J. J. R. MACLEOD

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SPECIAL LECTURE*
J. J. R. MACLEOD AND THE DISCOVERY OF INSULIN

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For most people the discovery of insulin at the University of Toronto in 1921–2 is the story of medical researchers' wonderful discovery of a near-miraculous, life-saving therapy for diabetes. It was perfectly fitting that the 1923 Nobel Prize in physiology or medicine was awarded for this great discovery. Unfortunately the award left a legacy of continuing controversy because one of the Nobel laureates, Frederick Banting, believed that his student assistant, Charles Best, should also have been honoured. Banting divided his share of the Nobel Prize money equally with Best. His co-laureate, J. R. R. Macleod, divided his money with a fourth member of the team, J. B. Collip. Then as the discovery passed into medical history, with first Banting and then Best retelling their version of the story many times, J. J. R. Macleod's role in these events became clouded and confused, and somewhat blackened. The notion got about that Macleod had not really deserved to share in the prize awarded for the research of those men with such alliterative, assonant and Canadian names, Banting and Best. Particularly in Canada Macleod's role in the discovery of insulin was almost forgotten, and at the University of Toronto, which possesses innumerable monuments to Banting and Best, there was no remembrance whatever of the presence and achievements of the University's greatest Professor of Physiology.

The research that led to my book *The Discovery of Insulin* (Bliss, 1982*a*), and the televised dramatization based on it, *Glory Enough for All*, has gone a considerable way to locate J. J. R. Macleod's true role in the discovery of insulin. In this paper I rediscuss these events with a stronger focus on J. J. R. Macleod as a physiologist of his time. His deep conservatism as a scientist, I suggest, leads to the irony that a co-discoverer of insulin was never particularly interested in either the pancreas or the endocrine system of the body. On the other hand it was exactly the qualities associated with Macleod's conservatism – particularly his vast knowledge of the complexities of his subject and his commitment to the scientific vocation – that made it possible for him to play a vital role in the discovery of insulin. Behind the highly televisual fights of passionate, flawed scientists in the labs at Toronto and the near-resurrections that insulin really did effect, there stood a gentle, learned physiologist, doing his job with dignity and diligence as he orchestrated one of the great achievements in the history of medicine.

John James Rickard Macleod was born at Cluny, Scotland, in 1876. A minister's son, he was educated at Aberdeen Grammar School, and in medicine at Marischal College, University of Aberdeen, graduating with honours in 1898. He further studied at Leipzig and Cambridge and held brief appointments at The London Hospital Medical College. In 1903 he left the United Kingdom to become Professor of Physiology at Western Reserve University in Cleveland, Ohio, where he taught and did research for the next 15 years. He was a prolific researcher, a professor deeply learned in his discipline, and an accomplished

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scientific writer at both advanced and introductory levels. His research interests evolved from early work with Leonard Hill on intracranial circulation to a concentration on metabolism with special emphasis on the body's use of carbohydrates. In 1907 he began publishing a long series of papers entitled 'Studies in Experimental Glycosuria', and in 1913 summarized the work in a monograph, *Diabetes: its Pathological Physiology*.

While later events made this early research of little more than antiquarian interest, it reveals much about Macleod as an investigator and about the historical unfolding of the problem of diabetes. Specifically it reminds us that both the pancreas and the idea of endocrine secretions were latecomers in the evolution of knowledge about diabetes. J. J. R. Macleod had been trained in the 1980s in the mainstream of physiology. This meant that he had absorbed conventional wisdom about the primacy of the nervous system in the control of physiological functions generally and also followed Claude Bernard's emphasis on the central role of the liver in carbohydrate metabolism. Macleod's concept of diabetes was the traditional one of a condition of hyperglycaemia and/or glycosuria which could be induced experimentally by cerebroventricular puncture, phlorhizin poisoning, or asphyxiation. His studies seemed to confirm the view that the primary functional disorder in diabetes was hepatic, involving a failure of glycogen production and storage leading to increased production of glucose, indeed a flooding of the system with it. It seemed important to Macleod to investigate the triggering mechanism of this process, which seemed related to nerve impulses acting on the liver.

As a chemical physiologist Macleod took little interest in diabetes as a clinical condition; in the only comment I have found about the causes of clinical diabetes in his early writing, he attributes the disease, revealingly, to excessive nervous stimulation, writing in 1914 that 'Diabetes is common in locomotive engineers and in the captains of ocean liners, that is to say, in men who in the performance of their daily duties are frequently put under a severe nerve-strain. It is apparently increasing in men engaged in occupations that demand mental concentration and strain, such as in professional and business work' (Macleod, 1914).

Speculative flights like this are mercifully rare in Macleod's writing, because the normal hallmark of his work was a conservative empiricism, which caused him seldom to be out of touch with recent research findings, particularly those of a negative variety, and also seldom to speculate without solid empirical data on hand. The problem with this caution was that the more Macleod learned about carbohydrate metabolism, the more baffling its physiology seemed to become – particularly because of the way that the pancreas and new ideas of hormonal action kept inserting themselves into the familiar and comfortable models of diabetes as a nervous and hepatic disorder.

The pancreas had made a somewhat sudden, somewhat unexpected and belated appearance in the diabetes story with the discovery by von Mering and Minkowski in 1889 that its extraction leads to the development of severe, fatal diabetes (von Mering & Minkowski, 1890). At first no one knew or could intelligently speculate why that should be so, but by the turn of the century other discoveries involving ductless glands made it conceivable to speculate about the pancreas releasing some kind of internal secretion or (after the coining of the term at the instigation of Bayliss and Starling; see Medvei, 1982) some kind of hormone that played a vital role in the regulation of carbohydrate metabolism. But both the existence of that hormone and its mode of action remained hypothetical as Macleod and other researchers probed the mysteries of the supply of sugar in the body (see Bliss 1982*a*; Medvei, 1982). Indeed the role of the pancreas in metabolic events remained more obscure and appeared less important than that of the adrenal medulla, for the isolation of adrenaline (epinephrine) in the late 1890s soon led to the

discovery of its hyperglycaemic effects and the necessity of integrating an apparently hormonally induced form of diabetes into more traditional models of the disease. In his studies of glycosuria Macleod was able to do this more or less to his satisfaction by highlighting the role of the sympathetic nervous system in releasing adrenaline to work on the liver. So the new organ and its secretion had been fitted into the neural–hepatic model; indeed it was Walter Cannon's pioneering studies in emotional states and the release of adrenaline that supported Macleod's belief in stress as a principal cause of diabetes.

But always there remained the pancreas and its hypothetical hormone, and a rapidly increasing body of evidence – pathological, anatomical (as the Islets of Langerhans were explored), and experimental – that pancreatic diabetes was not just an odd form of experimental diabetes, but was somehow always at the centre of the puzzle. By about 1914 the idea that the pancreas produced an internal secretion was the most logical explanation of its function, but Macleod knew that scores and scores of attempts to isolate this hormone had gone nowhere. No one had been able, through pancreatic feeding or injection of pancreatic extracts, to demonstrate that they had captured the active principle that seemed to be lost in pancreatic diabetes.

As Macleod (1914) noted in reviewing some of the most recent attempts to find the elusive pancreatic hormone, there were 'extreme technical difficulties' in tackling the problem. For decades it had been next to impossible to trace the behaviour of sugars in the blood because measuring techniques were so primitive, thus forcing researchers to concentrate on the study of glycosuria where they were gravely handicapped by the effects of renal intermediation. And even though recent improvements in techniques, which greatly interested Macleod, now facilitated study of the blood sugar, there remained the baffling problem of the relationship of blood glucose to glycogen and the hepatic function generally; in other words there was on-going confusion about the course of physiological events in diabetes. As a cautious researcher Macleod tended to favour the traditional view of hyperglycaemia as the result of excess sugar production in the liver, but again there was a growing body of evidence suggesting that the real problem might lie in the inability of the tissues to burn sugar. Here was another and even more difficult problem of measurement, which led Macleod and others into elaborate attempts to estimate the oxidation of sugars in the cell as measured through studies of respiration.

Macleod's work in experimental glycosuria established his reputation as a most learned expert in the field, but by 1914 it seemed to have led to a dead-end characterized by his realization that the problem was too complex to be unravelled with the experimental techniques then available. He cut back his work on carbohydrate metabolism, wrote what became a famous textbook in physiology (*Physiology and Biochemistry in Modern Medicine*), and became increasingly unhappy at the United States' non-participation in the Great War and with his position at Western Reserve. In 1918 he returned to British soil by accepting the chair of Physiology at the University of Toronto. His main research interest now centred on attempts to explore centres of respiration (again seeing the problem as a study in the relations of nervous and chemical factors), but he did maintain a watching brief in the field of carbohydrate metabolism. While preparing this paper I found in the University of Toronto archives evidence that in 1921 Macleod was preparing his students to undertake new studies in puncture-induced diabetes. These were interrupted, however, by the advent in Macleod's life and laboratory of Frederick Banting and his ideas for work on pancreatic diabetes.

Macleod knew that Banting's proposal to ligate pancreatic ducts in the hope that intact islet cells and their secretion would survive had been tried before. As a liver man, rather

than a pancreas expert, Macleod may have been a little fuzzy in his knowledge of the exact state of research on atrophy of the pancreas after duct ligation, and he may not have expressed an opinion on Banting's notion that this procedure would be a way of frustrating the supposed destruction of the pancreas's internal secretion by its powerful external secretion (this seems to be a logical explanation of what some have seen as surprising gaps in Macleod's knowledge and/or shortcomings in the advice he gave to Banting, and underlay Sir Henry Dale's patronizing – and not unenvious remark – that insulin could only have been discovered in a lab whose director was slightly stupid (see Bliss, 1982*a*, pp. 208 and 278). He apparently did realize that no one had succeeded in following Banting's exact proposal before (unfortunately Banting's exact proposal is not fully clear from the documents; it seems to have been a double surgical procedure, aimed at showing that a graft of atrophied pancreas would restore normal metabolism in a depancreatized animal; in fact this would be what we would now recognize as an islet cell transplant) and for this and other reasons involving the under-utilization of his facilities and the desirability of encouraging all kinds of medical research at Toronto, he agreed to open his lab to Banting in the summer of 1921 and give him appropriate support and direction. Much direction was required because Banting, a dabbler who had worked out his idea after reading a journal article one night, was woefully ignorant of the field, inexperienced at research, unsure of his methods, and ignorant of the testing procedures he would have to use.

Macleod's support for Banting included giving him the help of his student assistants, notably Charles Best, advising him on the plan of the research, including methods of pancreatectomy (which he demonstrated to Banting), suggesting a research plan moving from transplants through the injection of extracts of atrophied pancreas, and explaining to Banting how to prepare an extract. After setting Banting and Best to work and consulting with them during the first several weeks of their research, Macleod left Toronto for Scotland for the balance of the summer of 1921. When Banting and Best reported to him their initial success in lowering the blood sugar of a depancreatized dog with their extract – in late July – Macleod gave instructions for controls, suggested problems with their findings, and outlined other experiments to make the results more convincing. There is no evidence that at any time Macleod developed much regard for Banting as a scientist or as a man – and in fact in September, when Macleod returned to Toronto, the two of them quarrelled bitterly about research facilities – but he did gradually become convinced that the favourable pattern of Banting and Best's blood sugar readings suggested the presence in their extract of an active principle, i.e. the internal secretion of the pancreas. In the autumn of 1921 he gave Banting and Best better facilities, and encouraged the work to continue.

The problem was how to complete the proof by producing something that would be conclusively recognized as the internal secretion. Other researchers, including Kleiner (1919) in the United States and Paulesco (1921*a*, *b*) in Roumania, had gone as far as Banting and Best and had from time to time cleared up glycosuria or hyperglycaemia with pancreatic extracts. But blood sugar could go down for many reasons after administration of pancreatic extract. What would count as indisputable evidence that these extracts contained the internal secretion? 'There is but one experiment...' Macleod had written apropos of this problem in 1914. 'This consists in seeing whether the symptoms which follow pancreatectomy are removed, and a normal condition reestablished, when means are taken to supply the supposed missing internal secretion to the organism.'

We do not know the exact details of his discussions with Banting and Best that autumn. We do know that Banting was dissuaded by someone from dissipating his energies in

pancreas grafting experiments, and we know that Banting independently managed to find that extracts of fetal pancreas and then fresh chilled pancreas were as effective as the earlier extracts of ligated, atrophied pancreas. We know that it was another member of Macleod's department who suggested to Banting and Best that a longevity experiment on a diabetic dog would be helpful in proving the extract's ability to supply the missing secretion. We know that it was Banting who asked Macleod to add to the team the biochemist, J. B. Collip, who was in Toronto on sabbatical that year from the University of Alberta to work with Macleod. After Collip joined the team in December, 1921, the group met daily for lunch. Macleod was the supervisor and organizer of the work, suggesting improvements in the preparation of extract (alcohol was now being used as an extractive, possibly on Macleod's suggestion) and outlining the new experiments that should be tried. He saw the need to explore the extract's effect in other kinds of experimental diabetes and above all wanted to know what it did to the liver and glycogen formation.

While Banting and Best ran into great difficulties in the preparation of their extract, it was Collip who went from strength to strength applying standard experimental techniques to the problem. His most exciting result, which took place just before Christmas, 1921, was his discovery that the extract enabled a diabetic liver to store glycogen (Collip, 1923*a*). This proof that the group had much more than a blood-sugar reducer, and that the extract acted at what Macleod believed was the centre of glucose metabolism, was quickly supplemented by Collip's discovery that the extract also cleared up ketoacidosis – and all of this in the context of Banting and Best's apparent success with their longevity experiments. This was the evidence Macleod cited to his associates in the American Physiological Association at its New Haven meeting that Christmas holiday during the discussion of the paper (Banting, Best & Macleod, 1922) given by Banting, and after Banting had failed to respond adequately to critical questioning about his and Best's experiments. However, it was precisely that intervention in the discussion which convinced Banting, who had never liked Macleod or felt comfortable in his presence, that both the work and the glory was being taken out of his hands by Macleod and Collip.

In January of 1922 the young men moved forward in an atmosphere fouled by rivalry and paranoia. Collip was attempting to purify the extract for what would surely be the ultimate test, on a human diabetic. Banting and Best had already tried such a test, apparently without telling Macleod, and it had failed. Macleod did consent to Banting and Best's extract being the first to be tested formally, on a 14-year-old boy named Leonard Thompson, in Toronto General Hospital on 11 January 1922. That test failed (Banting, Best, Collip, Campbell & Fletcher, 1922). Twelve days later, however, Collip developed a process by which he could remove the toxic contaminants from the extract while holding it in solution, and then precipitate out relatively pure active principle. Collip's extract worked on Leonard Thompson (Collip, 1923*b*).

Macleod was the man in charge of a situation of intense, almost unimaginable pressure, excitement, challenge and potential. The research team had found its way to a Holy Grail and now they had to present it to humanity, and to a sceptical scientific community. The packaging and presentation of the discovery would not be easy. The team desperately needed to learn more about the substance they had – its impact on the body, its chemical composition, even its origin in the pancreas. Macleod organized this on-going research and did much of it himself (e.g. Macleod, 1922; Best & Macleod, 1923). They had to explore its clinical impact on diabetes, work that Macleod co-ordinated with his fellow professor of medicine, Duncan Graham, and the appropriate clinicians, notably Walter Campbell. They had to organize production of much larger quantities of the extract, a process

Macleod assigned to Collip – until Collip, using primitive apparatus and working with more variables than he could control, lost the ability to make it, whereupon Macleod had to orchestrate the second search for the metabolic Grail. While it was being found Macleod had to hold together a team of researchers who had literally clawed at each other's throats (as Banting twice attacked Collip); had to organize their publications to present the discovery to the world (he suggested they follow what I'm told had been a Scots practice and publish alphabetically); had to give the substance a name (it was Macleod who suggested insulin from the Latin root for islet, and only later did they realize that at least two previous researchers had suggested the same name for the internal secretion); and had to carry on the delicate, pioneering negotiations with an American drug company, Eli Lilly and Company, and various patent attorneys, for a licensing arrangement which would bring Lilly's resources to bear on the production problem without sacrificing the group's control of the extract. He also had to protect himself from Banting's bitter, malicious attacks on his integrity as a scientist and a man.

This was J. J. R. Macleod's finest hour, a time when he employed all of his experience and skills as a scientist, an administrator, and a wise human being, to keep the lid on a tremendously volatile situation, keep the work going steadily forward, organize insulin production, testing and research, and generally carry on the elaboration of the discovery in such a way that the world of science and diabetes quickly realized that Macleod's physiology lab at Toronto was giving it a very important, very precious gift. While Banting raged and sulked, drank himself into oblivion, conspired for credit, and finally forced himself back into the picture as a clinician giving insulin to patients, Macleod carried an enormous burden of work and responsibility with immense patience, professional sure-footedness of the first order, and quiet dedication.

By the summer of 1922 insulin was performing those wonderful miracles with dying diabetics and the glory was being showered on the insulin man, the brilliant, shy Dr Banting, who was never shy about telling people how he and Best had struggled against Macleod's stinginess and disparagement and intellectual dishonesty. Macleod, on the other hand, was in a lab in Atlantic Canada trying to nail down the hypothesis that insulin actually was produced in the islet cells of the pancreas (he did this by drawing on much earlier research done here in Aberdeen by Rennie & Fraser (1907) using species of fish whose islet cells are anatomically separate from the rest of the pancreas; Macleod, 1922). When he returned to Toronto that autumn he faced more attacks from Banting. At the invitation of the Chairman of the Board of Governors of the University, Macleod wrote his only personal statement about these events, a 5000 word *History of the Researches Leading to the Discovery of Insulin*. It was not made public until 1978. It is a dry, factual, carefully composed document, stressing the collaborative nature of the work. Perhaps Macleod's pride in his achievement is evident in the final paragraph when he writes, 'Through concentrated effort, for the co-ordination of which I have been responsible, we have given to Science in little more than one year a practically completed piece of research work – we have proved the value of Insulin' (Macleod, 1922/78).

Macleod was not self-effacing to the point of abdicating his rightful claim to credit for his contribution. In his private and public accounts of the discovery of insulin he was very careful to credit Banting with having initiated the work and having confirmed the hypothesis that the pancreas contained an internal secretion. But he then insisted that the isolation and investigation of that secretion had been a collaborative effort under his direction in which Collip had played a particularly important role. This was the view adopted by the Nobel Committee, which was particularly influenced by the great Danish

physiologist, August Krogh, who, as the result of a visit to Toronto in the autumn of 1922, had nominated Banting and Macleod jointly, arguing that each was indispensable to the discovery process (see Bliss, 1982*a*, drawing on the Nobel archive). I agree with this view, though I would be inclined to have added Collip's name to the prize, for his breakthrough in purifying the extract to the point where clinical success was unambiguous seems to have been the single achievement separating Toronto's work from the failures of predecessors. It was the product of hard work by a well-trained biochemist using the most advanced techniques in a very well-equipped laboratory.

J. J. R. Macleod's Nobel address, given in Stockholm in 1925, began with a tribute to the 'numerous investigations over many years' by 'workers in various fields of medical science' which had preceded the Toronto research. His lecture was entitled 'The physiology of insulin and its source in the animal body', and Macleod used the opportunity to discuss the follow-up work his lab had been doing on insulin since 1923. After having proved insulin's source in the islet cells, Macleod left the pancreas, and in a sense left the exploration of insulin itself (the next important step in its story was Abel's crystallization of insulin in 1926), to go back to what for him was the key physiological problem, which was how insulin worked in the body to facilitate the metabolism of sugar.

Macleod's interests still centred not on the pancreas, but on the liver, for he was certain that insulin lowered blood sugar by stimulating glycogen formation and storage. It was 'a great surprise' he acknowledged in perhaps his most emotional statement in a scientific paper, when he and his students found that this hypothesis was not correct (Barbour, Chaikoff, Macleod & Orr, 1927). By the time of his Nobel lecture Macleod understood, as a result of his own and others' research, that insulin's principal action was in facilitating the passage of sugar into the cells. At that level he came upon, as it were, a brick wall: 'we know nothing of the fate of the glucose which disappears [into the cell]', he wrote. He concluded his Nobel lecture, not with a summary of past accomplishments, but with a scientist's simple look forward: regarding 'the perplexing problem of (insulin's) action in the animal body', he wrote, 'Facts of importance in this regard come almost daily to light and it is to be anticipated that, as these accumulate, a great advance will become possible in our knowledge of the history of carbohydrates in the animal body'.

After 1928 Macleod's role in developing this knowledge diminished. In that year he decided to leave Toronto to return to Aberdeen as holder of the Chair in Physiology. In Aberdeen he would not have facilities for research comparable to those he commanded in Toronto, but this was perhaps the one time in Macleod's life that he acknowledged a stronger pull than physiology. He was coming home to Scotland and to Aberdeen. He was also leaving a city and a university whose splendidly equipped laboratories could no longer hold him in a climate spoiled by the on-going rancour of his fellow Nobel laureate, Banting, with whom he did not speak. Sitting in the club car as the train was about to take him from Toronto for the last time, Macleod told a friend that he was shuffling his feet 'to wipe away the dirt of this city' (Bliss, 1982*a*, 1984).

Macleod may have loved his home in Scotland beyond reason, for after returning to Aberdeen he suffered from crippling arthritis, which was not helped by this North Sea climate. None the less he continued to lead a busy and by all accounts a reasonably happy life, furthering medical education at the University, working to improve its research facilities, carrying on research himself with the aid of students drawn to the University by his fame, including a young refugee from Hitler's Germany named Hans Kosterlitz. J. J. R. Macleod was one of Aberdeen's most famous sons, honoured in his native land for his distinguished career in physiology, and apparently untroubled by the disgraceful campaign

against him that occasionally rippled across the north Atlantic from Toronto. J. J. R. Macleod died in Aberdeen in 1935. In his last research he was still trying to locate the centre in the brain where nervous control of carbohydrate metabolism originated. The co-discoverer of insulin was never comfortable with the endocrine system. On the other hand, it may not be too fanciful to suggest that there is at least a tenuous link between this conservative physiologist's belief in the primacy of the nervous system and the on-going work related to neural transmission by Kosterlitz and his students which led to Aberdeen's central role in the discovery of the endorphins some forty years after Macleod's death.

When laymen and even some scientists promulgate an image of scientific development as miraculous breakthroughs made by passionate geniuses engaged in cut-throat competition, there is a real danger of getting the business backwards. When we cut away the undoubted drama, passion, and tensions of the insulin story, at the centre of things we find, in J. J. R. Macleod, a professional physiologist – a hard-working, conservative, cautious, even unimaginative man, but deeply studious and deeply devoted to his calling – without whom the Toronto research would have fallen apart or dribbled away in blind alleys. J. J. R. Macleod's mastery of his discipline, his strength of character and his dedicated professionalism were essential in Toronto's presentation of what was indeed a great and sensational gift of medical science to humanity. He has been dead for half a century now. I am sure he would be pleased to realize that his contribution to science is now understood by history. But if he could return today, J. J. R. Macleod would probably not be particularly interested in learning about the longevity of some of those early insulin-dependent diabetics or in John Woodvine's portrayal of him in *Glory Enough for All*. He would probably be most intrigued by what his fellow physiologists could now tell him about insulin receptors and 'the history of carbohydrates in the animal body'.

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University of Toronto Libraries: Manuscript collections in the Fisher Rare Books Library and the University of Toronto Archives include substantial private correspondence by Macleod, Banting and Best, as well as the complete notebooks of Banting and Best.