Canadian Contributions towards the Comprehension of Hyperinsulinism: the First Successful Excision of an Insulinoma

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The authors review briefly the contributions to the “insulin story” made by Canadian doctors. A.G. Nichols from the department of pathology, McGill University, first described an adenoma arising from the islets of Langerhans. The authors also review the background to the first successful excision of a functioning tumour of the pancreas by R.R. Graham in 1929; in the preceding 2 years W.J. Mayo had found a malignant islet cell tumour with hepatic metastases and J.M.T. Finney had operated on a patient suffering from functional hypoglycaemia. Graham found and successfully excised what was probably a solitary benign islet cell adenoma. The authors believe the patient was cured.


In 1869 Langerhans first described the pancreatic islets, but could only speculate on their possible function. In 1902 A.G. Nichols, then a lecturer in the department of pathology at McGill University in Montreal, found a solitary nodule in the pancreas at autopsy. It was the size of a “marrow fat pea” and it differed from adenomas of the exocrine pancreas which had frequently been described. As it resembled the islets of Langerhans histologically it may be considered the first description of an islet cell adenoma. Nichols commented that it was difficult to determine whether the adenoma was benign or malignant, a statement that is still frequently made.

From 1909 onwards, various case reports were published describing the excision of what were probably adenomas of the pancreas, but the reports did not define whether the tumours were from the exocrine or endocrine pancreas. Clearly most of them were cystadenomas. In one report the photographs are sufficiently clear that our pathology colleague Professor C.L. Dolman believes the tumour was an islet cell adenoma. In 1926 Warren Shields gathered from the literature 20 cases of benign islet cell adenoma found at autopsy. He discussed the difficult differential diagnosis between multiple adenoma and adenomatisis. Although these were nonfunctioning tumours there was surprisingly no discussion of the possibility of functioning islet cell lesions. This is surprising because there was an appreciable body of knowledge at that time about the physiology of the pancreatic islets.

In the late 1800s there was much speculation about the possible relation between the pancreas and diabetes mellitus, although Harris noted that Osler had predicted as early as 1895 that the secretion of the pancreas would one day be isolated and used to treat diabetes! This debate continued into the early 1900s despite Von Mering and Minkowski’s demonstration that pancreatectomy in dogs led to their death from diabetes mellitus. The possible role of the islets was even more in doubt, although Shaffer thought they were ductless glands. The Canadian surgeon Frederick Banting with the help of his University of Toronto graduate student Charles Best, and later the biochemist J.B. Collip from the University of Alberta, in the early 1920s had clearly satisfied all of “Koch’s postulates”, about the relation between the islets and diabetes mellitus. By 1922 W.R. Campbell and A.A. Fletcher had successfully treated the first patients.

Although islet cell adenomas had been surgically excised and pathologically recognized for at least two decades, the possible existence of the clinical syndrome of hyperinsulinism was apparently not suspected until 1923. In March of that year Seale Harris, a physician from Birmingham, Alabama, visited Banting in Toronto.
and on the wards of the Toronto General Hospital he saw the clinical picture produced by an overdose of insulin. When he returned home he looked for cases of spontaneous hypoglycemia and found them, publishing his findings in 1924. His cases were probably not due to hyperinsulinism. The first diagnosis of an insulin-producing tumour was made by a surgeon on himself soon after the report of Harris and he was operated on in 1927 by W.J. Mayo. Carcinoma of the pancreas with hepatic metastases was found but a biopsy was not done. He died 1 month later; fortunately Banting and Best had been notified in the interval and were ready to search for evidence of insulin in the tissue. Extracts from the metastases given intravenously reduced the blood sugar in rabbits, establishing for the first time the diagnosis of an insulin-producing islet cell tumour.13

In 1928 two cases were reported that were quite similar in that the patients presented with what would now regard as typical symptoms extending over a long period, their blood sugar was low and they died in coma. In the first case the possible importance of the hypoglycemia was missed. At autopsy a nodule (1.5 cm in diameter) was found on the surface of the pancreas; it was interpreted as a malignant islet cell carcinoma. (Today it would probably be called benign.) In the second case glucose was given by gavage, by rectum and intravenously in an attempt to correct the hypoglycemia.13 At autopsy there was hyperplasia of the islets of Langerhans and a small benign adenoma on the surface. Tissue was sent to Toronto for bioassay but it was not suitable on arrival. The question of surgery was not raised in these two papers. In 1928 Finney14 operated on a patient with hypoglycemia who had been considered hysterical by the two psychiatrists who had seen her at various times. Finney did not find any lesion in the pancreas at operation and resected the tail and body without affecting the patient's condition. The resected specimen appeared normal. This was the first of many futile resections which have been done for functional hypoglycemia.

This then was the "accumulated wisdom of the race" when a 54-year-old female lawyer was admitted to the Toronto General Hospital in January 1929. She had been having "attacks" of increasing severity and frequency since 1922. Like the surgeon operated upon by Mayo and the second case reported in 1928 she had found that food, particularly candy was partially effective in aborting the attacks. The late Ray Farquharson, a young physician at that time, suggested she might be suffering from hypoglycemia due to hyperinsulinism. The presence of hypoglycemia was subsequently confirmed. After extensive investigation and after attempts at medical treatment had failed, a surgical consultation was requested. Before the operation she was seen by a psychiatrist who, in contrast to the psychiatrists in Baltimore a year earlier, was of the opinion that this patient was not suffering from hysteria.

The late R.R. Graham was asked to explore her in the hope that an insulin-producing lesion might be found. Fortunately, the literature available on the subject at that time could be read in an evening, but unfortunately Graham could not follow well trodden surgical paths. It is interesting to speculate on his preparation for this epic operation and his mental state prior to it. Those of us who were fortunate enough to work with him can believe that he would be concerned but completely confident. Very little pancreatic surgery had been done. Of course there had been numerous excisions of cysts and benign lesions of the pancreas. In 1910 Finney had resected a portion of the body of the pancreas for a benign tumour and had resutured the divided ends with a successful result.15 The organ was thought to be essential to life like the liver, both with respect to its endocrine and exocrine function. This erroneous concept, which was not dissipated until the next decade16 had undoubtedly held back the development of pancreatic surgery. As so often happens the conservative opinions of senior surgeons were given too much credence. In his 1928 paper14 describing his unsuccessful search for insulin-producing tissue at operation, Finney referred to "Mikulicz's well known opposition to pancreatic surgery". Surgery for malignant tumours was limited to local excision of the duodenum or ampulla of Vater and pancreatic tissue was not resected. By 1929 there had only been 58 local excisions for periampullary carcinoma and 4 for carcinoma of the ampulla.

Preoperatively Graham wrote that he was prepared to resect a portion of the pancreas if an adenoma was not found. At operation on Mar. 15, 1929 he found a tumour on the anterior aspect of the mid-pancreas. There were no visible metastases. He mobilized the pancreas from its bed on either side of the lesion and enucleated it. The raw surfaces of the pancreas were approximated with interrupted sutures and this was covered with a free omental graft. Although the area was drained for 4 days there was no drainage. The tumour gave a positive bioassay for insulin, the assay being done by Best. The lesion was labelled islet cell carcinoma of β-cell origin but the patient was well more than 20 years later (Campbell RM: Personal communication, 1979). As the original specimen, blocks and slides have been discarded the pathological diagnosis cannot be re-evaluated. This case was reported twice in 1929 in the medical and neurologic literature as "dysinsulinism" by the physicians involved but Dr. Graham’s name does not appear among the authors.17,18 In 1939 a paper19 was published, again in a medical journal, by Campbell, Graham and Robinson giving a 10-year follow-up on the first case and describing four more cases. Graham wrote extensively and it is difficult to understand why he did not publish a surgical article himself on this historic case, which was the first case of a β-cell tumour treated successfully surgically.

Since 1929 we have continued to find that hypoglycemia can be secondary to many conditions other than hyperinsulinism. There are tumours that produce peptides other than insulin which cause hypoglycemia. There are tumours, such as carcinoids, that produce insulin "inappropriately". There are familial multiple endocrine adenomatoses. In addition to the single, multiple or ectopic benign adenoma or carcinoma there are histologically malignant, clinically benign tumours. In addition to hyperplasia there can be adenomatosis. The solitary adenoma continues to be by far the commonest cause of hyperinsulinism. Because the differential diagnosis of hypoglycemia has become progressively more difficult it was indeed fortunate that the former rough bioassay for insulin was replaced in 1960 by the more precise immunoreactive method.20 False-positive findings, leading to fruitless laparotomy and often partial or subtotal pancreatectomy, are now much less common. The concomitant exhibition of calciuria, which has been so helpful as an evocative test in the Zollinger-Ellison syndrome is also helpful in diagnosing hyperinsulinism.21
References


BOOK REVIEWS continued from page 399

comments on performance checks, which remind one that the velocity of sound is temperature dependent. The chapter on interpretation and reporting contains many useful hints and describes the difficulties that may be encountered. The section on routine obstetrics is well done and gives valuable tips on how to obtain the biparietal diameter, the pitfals thereof and the likely causes of inaccuracy. The chapter on obstetrical abnormalities and complications contains brief explanations of conditions that would be helpful for physicians but are redundant for obstetricians. The same applies to the descriptions of some complementary radiologic and nuclear medicine techniques (e.g., intravenous pyelography). Appendix A outlines the essential physics with equations and line drawings. Real time, which is of increasing importance, is very briefly covered under future developments in Appendix B.

It is unfortunate that the standard of the plates does not match that of the rest of the book, which is well done, although the paper is out of date. The cheaper paperback version is all that can be recommended to beginners in ultrasonic B-scanning and the reader is advised to look elsewhere for illustrations of scans.

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This book is a concise and detailed guide to the use of skin grafts. It combines meticulous description and excellent illustrations of the various types of grafting instruments and techniques with an up-to-date referenced review of the literature on skin grafting and wound healing.

The book opens with a brief discussion of wound healing, stressing the process of wound contraction and the limitations of natural wound healing leading to the use of skin grafts for closing extensive wounds.

Several chapters describe the methods of preparing a wound to provide a healthy vascular bed for the graft and the types of skin grafts that may be applied to wounds in various locations. Graft selection depends on the requirements of the wound to be closed, as well as the availability and nature of donor sites. The characteristics of split-thickness and full-thickness grafts, including colour, contraction, stability, hair growth and mucous production are described.

Following these chapters is a beautifully illustrated section on the cutting of skin grafts with the common drum-type and power-driven dermatomes as well as with the scalpel. The author describes many useful little tricks—usually learned only by experience—to make grafts easy to procure. The various techniques of graft dressing and immobilization and the regimen to be followed after the initial application of dressings are discussed.

The healing or "take" of grafts, their later maturation and the reasons for graft failure along with biology and care of graft donor sites are then dealt with.

Special techniques of autografting are described. They include mesh grafting, harvesting of grafts from avulsed skin and use of dermis, mucosal and composite grafts in particular clinical situations.

Finally, the recent developments in skin banking, using both viable and nonviable human skin, are discussed, followed by a brief description of the use of substitutes for human grafts, such as xenografts and biologic and synthetic membranes. The closing chapter details some of the techniques of experimental grafting in animals.

Although crammed with useful information and practical clinical advice, this book contains only about 200 pages, many of which are photographs and drawings, so that the work may be read easily in one or two evenings. It should be a source of useful information for any surgeon about to undertake a skin grafting procedure and is highly recommended as a handbook for residents in plastic surgery to whom skin grafting will become as familiar a technique as "the closure of many broad wounds as suturing is for linear wounds".

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This new atlas presents an up-to-date synthesis on the state of the art in neonatal surgery. It illustrates well how pediatric surgery has become relatively standardized for the greater benefit of our patients, thanks to the activities of professional societies and the official recognition in both Canada and the United States of pediatric surgery as a specialty.

Although this is a multiauthored text, it originates from a single institution and successfully avoids the eclecticism and variable quality sometimes seen in such joint endeavours.

This is more than a simple atlas. The accompanying text details meticulously all the minutiae of the procedures described; I think this is the book's great-