimenters on Saturday, 30 July, injected an extract into a dog whose pancreas had been removed. Over the next hour, the dog's blood sugar level dropped 40 percent and its clinical condition improved. On Monday, 1 August, Banting and Best injected 8 milliliters of their extract into a depancreatized collie that was on the brink of death. One hour later, the dog came out of the coma, stood up, and walked about the lab. "I have so much to tell you," Banting wrote to Macleod on 9 August, "that I scarcely know where to begin." More than a month later, on 21 September, Macleod returned from his vacation.

The period of peace and excitement started to erode in the fall of 1921 when Banting had to pressure Macleod into giving him a salary, more dogs, and a room in addition to the operating area. Macleod, though he clearly saw the merit of the work, told Banting and Best their demands meant other research would suffer. He eventually capitulated, and even encouraged other researchers to enter the field.

In January 1922, daily injections of insulin were given to a 14-year-old dia-

*In Canada, McClelland and Stewart Limited, Toronto; in the United States, University of Chicago Press, Chicago.

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betic at the Toronto General Hospital, the first human subject. Pale and weighing 65 pounds, the boy had lost much of his hair and his stomach had swollen. The injections quickly brought great improvement.

Headlines around the world followed, and by the fall of 1922 Banting and Macleod were deep in their fight. Touching off the argument was an article in the Toronto *Star* in September that quoted a British scientist to the effect that credit should go entirely to Macleod. Best took the article to Macleod, who said "Banting will have to get used to it," perhaps meaning misstatements in the press. To Banting, hearing it secondhand, it seemed Macleod was saying he had better get used to all the credit going to Macleod. Confrontations between Banting and Macleod ended with new headlines and greater hatred.

An attempt to end the dispute was made in the third week of September by a prominent member of the University of Toronto Board of Governors, Colonel Albert Gooderham. He asked Banting, Best, and Macleod to pen their individual versions of the discovery and, according to Bliss, he "planned to compare the statements and then meet with the trio to harmonize them."

Macleod, who wrote the longest account, was certain he had given support, encouragement, and advice. If he had been critical of Banting's early proposals, it was because Banting had come to him with such superficial knowledge. The work was ultimately a team effort, directed by himself. It was, for instance, the biochemist J. B. Collip who worked out the details of the purification of the extract, and who therefore played an important role in the success with the first human diabetic. Yet, Macleod continued, Banting and Best deserved full credit for the initial experiments. He had declined an offer to add his name to the first paper, published in the February 1922 *Journal of Laboratory and Clinical Medicine*, even though it was within his right. Wrote Macleod in a revealing passage: "In many, if not most, laboratories it is the custom for the 'chief' to have his name on the papers when the investigation is in a subject related to that in which he is engaged and if he stands responsible for the conclusions and has participated to the extent that I did in the planning of the research. By this step I made it perfectly evident that I considered the full credit for this investigation to be Banting and Best's. This is surely what counts in questions of priority."

Banting in his account, according to Bliss, "tended not to remember any of

University of Toronto Archives

Banting (right) and Best with the dog that received first injection of crude insulin.

Macleod's specific suggestions, or remember them being of any value, only that Macleod had not done any of the experiments, not a single one." This is unfair, according to Bliss. It was Macleod who right from the start suggested a method of refrigeration that stopped self-digestion of pancreatic material, and it was Macleod who in October 1921 kept Banting from taking up what appeared to be a futile grafting experiment. Nonetheless, Banting was willing to credit Macleod only with work on the investigation of insulin's physiological action, work started around February 1922, long after the completion of the basic discovery.

Reconciliation through Gooderham's good offices never took place. The principals disagreed on too many points. The documents were not made public, and no more statements were made to the press in 1922. Late that autumn, talk of a Nobel Prize started to circulate in Toronto's medical circles.

Indeed, a Nobelist soon appeared in the city. August Krogh, a Dane who had won the prize in 1920, came to find out more about the discovery that was everywhere the talk of American medical men. In November 1922 he stayed with Macleod, talked with Banting, and gave guest lectures at the university. Krogh, as is the duty of a Nobelist, soon made a nomination for the prize. He chose Banting and Macleod, citing them for the discovery of insulin *and* their exploration of its clinical and physiological characteristics.

Krogh wrote to his colleagues in Sweden: "According to the information I personally obtained in Toronto . . . credit for the idea of the work that led to the discovery unquestionably goes to Dr. Banting. He is a young and apparently very talented man. But he would surely never have been able to carry out the experiments on his own, which from the beginning and at all stages were directed by Professor Macleod."

Remarks Bliss, it seems the only "instance of Macleod telling a fellow scientist that Banting and Best would have gone off on the wrong track in 1921 without his advice."

Macleod's message came through loud and clear at the inner sanctum of Caroline Institute's Nobel committee. According to one of two internal evaluations of the evidence: ". . . it is very possible that the discovery would not have been made or at least not made as quickly, were it not for Macleod's guidance. It is even said that Banting was about to make an experiment which would not have led them to the goal, until he was corrected by Macleod."

The Nobel committee called for the prize to go to Banting and Macleod. The detailed recommendation (which mentioned Krogh's testimony but not his name) went to the Nobel Assembly, at the time all the faculty members of the Caroline Institute. Debate centered on whether Banting alone should get the award, or Banting and Macleod. On 11 October 1923, the assembly threw the joint nomination back to the committee for reconsideration. Wrote assembly member Alfred Pettersson in a letter to the committee: ". . . the justification of the award has never been based on hearsay evidence from unknown persons, on statements like 'it is beyond doubt,' on things that are thought of as 'very possible.' In my opinion, it is necessary that the Assembly adhere only to verifiable facts."

The committee reconsidered and came to the same conclusion: Banting and Macleod. In a formal letter to the Assembly it named August Krogh as the provider of the "hear-say" evidence, and emphasized that the Nobel laureate had visited the scene of discovery—the only emissary of the Nobel Foundation to do so: "Krogh, who personally visited Toronto and there for a time followed the work, discusses the prize-award very thoroughly and concludes that Macleod's part in the work merits the prize."

On 25 October, the 19 professors that made up the Nobel Assembly voted by secret ballot to award the 1923 prize to Banting and Macleod "for the discovery of insulin." The citation, in contrast to Krogh's nomination, made no mention of the exploration of insulin's clinical and physiological characteristics.

Nobody, writes Bliss, had ever seen Banting quite so angry. Upon hearing the news on the morning of 26 October, he rushed to the university, ready to renounce the award and tell Macleod exactly where to go. "Oh, he was furious," recalled an eyewitness. "He could have torn the whole building down."

Restrained by a colleague and counseled by a father figure who talked of obligations to Canada and science, Banting calmed down and announced the same day that he would share the cash and the credit with Best.

Nothing is known of Macleod's immediate reaction. A week or so after the announcement, he telegraphed Collip and asked him to share the prize money. On 7 November Macleod gave a brief statement to the press: "It would be invidious and quite unnecessary to try to dissect or divide up the work on insulin . . . it is teamwork that did it."

Was Macleod guilty of basking in the glory of his subordinates? Given his early statement to Gooderham and his subsequent reappraisal, one might conclude this was the case. Bliss does not. He argues that the true "discovery" of insulin did not take place during those early experiments, but only after purified extract had been successfully tested on humans. "Banting and Best alone did not discover insulin," writes Bliss toward the end of the book. "Their work . . . began the process that led directly and without significant interruption to success at Toronto. But it was a multistage or multi-step process, to which Collip, Macleod, and perhaps others made vital contributions." Bliss especially rails at Banting's Great Idea, the duct ligation, which was not only wrongheaded, but "played no essential part in the discovery." Indeed, Banting's hypothesis may have been wrong (the ligation probably did not stop all the external secretions of the pancreas), but it led, as Bliss notes earlier in the book, to essential further work, including the discovery by Banting and Best that the difficult ligation could be forgone in favor of extracting insulin directly from the whole pancreas.

Macleod's dalliance with the truth was unnecessary, according to Bliss. "Given what happened in Toronto in 1921–22 and given the fact that the Nobel Prize could not have been awarded to insulin's four discoverers, it is hard to see how the Nobel Prize committee could have made a better recommendation than Banting and Macleod." Perhaps not all readers will agree with this conclusion, and the conventional wisdom may continue to hold sway despite the scholarly researches of Bliss. The beauty of the book is that it tells the story in such a way as to leave room for the reader to make up his own mind on the question of who discovered the secret of insulin.

—WILLIAM J. BROAD

Stanford Doctors Try Consulting Inc.

The Department of Medicine has turned itself into a consulting collective to raise money for research by junior faculty

Faced with declining federal research budgets, universities across the country have turned hopefully to industry for support. A few, including Harvard and Washington University, have hit the jackpot with multimillion-dollar deals,* but less spectacular arrangements also have their place in the scheme of things in the growing academic-industrial complex. A case in point is a novel device by which the Department of Medicine at Stanford has, in effect, turned itself into a consulting collective to raise money to support the research of junior faculty.

About a year and half ago, the Institute of Biological and Clinical Investigation was officially established as a kind of consulting firm–cum–granting agency within the department. Its purpose is to link the department to industry while precluding conflict of interest or the rise of wealthy scientist-superstars. So far, two industrial sponsors—Syntex and Hewlett-Packard—have joined the Institute, each with pledges of $250,000 a year for 3 years, and half a dozen young faculty members have received grants from the Institute. According to Kenneth L. Melmon, who as chairman of medicine also heads the Institute, a Japanese company, Sumitomo, may sign up soon if negotiations are successful.

The Academic-Industrial Complex

This is the fifth in a series of occasional articles about the emerging relationships between industry and universities.

As Institute sponsors, Syntex and Hewlett-Packard have purchased a right to a fixed amount of consulting time from the department's senior faculty, who have agreed to respond "in a priority manner" to their requests for advice. Already, Melmon reports, department scientists, acting through the Institute, have held five major and two minor conferences with Syntex researchers on topics ranging from rheumatoid arthritis to interferon. The program with Hewlett-Packard, which is concentrated exclusively in the cardiovascular area, is just getting started.

Creation of the Institute, which was Melmon's brainchild, was preceded by nearly 2 years of groundwork, as industry, Stanford administrators, and members of the department were persuaded it could serve a useful purpose. "Each for their own different reasons was dubious of the plan," he says. It wasn't easy. Melmon noted that industry's relations with faculty usually involved only selected individuals who were asked to help with very highly defined problems, "usually related to the fine tuning of a product that had already been discovered. We reasoned that it was rare for industry to analyze carefully the developing edges of biology in relation to the industry's particular product lines and scientific strength." He figured that the combined talents of the 80-member Department of Medicine would be an attractive lure to forward-looking companies. "We thought that if we could develop a long-term, very responsible research strategy and joint planning of activity, confidence between the two parties would develop and, more important, that fundamental university-based research projects with no obvious product-connection might eventually be funded by industry," he says. What he found, he recalls, was that a number of people in industry just thought he was looking for a "handout" and that, in many cases, the research directors of several companies saw his proposition as

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