Insulin: passion and the prize

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The Discovery of Insulin. By Michael Bliss.

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MANY years ago now, I heard Michael Polanyi give his lecture on "Passion and Controversy in Science", later published in the *Lancet* (June 16 1956, pp.921-925). Anyone who doubts his view that scientific debate may be coloured by emotion should read the story of the discovery of insulin, which has now been told by a Canadian professional historian. Polanyi's two elements were fully displayed, together with more than a touch of ineptitude in high places.

However, before looking at the more controversial aspects of the way in which insulin was discovered, and the way in which credit for the discovery was apportioned, it is worth underlining the importance of the discovery itself in the development of medical science. Some 300 years earlier, Harvey had exhorted us to "search and study out the secrets of Nature by way of experiment"; and had himself shown the way in his proof of the circulation of the blood. Between Harvey's day and the present century, much knowledge had accumulated on the natural history of disease, and on the physiology of the body; and of course some empirical remedies such as digitalis had been placed on a sound footing. It was however the discovery of insulin which made it plain to the whole world that physiological knowledge could be applied in such a way as to cure a previously fatal disease. The mould of therapeutic nihilism was broken; the liver treatment of pernicious anaemia followed soon after, and in due course other replacements for vital factors which had been lost.

In the second century AD, Aretaeus of Cappadocia had recognized diabetes as "a melting down of the flesh and limbs into urine". In 1679, Thomas Willis in his account of "the pissing evil" distinguished diabetes mellitus from diabetes insipidus by the "honeyed taste" of the urine. In 1889, Minkowski found that removal of the pancreas in a dog produced diabetes; and in 1900 Opie reported lesions of the pancreatic islets of Langerhans in diabetic patients. In 1905, Starling in his Croonian Lectures had developed the concept of internal chemical messengers, which he named "hormones"; and in 1916 Sharpey-Schafer suggested that diabetes might be caused by a lack of such a hormone. The conceptual stage was thus fully set for the discovery of insulin; and, as described by Bliss, pancreatic extracts of various kinds had been prepared by Paulesco in Romania, Zuelzer in Germany and Scott

and Kleiner in the United States. There was just one problem with all these extracts; they didn't work.

In the autumn of 1920, Frederick Banting in Toronto had the idea that "by the experimental ligation of the duct and the subsequent degeneration of a portion of the pancreas, one might obtain the internal secretion free from the external secretion". He spoke to the Professor of Physiology, J.J.R. Macleod, who rather reluctantly gave him laboratory facilities, and also the help of a student, Charles Best. Work began in the summer of 1921, and is described in detail in Bliss's book, using the original notebooks. There were many difficulties with a high operative mortality, and severe reactions from the crude extracts; but the workers stuck to their task, and eventually it was possible to maintain a pancreatectomized dog for many weeks. It also became apparent that ligation of the pancreatic duct was not necessary, and this of course greatly increased the potential supply of pancreas for extraction. Extracts were first given to diabetic patients in the early months in 1922, but they were very crude — "a thick brown muck" — and they caused fever and other reactions. But they worked. J.B. Collip played an important part in refining the extracts, and thus making the use of insulin in treatment really practical.

Unfortunately, as the importance of the discovery became more apparent, animosi-

ty among the workers grew. Bliss picks his way carefully through a sequence of acrimonious disputes. Banting suspected Macleod of seeking to obtain the credit, following an occasion at a meeting when a clumsy presentation of the early results by Banting had to be clarified by Macleod from the chair. On another occasion Collip, who had been brought into the team by Macleod, refused to divulge to Banting and Best his methods of purification. There was a considerable quarrel, but in the event Banting, Best, Collip and Macleod signed an agreement. The award of a Nobel Prize in 1923 to Banting and Macleod led to further disagreements, however; Banting at once shared his prize with Best, and Macleod his with Collip. Banting quarrelled at one time or another with all the other three; Macleod seems to have been the most patient. But even he said on one occasion, "If every discovery entails as much squabbling over priority etc as this one has, it will put the job of trying to make them out of fashion".

The final paragraph of Bliss's book puts these matters into perspective, and part of it may be quoted:

Fred Banting, J.J.R. Macleod, Bert Collip and Charley Best knew they were making medical history . . . But perhaps the group at Toronto misjudged both their situation and posterity's viewpoint. They did not realize that those who understand history would eventually come to honour all of them. Above all, we would honour their achievement.

I would strongly recommend this book as a balanced account of a notable medical discovery, which might even be said to mark the dawn of major practical application of physiological knowledge to clinical medicine. □

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Making history — Charles Best (left) and Frederick Banting on the roof of the Medical Building at the University of Toronto, in 1921 or 1922.