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Pancreatic Organotherapy for Diabetes, 1889–1921

ROBERT TATTERSALL*

Introduction

The isolation of insulin by Banting and Best in 1921 and its rapid commercial exploitation revolutionized the treatment of diabetes. The story, frequently told as a romance of medicine, is that a young orthopaedic surgeon, Frederick Banting, went to the local Professor of Physiology, J J R Macleod, asking for facilities to try to isolate the internal secretion of the pancreas. Macleod was sceptical but provided a lab, dogs and a student assistant to measure blood sugar. After only three months, Banting and Charles Best isolated a potent anti-diabetic substance which was first used on a human diabetic in January 1922. Controversy followed when Banting and Macleod, not Banting and Best, were awarded the 1923 Nobel Prize. Much has been written about the events in Toronto in 1921–1922[1] as well as about the priority disputes which followed.[2]

Two editorials in the *Lancet* in 1923 questioned why this discovery had taken so long.[3] The seductively simple critique ran as follows: in 1869, Paul Langerhans described his eponymous islands, in 1889 Oskar Minkowski produced severe diabetes in dogs by pancreatectomy, in 1891 George Murray cured myxoedema by injections of thyroid extract and in 1893 Gustave-Edouard Laguesse suggested that the islands of Langerhans produced "an endocrine secretion" which controlled carbohydrate metabolism. How could it have taken thirty years for therapeutics to exploit the physiological suggestion? The origins of the hormone concept and the history of organotherapy in general have been explored in detail by Merriley Borell.[4] Her work focuses on the role of physiologists,

*Professor Robert Tattersall, Diabetes Unit, University Hospital, Nottingham NG7 2UH.

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[1] The best general account of the background and the events surrounding the discovery is Michael Bliss, *The discovery of insulin*, University of Chicago Press, 1982. Also published in the United Kingdom and Europe by the Macmillan Press, 1987.

[2] See J H Pratt, 'A reappraisal of researches leading to the discovery of insulin', *J. Hist. Med.*, 1954, **9**: 281–9, and W R Feasby, 'The discovery of insulin', *J. Hist. Med.*, 1958, **13**: 68–84.

[3] 'Recent work on blood sugar', *Lancet*, 1923, **i**: 707–8; 'The story of insulin', *Lancet*, 1923, **i**: 911.

[4] Merriley Borell, 'Origins of the hormone concept: internal secretions and physiological research 1889–1905', DPhil Thesis, Yale University, 1976. A copy of this thesis is in the Wellcome Institute Library, but parts of it have also been published. See particularly, M Borell, 'Brown-Séquard's organotherapy and its appearance in America at the end of the nineteenth century', *Bull. Hist. Med.*, 1976, **50**: 309–20; *idem*, 'Organotherapy, British physiology and discovery of the internal secretions', *J. Hist. Biol.*, 1976, **9**: 235–68; *idem*, 'Setting the standards for a new science: Edward Schäfer and endocrinology', *Med. Hist.*, 1978, **22**: 282–90.

whereas in the present paper I concentrate on the perspective of clinicians and examine their attempts to treat diabetes between 1889 and 1921.

The announcement that extirpation of the pancreas caused diabetes was received with great surprise because between 1850 and 1889 diabetes was held to be a disease of the liver, largely as a result of the work of Claude Bernard. After Murray's report in 1891 that myxoedema could be cured by thyroid extract, it was widely believed that the pancreas controlled carbohydrate metabolism by producing an internal secretion and, at least to physiologists, the likely source of this material was the internal vascular islets. In the decade after 1889 numerous attempts were made by clinicians to treat diabetes by feeding or injecting extracts of the pancreas, and their evident failure led them to doubt whether diabetes really was due to lack of an internal secretion. Myxoedema and Addison's disease, known or suspected to be due to absence of an internal secretion, were associated with shrunken glands but, in an age still dominated by morbid anatomy, the failure to find consistent changes in the pancreas of diabetics was regarded as evidence against the internal secretion theory. Some of the clinical scepticism was prompted by the disrepute into which organotherapy fell as a result of the work of C E Brown-Séquard and the commercialization of organ extracts. Also clinicians recognized many possible causes of diabetes including pancreatic, hepatic, neurogenic and other forms. In fact, because of the difficulty of measuring blood sugar before 1915, diabetes was usually equated with glycosuria and when testing the effect of organotherapeutic or other preparations clinicians used urine glucose and volume as the endpoints. This practice was frequently criticized by physiologists who advocated blood sugar or indices of total metabolism such as the dextrose/nitrogen ratio. Many physiologists and clinicians continued to hold that the pancreas (and/or particularly the islets of Langerhans) must produce an antidiabetic substance, but they had become so discouraged that between 1915 and 1920 only four or five individuals were actively working on the problem.

"One of the most Inscrutable of Diseases":[5] Ideas about the Aetiology of Diabetes to 1889

Diabetes, as a clinical disorder, has a continuous history in medical texts. One of the first, and most elegant, clinical descriptions is that of Aretaeus who practised in Cappadocia, probably around 120 AD. He described it as:

> A wonderful affection not very frequent among men, being a melting down of the flesh and limbs into urine . . . . The kidneys and bladder, the usual passageways of fluid, do not cease emitting urine, and the outpouring is profuse and without limit. It is just as though the aqueducts were opened wide. The development of this disease is gradual, but short will be the life of the man in whom the disease is fully developed. Emaciation proceeds quickly and death occurs rapidly . . .[6]

The sweet taste of diabetic urine was reported in the middle of the seventeenth century by Thomas Willis (1621–1675), and in 1776 Matthew Dobson evaporated the urine of a

[5] The Guy's physician F W Pavy (see note 17 below) used this phrase in most of his published works on diabetes.

[6] J A Reed, 'Aretaeus, the Cappadocian', *Diabetes*, 1954, **3**: 419–21.

diabetic patient leaving a residue which not only smelled and tasted like sugar but could be fermented.[7]

In the middle of the nineteenth century tasting the urine was superseded by the invention of chemical tests such as Trommer's (1841), Moore's (1844), and Fehling's (1849) which detected reducing substances in the urine.[8] It was soon clear that the copper solution, which formed the basis of these tests, could be reduced by substances in the urine other than glucose. Also some people who were not ill but whose urine was tested (usually for life insurance purposes) showed a reducing substance which by fermenting was proved to be sugar. This did not change clinicians' picture of the disease and most, like a Dr Daniel Hooper writing to the *Lancet* in 1873, dismissed the reduction of Fehling's soluion by the urine of apparently healthy people as "mere glycosuria", not true diabetes.[9] True diabetes it was agreed was a fatal disease characterized by polyuria, thirst, progressive weight loss and debility. A typical description is that of Bristowe, who in 1882 wrote:

> The prominent features of this disease are: the excretion of an excessive quantity of urine loaded with glucose, intense thirst, voracious appetite together with progressive emaciation and debility, followed after a longer or shorter time by death . . . for the most part the patient succumbs in one to three years.[10]

True diabetes could be distinguished by the persistence of glycosuria, its degree and its association with polyuria.[11]

By 1850 ideas about the seat of the disease centred on the liver, mainly as a result of the work of the French physiologist Claude Bernard (1813–1878). When Bernard began his work in 1843, the prevailing view was that sugar could be synthesized only by plants and that when eaten by animals it was either burned in the lungs or destroyed in the general circulation. It was also held that the blood contained sugar only after meals or in pathological states such as diabetes. Between 1846 and 1848[12] Bernard reported that sugar[13] was present in the blood of normal animals, even when starved, a finding which he at first found so astonishing that he doubted the specificity of his analytical method. He also reported that the concentration of sugar was higher in the hepatic than in the portal vein and that sugar was present in "enormous quantities" in the liver but not in any other organ. Bernard's hypothesis was that sugar absorbed from the intestine was converted in the liver into glycogen.[14] The liver then acted, in Bernard's words, as a

[7] Thomas Willis in *Practice of physick, being the whole works of that renowned and famous physician*, London, 1684, p. 76.

[8] S J Reiser, *Medicine and the reign of technology—chemical signposts of disease and the birth of the diagnostic laboratory*, Cambridge University Press, 1978, pp. 122–44.

[9] D Hooper, 'On Fehling's test' and the significance of sugar in the urine', *Lancet*, 1873, **i**: 360.

[10] J S Bristowe, *A treatise on the theory and practice of medicine*, London, Smith, Elder, 1882, 4th ed., p. 836.

[11] F Taylor, *A manual of the practice of medicine*, London, J & A Churchill, 1891, 2nd ed., p. 779.

[12] M D Grmek, 'First steps in Claude Bernard's discovery of the glycogenic function of the liver', *J. Hist. Biol.*, 1968, **1**: 141–54.

[13] In the latter half of the nineteenth century it was well known that the reducing substance in diabetic urine was dextrose or grape sugar but until the 1920s it was described simply as sugar and I shall use this terminology.

[14] Glycogen was discovered independently by Victor Hensen. See R Porep, 'The priority dispute between Claude Bernard and Victor Hensen about the discovery of glycogen', *Medizinische Monatsschrift*, 1971, **25**: 314–21.

syringe which constantly replenished the level of sugar in the blood during fasting.[15] The crux of Bernard's theory was his claim that there was always more sugar in the hepatic than the portal vein. In fact he found a complete absence of sugar in the portal vein but concentrations of 700–9000 mg% in the hepatic.[16]

In England the main opponent of Bernard's glycogenic theory was the Guy's Hospital physician Frederick William Pavy (1829–1911), described in his obituary as "the leading authority on diabetes" for more than a generation.[17] Pavy regarded the breakdown of glycogen as "simply a post-mortem fact", denied that there was a leak point (i.e. renal threshold) below which glucose did not appear in the urine, and strenuously maintained that the liver acted as a barrier to the entry of carbohydrates into the system. Pavy was treated with extraordinary deference by his contemporaries, but towards the end of his life his views were apparently regarded as archaic and, according to an epitaph, "he was gradually forced, not so much by the results of others, which he seldom read, as by his own experiments, to give up his original position bit by bit".[18]

Bernard's views were generally accepted by physiologists, and in 1879 Michael Foster, later Professor of Physiology at Cambridge, summed up what was known about the cause of diabetes:

> Sugar in the urine means an excess of sugar in the blood. How in natural diabetes that excess arises, we have at present no facts to show: but it is extremely probable that the sources of the excess may be various and hence that several distinct varieties of diabetes may exist . . . In many cases, the sugar continues to be discharged, even though the diet be perfectly free from carbohydrates; and in many other cases the sugar in the urine is far in excess of that taken as food. In these cases the sugar must have a non-amylaceous source.[19]

To those who accepted Bernard's hypothesis such as Thomas Lauder Brunton,[20] the excess of sugar might arise in three ways: (1) failure of the liver to form glycogen, (2) excessive breakdown of glycogen, or (3) diminished combustion of sugar, mainly in the muscles.[21] Failure of nervous control of the liver was the preferred mechanism. Claude Bernard had reported that glycosuria could be caused by lesions in the 4th ventricle

[15] F L Holmes, *Claude Bernard and animal chemistry*, Cambridge, Mass., Harvard University Press, 1974, p. 424.

[16] J M D Olmsted, *Claude Bernard: physiologist*, London, Cassell, 1939.

[17] F W Pavy, obituary, *Br. med. J.*, 1911, **ii**: 777–8.

[18] Editorial, 'Pavy and Diabetes', *J. Amer. med. Ass.*, 1913, **60**: 1159–60. The editorial writer quoted Sir William Gull's satirical question, "What sin has Pavy committed or his fathers before him, that he should be condemned to spend his whole life seeking for the cure of an incurable disease?" That there was bad blood between Gull and Pavy, both physicians at Guy's Hospital, is shown by the fact that they were reprimanded in 1881 by the Royal College of Physicians for becoming embroiled in professional disputes in public. See M Jeanne Peterson, *The medical profession in mid-Victorian London*, Berkeley and Los Angeles, University of California Press, 1978, p. 255.

[19] M Foster, *A textbook of physiology*, London, Macmillan, 1879, 3rd ed., p. 390–3.

[20] T Lauder Brunton (1844–1916), later Sir Thomas Lauder Brunton, was at the turn of the century the most widely known consulting physician in London. After graduating at Edinburgh he spent three years on the Continent, after which "he was probably better acquainted with modern methods of physiology and pharmacology than anyone else in this country" (Sir Edward Sharpey-Schafer, *History of the physiological Society . . . 1876–1926*, London, Cambridge University Press, 1927, p. 31). Brunton, like Pavy and Michael Foster, was a founder member of the Physiological Society.

[21] T Lauder Brunton, 'Lectures on the pathology and treatment of diabetes mellitus', Lecture I, *Br. med. J.*, 1874, **i**: 1–3, p. 2.

(piqûre diabètes)[22] and, because of the proximity of the vasomotor and a postulated diabetic centre in the medulla, it seemed to him that the excessive conversion of glycogen into sugar was the result of a vasomotor disturbance in the liver.[23] Another possible mechanism was diminished combustion of sugar. Brunton postulated that diabetes might arise from reduced combustion in the muscles as a result of insufficiency of a ferment, a change in the sugar making it resistant,[24] or diminished circulation through the muscles.

The use of drugs in diabetes was disdained by experts in the 1870s and 1880s, although every year there were reports that various nostrums were particularly effective in the hands of such-and-such a doctor. William Osler, a noted therapeutic nihilist, is famous for his comment that only opium stood the test of experience as a remedy capable of limiting the progress of the disease.[25] In 1874 Brunton[26] suggested that, inter alia, treatment should exclude all articles of food containing starch or sugar, reduce the circulation in the liver by hot baths and warm clothing, and lessen the excitability of the hepatic nerves with morphine or codeine.[27]

After the introduction of organotherapy Brunton claimed credit for having been the first to use animal extracts.[28] Reasoning that since the muscles were the site of sugar breakdown, they were likely to contain "the necessary ferment", he gave diabetic patients raw meat and also made a glycerine extract of muscle for subcutaneous injection.[29] His one test case was a failure. I Burney Yeo wrote that he had used raw meat in 1873 on the basis of reports that "a medical man in Constantinople" had obtained a great reputation for curing diabetes with it. Yeo tested it on two patients without notable results and mused that its failure might have been due to the type or preparation of meat. After all, he commented, "There is raw meat and raw meat. The dry blanched veal of this country must be a very different thing from the dark juicy veal of the Continent".[30]

[22] C Bernard, *Leçons de physiologie*, Paris, J-B Baillière, 1855, p. 315, quoted by D A Pyke in 'Diabetes: the genetic connections', *Diabetologia*, 1979, **17**: 333–43. The nervous origin of diabetes greatly preoccupied physicians in the period 1890–1914 although they knew that glycosuria following piqûre lasted less than 24 hours and could not be induced if the liver was depleted of glycogen. As an example of the concern that strain caused diabetes, J J R Macleod wrote in 1914, "Diabetes is common in locomotive engineers and 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." ('Recent work on the physiologic pathology of glycosuria', *J. Am. med. Ass.*, 1914, **113**: 1226).

[23] T Lauder Brunton, 'Lectures on the pathology and treatment of diabetes mellitus, Lecture II', *Br. med. J.*, 1874, **i**: 39–41.

[24] Bernard had already considered this possibility. He obtained sugar from the urine of diabetics and injected it intravenously into animals. It disappeared in exactly the same way as pure grape sugar without producing glycosuria. Holmes, op. cit., note 15 above, p. 410.

[25] W M Osler, *The principles and practice of medicine*, New York, D Appleton, 1892, 1st ed., p. 299.

[26] T Lauder Brunton, 'The pathology and treatment of diabetes mellitus', Lecture III, *Br. med. J.*, 1874, **i**: 221–3, p. 223.

[27] It was widely believed that diabetics could tolerate large doses of opium without becoming addicted. Thus, in Bristowe, op. cit., note 10 above, p. 842, "Diabetic patients are said to be little susceptible to the influence of opium and may therefore take it with safety in comparatively large quantities".

[28] T Lauder Brunton, 'Organs of animals in the treatment of disease', *Lancet*, 1894, **i**: 1096–7, "I believe the attempts I made in 1873 to treat diabetes were the first in which cure of a disease was sought to be effected by the administration of ferments derived from solid organs and not from glands connected with the alimentary canal".

[29] Brunton, op. cit., note 26 above, p. 223.

[30] 'Raw meat in diabetes', *Lancet*, 1894, **i**: 1160. Isaac Burney Yeo (1835–1914) became Professor of Clinical Therapeutics at King's College Hospital in 1885 and Professor of Medicine in 1896.

Pancreatic Diabetes

In early times the pancreas was regarded as a mechanical packing to support the stomach and branches of the aorta.[31] A connection with diabetes was not suggested until the 1870s when the French physician Apollinaire Bouchardat (1806–1886) pointed out that lesions of the pancreas were sometimes found in diabetic post-mortems.[32] He apparently tried to pancreatectomize animals but failed because his surgery was too crude. This experiment was done in April 1889 when Oskar Minkowski (1858–1931), First Assistant to Professor Bernhard Naunyn in the University of Strassburg, met Josef von Mering (1849–1908), the discoverer of "phloridzin diabetes",[33] in the library where they discussed the latter's research in patients with pancreatic (exocrine) insufficiency. In this idealized account, recalled thirty years later, Minkowski asked whether his colleague had done any experiments to prove that free fatty acids in the diet were beneficial; von Mering answered, "No, because even ligating the pancreatic duct does not completely exclude digestive enzymes". "Well, then", said Minkowski, "remove the whole pancreas". A spare dog was available, and the same afternoon

> von Mering and I removed the gland in toto . . . the animal withstood the operation surprisingly well, and we thought we would use it for the absorption experiments as soon as the wound healed. We did not think of diabetes; hence, we did not test the urine for glucose".[34]

Minkowski pancreatectomized three more dogs; the first two died, but the third survived and, from the second day after the operation, had persistent diabetes. Minkowski presented his results[35] at the First International Congress of Physiology in Basle in September 1889, and the same month the *Lancet* announced that

> Doctors von Mering and O Minkowski report a large number of experiments from their lab at Strassburg, all showing that extirpation of the pancreas results in true diabetes with all its ordinary symptoms. A dog whose pancreas had been removed secreted after 48 hours' fasting from five to six percent of sugar in his urine. Another dog weighing 15 lbs secreted under an exclusive meat diet two pints of urine daily with 6–8% of sugar . . . The percentage of sugar in the blood was likewise much increased. Glycogen at the same time disappeared altogether.[36]

[31] H D Rolleston, *The endocrine organs in health and disease*, Oxford University Press, 1936, p. 422.

[32] E P Joslin, 'Apollinaire Bouchardat', *Diabetes*, 1952, **1**: 490–1.

[33] Phloridzin (sometimes spelt phlorizin) is a glucoside from the root-bark of the cherry, apple, pear and plum. Its glycosuric effect was discovered by and intensively investigated by von Mehring. What impressed him and other investigators was "the absence of the hyperglycaemia which accompanies every other form of intense glycosuria" (F M Allen, *Studies concerning glycosuria and diabetes*, Boston, W M Leonard, 1913, p. 620). Much effort was expended to find the site of action of phloridzin and this was eventually established as the kidneys. It is now known to be a potent inhibitor of renal glucose transport.

[34] O Minkowski, 'Die Lehre vom Pankreas-Diabetes in ihrer geschichtlichen Entwicklung', *Munch. Wed. Woch.*, 1929, **76**: 311–15 (reprinted as 'Historical development of the theory of pancreatic diabetes' in *Diabetes*, 1989, **38**: 1–6). In this article Minkowski suggested that "the discovery of pancreatic diabetes tended to validate the view that a piece of scientific research may actually profit from total ignorance on the part of the investigators of any prior attempts and results".

[35] Throughout I have referred to Minkowski as the discoverer of pancreatic diabetes because, although he assisted at the first operation, von Mering played no further active role. Minkowski wrote their joint papers and put their names in alphabetical order. For further discussion see B A Houssay, 'The discovery of pancreatic diabetes: the role of Oscar Minkowski', *Diabetes*, 1952, **1**: 112–16.

[36] *Lancet*, 1889, **ii**: 552.

The announcement that pancreatectomy caused diabetes surprised many but it was widely accepted within two or three years. In November 1890, the *Lancet* reported[37] the experiments of Hédon,[38] who had excised the pancreas in 22 dogs, all of which then passed sugar and developed diabetic-like symptoms. In his Bradshaw Lecture of 1890, Robert Saundby pointed out that ever since Lancereaux drew attention to the frequency of pancreatic atrophy in diabetes and associated it with *diabète maigre*[39] "the changes in this organ have been interesting, but they are especially so since the experiments of Minkowski, Lepine and others". He also noted that the pancreas was often rather superficially examined by pathologists but agreed with Lancereaux that it was shrunken in all cases of typical wasting diabetes.[40]

In their original paper von Mering and Minkowski emphasized that they had not damaged the solar plexus but others continued to wonder whether injury to the abdominal sympathetic nerves was the real cause of diabetes after pancreatectomy. This hypothesis was floated by the *Lancet* in October 1891 reporting a meeting at the Académie de Médecine in Paris where Lancereaux had shown a dog which survived hemipancreatectomy in good health but developed diabetes after the other half was removed. In the discussion which followed, the *Lancet* reported that various and conflicting views were expressed; some held that diabetes was of three varieties—pancreatic, gouty and traumatic, while others asserted that the gouty variety should not be called diabetes at all as the glycosuria was merely a symptom of another condition.[41] The same lack of agreement was also present in England; at a meeting of the Royal Medical and Chirurgical Society on 26 January 1892, Dr Tylden criticized the pancreatic theory mainly because lesions were not consistently found in the pancreas of diabetic patients.[42] The persistence of the neurogenic theory, also supported by Tylden, was shown by the comments of Dr Rolleston,[43] who suggested that any severe disease of the pancreas might reflexly stimulate the medulla oblongata so as to produce diabetes by increased metabolism of the liver. On the other hand Dr Bradford[44] declared that the best established fact in experimental pathology was that removal of the pancreas caused diabetes. It was idle, he believed, to suggest that diabetes was caused by damage to other organs in the vicinity since physiologists had repeatedly damaged them without producing glycosuria.

[37] *Lancet*, 1890, **ii**: 1002.

[38] From 1890 to 1913 Édouard Hédon (1863–1933) carried out transplantation and parabiotic experiments in dogs which conclusively showed that canine diabetes could be cured by a subcutaneous pancreas implant or transfusion of blood from a healthy dog.

[39] E Lancereaux, 'Notes et réflexions, à propos de deux cas de diabète sucré avec altération du pancréas', *Bull. Acad. Méd.*, 1877, **6**: 1215–40. Étienne Lancereaux was President of the French Academy of Medicine. As well as being remembered for his description of the thin diabetic ('Le diabète maigre: ses symptômes, son évolution, son prognostie and son traitement', *Un Méd. Paris*, 1880, **20**: 205–11), he was the teacher of Nicolas Paulesco, the Roumanian, who is often considered the co-discoverer of insulin.

[40] R Saundby, 'The Bradshaw Lecture on the morbid anatomy of diabetes mellitus', *Lancet*, 1890, **ii**: 381–6. Robert Saundby (1849–1918) started life as a tea planter and in 1885 became a full physician at Birmingham General Hospital. He wrote a review of diabetes for the *Medical Annual* for several years in the 1890s.

[41] 'Diabetes and the pancreas', *Lancet*, 1891, **ii**: 1001.

[42] *Lancet*, 1892, **i**: 254; Henry John Tylden (1867–1902) was a promising young pathologist who died of typhoid aged 35.

[43] Presumably Dr H D Rolleston, who later became Sir Humphry Davy Rolleston, Regius Professor of Physic at Cambridge University. He wrote a textbook of endocrinology. See note 31 above.

[44] John Rose Bradford (1863–1935), later knighted.

A Substance Lacking: the Doctrine of Internal Secretions

In 1922 Swale Vincent, Professor of Physiology at the Middlesex Hospital, claimed that the concept of internal secretions was introduced jointly by Claude Bernard and Brown-Séquard.[45] In fact, neither thought of them as specific chemical messengers; Bernard used the term to distinguish between the bile-producing (external secretory) and glycogenic (internal secretory) functions of the liver and also stated that other organs such as the spleen, thyroid, supra-renal capsules and lympathic glands produced an internal secretion.[46] His contemporary Brown-Séquard claimed priority from an address before the Medical Faculty of Paris in 1869 in which he suggested that all glands, with or without ducts, "supply to the blood substances which are useful or essential and the lack of which may produce physiological signs".[47]

In the same year that Minkowski announced his results, there occurred an event which Gley later claimed had caused "the idea of internal secretion to take possession of the general imagination and gave the question a totally different aspect".[48] This was a presentation by the 72-year-old physiologist and physician Charles Édouard Brown-Séquard[49] at a meeting of the Société de Biologie in Paris on 1 June 1889. Starting from the premise that "Seminal losses, from any cause, produce a mental and physical debility which is in proportion to their frequency", he argued that the testes produced a "dynamogenic" substance which might be extracted and injected into aging and debilitated animals to restore their strength. He prepared testicular fluid from animals and injected himself with it almost every day for two weeks, with what the *British Medical Journal* sarcastically described as results which appeared to him to warrant an immediate communication.[50] He claimed to be rejuvenated and have the same vigour as thirty years before with more regular bowels and an increase in the length of his jet of urine.[51] These observations, albeit made by a distinguished physiologist who was well known in England, were greeted with incredulity in the English medical press and, according to the *British Medical Journal*, his statements recalled the wild imaginings of medieval philosophers in search of an *elixir vitae*. It is said that Brown-Séquard's theories were at once accepted in

[45] S Vincent, The Arris and Gale lecture, 'A critical examination of current views on internal secretion', *Lancet*, 1922, **ii**: 313–20, p. 313.

[46] Claude Bernard, *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme*, Paris, Ballière, 1859.

[47] Cited by Artur Biedl in *The internal secretory organs: their physiology and pathology*, London, John Bale, Sons and Danielsson, 1913, p. 4. Biedl (1869–1933) was a pioneer in clinical and experimental endocrinology. His monograph on internal secretions was first published in 1903 and by 1910 had expanded into two large volumes.

[48] E Gley, 'The theory of internal secretion: its history and development', *The Practitioner*, 1915, Jan–June: 5–8, p. 5. This is a lecture which Eugène Gley (1857–1930), Professor of Physiology at the Collège de France, gave at the International Congress of Medicine in London in 1913.

[49] Brown-Séquard (1817–1894) was born in Mauritius, the posthumous son of an Irish American. Since Mauritius had been annexed by England in 1814 he was a francophone and an English citizen. By 1856 he was already famous for his description of the sensory decussation of the spinal nerves and discovery of vasomotor nerves. In 1860 he became physician to the National Hospital for the Paralysed and Epileptics (Queen Square) and in 1878 succeeded Bernard in the Chair of Medicine at the Collège de France. For a sympathetic view of this remarkable man, see J M D Olmsted, *Charles-Édouard Brown-Séquard: a nineteenth-century neurologist and endocrinologist*, Baltimore, The Johns Hopkins Press, 1946, and M J Aminoff, *Brown-Séquard: a visionary of science*, New York, Raven Press, 1993.

[50] Aminoff, ibid., pp. 159–73; 'The pentacle of rejuvenescence', *Br. med. J.*, 1889, **i**: 1416.

[51] Brown-Séquard was a compulsive self-experimenter who for years kept records of his own physiological functions. He was also an extraordinarily vigorous man whose "excessive zeal for work often led him to spend as much as 20 hours a day on his experiments", obituary, *Lancet*, 1894, **i**: 975–7.

France and, to some extent in England, although German physiologists and clinicians were extremely sceptical.[52] In March 1891 Brown-Séquard suggested that his assistant d'Arsonval[53] should make extracts of liver, spleen, kidney, suprarenal capsules, pancreas, thyroid, lungs, salivary glands, brain and spinal cord, because:

> I say now merely that all glands with an external secretion have, at the same time, like the testicles, an internal secretion. The kidneys, the salivary glands, and the pancreas are not merely organs of elimination. They are, like the thyroid, the spleen etc., organs giving to the blood important principles either in a direct manner or by resorption, after their external secretion.

The pancreas was of particular interest because, as Brown-Séquard noted, "When the pancreas has been suppressed (ablation, ligature of its veins etc.) there is diabetes" and he wondered whether this would be cured if people were given daily injections of pancreas extract from a healthy animal.[54]

The emerging doctrine of internal secretions and the potential of organ extracts[55] were given powerful support by the dramatic effects of thyroid extracts in the treatment of myxoedema first reported in 1891 and repeatedly confirmed within a year. Until the middle of the nineteenth century practitioners agreed that the function of the thyroid was not yet known but, in the mid-1880s, the Swiss surgeon Theodor Kocher[56] reported that total (but not partial) thyroidectomy created a condition analogous to myxoedema and Victor Horsley reported that he had produced an animal model of myxoedema by removing the thyroid in a monkey.[57] These reports were soon accepted and in February 1891 Dr George Murray showed a 46-year-old woman with florid myxoedema at a meeting of the Northumberland and Durham Medical Society.[58] He described how he intended to treat her with thyroid extract and his reasons for expecting it to work. Treatment began in April 1891 when 25 minims of glycerine extract of thyroid from a freshly killed sheep was given hypodermically twice a week. She gradually improved and Murray presented the case at the annual meeting of the British Medical Association in Bournemouth in 1891 and in the *British Medical Journal* in October 1891. Others soon showed that thyroid extract by mouth was equally effective and Murray's patient switched to 10 minims orally six nights a week and remained well until 1919, when she died of cardiac failure aged 74.[59] In 1893 the *British Medical Journal* declared that "In the treatment of myxoedema by thyroid extract, scientific medicine has achieved one of the most striking and significant triumphs which have ever been won in the field of practice".[60] The pharmacologist Arthur Cushny

[52] Biedl, op. cit., note 47 above, pp. 4–5.

[53] Arsène d'Arsonval (1851–1940) succeeded Brown-Séquard as Professor at the Collège de France.

[54] Olmstead, op. cit., note 49 above, p. 216–17.

[55] The therapeutic movement of treatment by animal extracts was most commonly known as organotherapy. In 1895 Landouzy introduced the term "opotherapy" (ὀpos=juice) and others were also used, including séquardotherapy, histotherapy and zoopotherapy. See H Batty Shaw, *Organotherapy or treatment by means of preparations of various organs*, London, Cassell, 1905, p. 2.

[56] An interesting discussion of Kocher's research is found in Thomas Schlich, 'Changing disease identities: cretinism, politics and surgery (1844–1892)', *Med. Hist.*, 1994, **38**: 421–43.

[57] V A H Horsley, 'A recent specimen of artificial myxoedema in a monkey', *Lancet*, 1884, **ii**: 827.

[58] G R Murray, 'Note on the treatment of myxoedema by hypodermic injections of an extract of the thyroid gland of a sheep', *Br. med. J.*, 1891, **i**: 796–7. George Redmayne Murray (1865–1939) was a pathologist in Durham at the time but in 1908 became Professor of Medicine in Manchester.

[59] G R Murray, 'The life-history of the first case of myxoedema treated by thyroid extract', *Br. med. J.*, 1920, **i**: 359–60.

[60] 'Thyroid extract in myxoedema', *Br. med. J.*, 1893, **i**: 252.

later described it as "one of the most satisfactory examples of rational therapeutic progress".[61]

By 1893 the *British Medical Journal* had overcome its incredulity sufficiently to publish two papers by Brown-Séquard; there was no doubt, he stated, that the pancreas had an internal secretion which was even more important than its external one, and he recommended the simultaneous use of orchitic and pancreatic liquid in all cases of glycosuria. Immodestly, he concluded that "the great movement in therapeutics as regards the organic liquid extracts has origin in the experiments I made on myself in 1889, experiments which were at first so completely misunderstood".[62] In an accompanying editorial the *British Medical Journal* acknowledged that "though many jeered at him as the discoverer of the secret of perpetual youth", there was perhaps something in it and that since the success of thyroid extract, this belief had strengthened.[63] The writer of the editorial nevertheless worried that there might be "an epidemic of universal injections", and this was what happened since, by the time Brown-Séquard made his last report to the Academy of Sciences in 1893, his orchitic fluid had been very widely tested and appeared to alleviate, if not cure, most known ailments.[64] For example, 314 of 405 cases of locomotor ataxia (tabes) had benefited, four of every five cases of pulmonary tuberculosis were cured and diabetes was alleviated. Brown-Séquard was careful to warn that his extract did not cure but simply strengthened the natural resistance of the organism.[65] Nevertheless, he predicted that:

> An immense field is open to practitioners who will want to employ liquid extract of diverse tissues and organs as a therapeutic medium . . . Thus, for example, one could administer thyroid liquid in myxoedema, exothalmic goitre or after thyroidectomy; in the cases of Addison's disease, liquid of the supra-renal capsules; in the case of wasting disease, pancreatic liquid; in the cases of leukaemia, liquid of the lymphatic glands, the spleen and the bone marrow.[66]

Pancreas Feeding and Injecting: 1893–1900

There are well known instances where clinicians recognized in an animal model a disease they had seen in the wards. In 1881 David Ferrier showed a monkey in which, by ablating the motor area of the left cerebral hemisphere, he had produced paralysis of the right arm and leg. Jean-Martin Charcot, recognizing the gait of a hemiplegic patient, exclaimed *"C'est un malade"*.[67] In 1910 when Harvey Cushing saw a hypophysectomized dog which was listless, fat and asexual he immediately said "Here is Frölich's sexual adiposity".[68] In

[61] A R Cushny, *A textbook of pharmacology and therapeutics*, Philadelphia and New York, Lea Brothers, 1899, p. 691. Arthur Cushny (1866–1926) held the Chair of Pharmacology at University College London from 1905 to 1918 and then the Chair of Materia Medica in Edinburgh. He was a persistent critic of the unthinking use of organotherapy.

[62] C E Brown-Séquard, 'On a new therapeutic method consisting of the use of organic liquids extracted from glands and other organs', *Br. med. J.*, 1893, **i**: 1145–7, 1212–14, p. 1213.

[63] 'Animal extracts as therapeutic agents', *Br. med. J.*, 1893, **i**: 1279.

[64] By the end of 1889 more than 12,000 physicians worldwide were using Brown-Séquard's fluid, which its inventor supplied without charge, asking only that the results of its use be communicated to him. Olmsted, op. cit., note 49 above, p. 209.

[65] Brown-Séquard, op. cit., note 62 above, p. 1214.

[66] This quotation is taken from Borell, 'Origins of the hormone concept', op. cit., note 4 above.

[67] W F Bynum, '*"C'est un malade"*: animal models and concepts of human diseases', *J. Hist. Med. Allied Sci.*, 1990, **45**: 397–413.

[68] L G Wilson, 'Internal secretions in disease: The historical relations of clinical medicine and scientific physiology', *J. Hist. Med. Allied Sci.*, 1984, **39**: 263–302.

the same vein physicians tried to identify a clinical variety of human diabetes analogous to experimental pancreatic diabetes. The most obvious candidate was the acute rapidly fatal condition seen in young people and, in 1892, Vaughan Harley wrote that:

> The signs and symptoms of diabetes, either depending upon or associated with pancreatic disease, are known to present in several respects marked differences from those usually manifested in cases of diabetes unconnected with a derangement of the pancreatic functions, the onset of pancreatic diabetes being usually exceedingly sudden . . .

It was also, according to Harley, rapidly fatal. He emphasized that in pancreatic diabetes "even the casual observer" would note that the faeces contained undigested food and floated in an oily liquid which, on cooling, hardened into a dirty yellowish grease.[69]

In fact, the diagnosis of pancreatic disease posed major problems. Claude Bernard had shown the importance of the secretion of the pancreas for digestion of proteins, fats and carbohydrates and in a few cases of extensive disease of the pancreas clinical observers had noted that the stools were fatty and contained many muscle fibres.[70] Hence the conclusion that in pancreatic disease there was poor absorption of fat and nitrogen.[71] However, in 1887 Friedrich Müller showed that fatty stools occurred in jaundice and claimed that in pancreatic disease without icterus there was no disturbance of fat and nitrogen assimilation.[72] Coming from such an eminent authority, this carried great weight. Until the introduction of the first pancreatic function test, Hermann Sahli's glutoid capsule, in 1897,[73] diagnosis of pancreatic disease depended on the bulk of the stools and presence of fat globules and undigested muscle fibres.

The success of thyroid treatment had led to high hopes of a cure for diabetes and on 7 January 1893, Dr R Mansell-Jones suggested that "pancreatic juice, administered either immediately before or after meals, should be given a fair trial in diabetes, as this disease appears in most cases to be due to disease or disordered function of this gland".[74] This was

[69] Vaughan Harley, 'Remarks on two cases of pancreatic diabetes: the one exceptionally acute, the other markedly chronic', *Br. med. J.*, 1892, **i**: 9–11. One was a 23-year-old medical student who at post-mortem had an atrophied pancreas containing one large and several small abcesses and the other a 64-year-old man with cancer of the pancreas. At the time Vaughan Harley was working in Leipzig but later became Professor of Pathology at University College, London. He contributed a 6-page article to the 1896 *Medical Annual* on pancreatic diabetes. That the subject was highly topical is suggested by the fact that the section on diabetes in general (by Saundby) is only 2½ pages.

[70] This phenomenon was first noted in the 1870s and became known as creatorrhoea. It was the basis of Schmidt's Beef Cube Test (1900) in which the patient swallowed small cubes of beef hardened in alcohol and wrapped in silk gauze to aid their identification in the faeces. It was thought that nuclei could only be digested by pancreatic "nuclases" so that their recognition in the cubes proved pancreatic insufficiency. One commentator wrote in 1913 that "An indeterminate result is very common and the process of finding the muscle fibres in the stools is neither easy nor inviting". A F S Sladden, 'Critical review: the diagnosis of pancreatic disease', *Q. J. Med.*, o.s., 1913–14, **7**: 455–83.

[71] J H Pratt, 'The functional diagnosis of pancreatic disease', *Am. J. med. Sci.*, 1912, **143**: 313–33. This and Sladden's article (op. cit., note 70 above) review the history of pancreatic function tests. Both state that there is probably no other organ whose physiological importance is combined with such a low level of clinical knowledge.

[72] F Müller, 'Untersuchungen über Icterus', *Zeitsch, für Klin. Med.*, 1887, **12**: 45. Friedrich von Müller (1858–1941) was one of the most eminent German clinicians before World War I.

[73] Gelatine capsules containing salol were hardened in formalin to make them resistant to gastric digestion but susceptible to pancreatic juice. Salol was excreted in the urine as salicyluric acid and recognized by the violet colour when ferric chloride was added. By 1912, according to Pratt (op. cit., note 71 above), "the test has few friends".

[74] R Mansell-Jones, Letter, *Br. med. J.*, 1893, **i**: 50.

done by various practitioners during the next five months, with a number of inconclusive but generally negative case reports. Hector Mackenzie[75] gave liquor pancreaticus[76] to two patients who felt better and less tired. Neville Wood, Clinical Assistant at the Victoria Hospital for Children, treated patients aged 13 and 24 with commercially available pancreatic extracts (zymin and pancreatin pills),[77] and Hale White published two more cases of young people who were given raw fresh sheep's pancreas and, when this was ineffective, injections of liquor pancreaticus subcutaneously night and morning.[78] Further essentially negative single case reports were published by Sibley of a 39-year-old patient,[79] Marshall of a 56-year-old patient,[80] and Wills of a 45-year-old patient.[81] Hale White and Wills observed their patients in hospital for six to twelve weeks and published extensive tables of the urine volume, specific gravity and sugar content. Hale White doubted if fresh pancreas by mouth or liquor pancreaticus subcutaneously was of any benefit; neither influenced the quantity of urine or its specific gravity but, he noted, "perhaps they decreased the amount of sugar passed and very slightly increased the weight and feeling of strength". Similar experiments were carried out on the Continent; in 1892 A Capparelli injected a saline extract of fresh pancreas into the abdominal cavity of a pancreatectomized dog but, although there was less glycosuria, the experiment was criticized on the ground that the pancreatectomy had been incomplete. In 1893 Jules Comby injected guinea pigs' pancreatic juice hypodermically for five days into a 25-year-old man with severe diabetes without any benefit, although the injections were well tolerated.[82] In Turin F Battistini injected extracts of pancreatic juice into the abdomen of two patients. Both felt better but the experiments were discontinued because of pyrexia and abscess formation.[83]

[75] H W G Mackenzie, 'The treatment of diabetes mellitus by means of pancreatic juice', *Br. med. J.*, 1893, **i**: 63–4. Sir Hector Mackenzie (1856–1920) was Assistant Physician at St Thomas's Hospital and became a full physician in 1900.

[76] Liquor pancreaticus was made by treating one part of pig's pancreas with a mixture of one part rectified spirit and three of water (W Hale White, *Materia medica, pharmacy, pharmacology and therapeutics*, London, J & A Churchill, 1897, p. 605). Its main use was for peptonizing milk. Benger's liquor pancreaticus was a solution of pancreatic enzymes in alcohol recommended for various forms of dyspepsia or to predigest foods before they were eaten (W Whitla, *Elements of pharmacy, materia medica and therapeutics*, London, Baillière, Tindall and Cox, 1910, pp. 429–30. The use of pancreatic enzymes by mouth was regarded as "problematical" by most pharmacologists, since they were known to be destroyed by acid.

[77] Neville Wood, 'The treatment of diabetes by pancreatic extracts', *Br. med. J.*, 1893, **i**: 64.

[78] W Hale White, 'On the treatment of diabetes mellitus by feeding on raw pancreas and by the subcutaneous injection of liquor pancreaticus', *Br. med. J.*, 1893, **i**: 452–3. At this time Hale White (1857–1949) was a Lecturer in Materia Medica and Assistant Physician at Guy's Hospital. He was later knighted. The clinical clerk for one of these cases was F G (later Sir Frederick Gowland) Hopkins.

[79] W K Sibley, 'On the treatment of diabetes mellitus by feeding on raw pancreas', *Br. med. J.*, 1893, **i**: 579–80.

[80] A L Marshall, 'Treatment of diabetes by pancreatic extract', *Br. med. J.*, 1893, **i**: 743. Marshall used a proprietary preparation, Savory & Moore's pancreatin "One cupola (grv) three times a day, one hour after meals".

[81] W A Wills, 'A case of diabetes treated by the administration of raw pancreas', *Br. med. J.*, 1893, **i**: 1265–6. William Alfred Wills (1862–1924) became Assistant Physician with charge of outpatients at the Westminster Hospital in 1893.

[82] K H Leichest, 'Insulin precursors—a historical sketch: the first attempts at treating diabetes with pancreatic extracts', in *Diabetes: its medical and cultural history*, ed. D von Engelhardt, Berlin and Heidelberg, Springer Verlag, 1989, pp. 397–404.

[83] 'Epitome of current medical literature', *Br. med. J.*, 1893, **ii**: 71 (abstract no. 359). F Battistini, 'Due casi di diabete mellito curati con iniezioni di estratto pancreatico', *Gior. d. r. Accad. di med. di Torino*, 1893, 3.s, **41**: 290–300.

In 1894 McNamara, Assistant Surgeon at the Harrow Road Dispensary, suggested that fresh uncooked pancreatic extract should be given per rectum and if necessary through the rectal veins. The rationale was that the "mysterious sugar restraining element acted directly on the liver and would be destroyed in the general circulation". Since these ideas had occurred to him, McNamara had not had a case of diabetes, but he offered them to "members of the profession who might be more fortunately circumstanced".[84] In 1894 Watson Williams treated a 15-year-old boy in the Bristol Royal Infirmary sequentially with minced pancreas and liquid extract by mouth, his own extract hypodermically, Brown-Séquard's pancreatic extract and finally orchitic fluid from a young bull. This took a month and, when it had clearly failed, Williams persuaded a surgeon to implant three pieces of the sheep's pancreas into the boy's subcutaneous tissue. Unfortunately the operation precipitated diabetic coma and the boy died three days later.[85]

A much delayed account was that of Cowles who in 1911 reported a case he had treated in 1897. A 26-year-old man, developed diabetes in 1894 and by 1897 was expected to die at any time; as a last resort he ate up to six raw calves' pancreata every day and, although his urine never became sugar free, he felt well enough to go back to work. Two months after starting the treatment he ate some stale pancreas, vomited and refused to eat any more. After another three months he developed an enormous carbuncle and died. Cowles tried the treatment in other cases without benefit, and attributed success in this one to the enormous amount of raw pancreas this patient was able to eat. He did not publish the case earlier because "the results seemed so simple and natural".[86]

It would be wrong to give the impression that in the decade after Minkowski's discovery, the pancreatic theory of the origin of diabetes was pre-eminent. In fact, it was generally agreed that diabetes was heterogeneous and John Rose Bradford, Professor of Materia Medica at University College Hospital, pointed out that:

> the disease diabetes is itself of mixed origin. Further, the lesions causing the malady may not only be functional or organic in nature, but even if organic they may be diverse, in one case a lesion of the liver and in another a lesion of the pancreas causing the disease.[87]

Bradford regarded the hepatic origin of diabetes as fully established by laboratory experiments, although he doubted the therapeutic value of liver extracts.[88] In his book on organotherapy, Batty Shaw noted that most work on hepatic extracts had been done by the French, who "not content with the use of various oils derived from the cod, seal etc., have sought to show that other substances can be extracted from the liver capable of producing favourable effects in various pathological conditions".[89] Gilbert and Lereboulet subdivided

[84] J McNamara, 'Suggestions for the treatment of pancreatic diabetes', *Br. med. J.*, 1894, **ii**: 126. By 1910 McNamara was Medical Officer of the UK Commercial Travel Benefit Society. Why he was interested in diabetes is unclear.

[85] P Watson Williams, 'Notes on diabetes treated with extract and by grafts of sheep's pancreas', *Br. med. J.*, 1894, **ii**: 1303–4. Cammidge mentions a case reported by J W Allan in which a cat's pancreas was used, but it "died and sloughed out". P J Cammidge, *Glycosuria and allied conditions*, London, Edward Arnold, 1913, p. 332.

[86] W N Cowles, 'A case of diabetes treated by feeding of calves' pancreas', *Boston med. surg. J.*, 1911, **164**: 921–2.

[87] J R Bradford, 'Recent experimental contributions to the pathology of diabetes', *The Practitioner*, 1900, n.s. **12**: 131. See note 44 above.

[88] 'The present day treatment of diabetes', *The Practitioner*, 1900, n.s. **12**: 152–60.

[89] Batty Shaw, op. cit., note 55 above, p. 67. Harold Batty Shaw (1866–1936) was at the time Assistant Physician at University College Hospital.

diabetes into mild glycosuria due to chronic insufficiency of the liver (anhepaty) and more severe cases due to excessive action of the liver (hyperhepaty).[90] Gilbert and Carnot gave liver extract subcutaneously and per rectum; an extract of 150 gm freshly minced pig liver per rectum was claimed to be of diagnostic value; in anhepaty, the liver was stimulated and glycosuria disappeared while, in hyperhepaty, there was an intensification of glycosuria. According to Batty Shaw, liver organotherapy for diabetes was never taken seriously in England.[91]

How often organic liquids were used for the treatment of diabetes or other illnesses needs further research but, in the last decade of the nineteenth century, manufacturing chemists were quick to jump on the bandwagon. By 1894 Ferris & Company of Bristol announced that they were the sole agents for the organic fluids prepared by Messrs Chaix & Remy, Paris, according to the processes of Dr Brown-Séquard and others. As well as pancreatic fluid "for the treatment of all cases of glycosuria" they could supply orchitic, renal, suprarenal, spleen and medulla of bone, grey matter of brain and muscular fluid. These were sold in sealed tubes each sufficient for one injection, and cost 17s.6d. per dozen (Figure 1).[92] By 1896 Burroughs Wellcome were offering organic principles of animal original in "tabloids". Noting that there was an enormous demand among the profession, they warned that the keeping powers of liquid extracts were uncertain and they were "generally inoperative and often harmful". Instead, Wellcome offered tabloids of thyroid gland, thymus, orchitic substance, pituitary body, ceribrinin, ovarian substance, pineal gland, bone medulla, suprarenal capsules and splenic substance. Tabloids of orchitic substance were indicated for "nymphomania, epilepsy, hysteria, neurasthenia and perverted sexual habits", while suprarenal tabloids were "claimed to be very energetic in their action on the renal and vascular systems".[93] Much was made in these advertisements of the potency of suprarenal substance. It was clearly implied that other organic fluids were equally potent.[94]

In the five years after the dramatic announcements of Minkowski and Brown-Séquard, attempts to cure diabetes by pancreas feeding and injecting were carried out very much on an *ad hoc* basis by clinicians and, as we have seen, manufacturing chemists marketed extracts of virtually all bodily organs. The interest of English physiologists in what came to be known as "internal secretions" can probably be traced to the fortituous discovery of the vasopressor effects of adrenal extract in 1894. The Harrogate physician George Oliver persuaded Edward Schäfer, Professor of Physiology at University College London, to inject his home-made suprarenal extract into a dog whose blood pressure was being

[90] A Gilbert, P Lereboulet 'Les opotherapies dans le diabète sucré', *Gaz. Hebdom. de Méd.*, 1901, **81**: 961, cited by Batty Shaw, op. cit., note 55 above, p. 57. In the same year these authors described the form of hyperbilirubinaemia which is now known as Gilbert's disease. In the late 1920s there was a resurgence of interest in the effect of liver extracts in diabetes. See Harry Blotner and W P Murphy, 'The effect of liver on the blood sugar level', *J. Am. med. Ass.*, 1929, **92**: 1332; Harry Blotner, 'The effect of liver on the blood sugar in diabetic patients', *J. Am. Dietetic Ass.*, 1929, **5**: 102; and Harry Blotner and William P Murphy, 'Effect of certain liver extracts on the blood sugar of diabetic patients', *J. Am. med. Ass.*, 1930, **94**: 1811–16.

[91] A Gilbert, P Carnot, 'Essais d'opothérapie hépatique', *Sémaine Médicale*, 1896, **16**: 580; *idem*, 'Actions des extraits hépatique sur la glycosurie expérimentale', *Sémaine Médicale*, 1896, **16**: 513; *idem*, 'De l'opothérapie hépatiques dans le diabète sucré', *Sémaine Médicale*, 1897, **17**: 189. Batty Shaw, op. cit., note 55 above, p. 55.

[92] *Medical Annual*, Bristol, John Wright and Sons, 1894, p. 799.

[93] *Medical Annual*, Bristol, John Wright and Sons, 1896, advertisements, p. xxix.

[94] Ibid., 1896, p. 675.

Figure 1: Advertisement for organic fluids from the *Medical Annual* 1894. For diabetes a combination of pancreatic and orchitic fluid is recommended.

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measured. It is said that Schäfer "stood amazed to see the mercury mounting in the arterial manometer till the recording float was lifted almost out of the distal limb".[95] What impressed Schäfer and his contemporaries was the tiny dose necessary to produce physiological effects; as little as $5^1/_2$ mg of dried suprarenal produced a maximal effect on the heart and arteries of a 10 kg dog.[96] In an address to the annual meeting of the British Medical Association in London in August 1895, Schäfer endorsed Brown-Séquard's view that all tissues and organs produced an internal secretion and concluded:

> These internal secretions have to be definitely reckoned with by the physician, while at the same time the therapeutist will be able to avail himself of the active principles they contain, and in certain cases to use extracts of internally secreting glands in place of the hitherto more commonly employed vegetable medicaments. That the subject has a vast future there can be no doubt . . .

One piece of evidence he relied on greatly was Minkowski's pancreatectomy experiment, Schäfer continued:

> The only fact that appears certain in connection with the manner in which the pancreas prevents excessive production of sugar within the body is that this effect must be produced by the formation of some material, secreted internally by the gland and probably by the internal vascular islets, and that this internally secreted material profoundly modifies the carbohydrate metabolism of the tissues.[97]

Schäfer's view that the internal vascular islands or islands of Langerhans produced the hypothetical internal secretion was, in an age still dominated by traditional morbid anatomy, not widely accepted.[98] In fact, the absence of lesions in the pancreas in ordinary post-mortems led many to deny the connection of the pancreas with diabetes. As Bunge remarked, "Up to the present, pathological anatomy has led to no conclusion. Post-mortem examination of the bodies of diabetics proves that there is not a single organ that does not occasionally show anatomical changes; on the other hand, there is not a single organ that does not frequently appear normal".[99] Nevertheless, at the turn of the century, Opie in the USA and Sobolev in Russia did describe pathological changes confined to the islets. In 1899, Leonid V Sobolev (1876–1919) became fascinated by the islets, which he thought could only be structures for internal secretion because they lacked ducts and were intimately related to capillaries. He suggested that they were functionally and anatomically independent structures which controlled carbohydrate metabolism. In thirteen of fifteen cases of diabetes he found quantative changes; in four, no islands were present, while in nine there were fewer than normal. He drew the conclusion that:

> By ligating the pancreatic duct we now have a means of isolating the islands anatomically and of studying their chemical properties freed from the digestive ferments. This anatomic isolation will

[95] Sir Henry Dale, 'Accident and opportunism in medical research', *Br. med. J.*, 1948, **ii**: 451–5. See also Borell, 'Organotherapy', op. cit., note 4 above.

[96] E A Schäfer (ed.), *Textbook of physiology*, 2 vols, Edinburgh and London, Young J Pentland, 1898, vol. 1, p. 957.

[97] E A Schäfer, 'Address in physiology on internal secretions', delivered at the annual meeting of the British Medical Association, London, 2 August 1895, *Lancet*, 1895, **ii**: 321–4.

[98] The islets were described by Paul Langerhans, then aged 22, in his doctoral thesis in 1869. Their function was not recognized until 1893 when Laguesse suggested that they might produce the hypothetical internal secretion of the pancreas.

[99] G Bunge, *Text-book of physiological and pathological chemistry*, trans. Florence A Starling, London, Kegan, Paul, Trench, Trübner, 1902, p. 386.

permit the testing, in a rational way, of an organotherapy for diabetes . . . We are justified in the hope that in the near future the question will be decided whether or not this method of approach will succeed in relieving the ills of the diabetic patient.

Convinced that it would not be possible to obtain enough tissue by duct ligation, Sobolev even suggested the use of newborn calves in which the islands are well developed in comparison to the acinar tissue.[100] Eugene Opie's interest in the islets was stimulated during his student days at Johns Hopkins, when his teacher William Welch told him to "Find out all you can about these islands of Langerhans".[101] In papers published in 1901 Opie proposed that the islands were secretory organs rather than modified or underdeveloped acinar cells.[102]

At the turn of the century many clinicians believed in a form of human pancreatic diabetes analogous to that produced by pancreatectomy in dogs. In the fifth edition of his textbook Osler included a three-quarter-page section, 'The pancreas in diabetes'; in it he concluded that the pancreas, like the liver, had a double secretion and that the source of the antidiabetic principle was the islands of Langerhans. He backed this up with autopsy findings of his Johns Hopkins colleague Opie in one of his patients, a 24-year-old woman in whom the glandular tissue was normal but the islets were represented by sharply circumscribed hyaline structures.[103] Tentatively, he divided cases of diabetes into lipogenic (the glycosuria of stout people), neurotic and pancreatic, but admitted that distinguishing them was difficult. Neither Osler nor the authors of other major textbooks[104] recommended pancreatic extracts and pharmacologists were scornful of attempts at organotherapy. In the first edition of his textbook in 1899, Arthur Cushny warned that advance in organotherapeutics was not to be expected from the indiscriminate use of gland extracts in every sort of disease. Such progress as had been made, he asserted, was due to "careful observation and experiment and not to haphazard use of the hypodermic syringe".[105]

Further Attempts to isolate the anti-diabetic Principle of the Pancreas: 1900–1914

At a meeting of the Society of Biology in Paris in December 1922 Eugène Gley asked that an envelope deposited by him in 1905 be opened and read. In this, he described how in 1900–1901 he had prepared extracts from pancreata degenerated by duct occlusion and found that when injected they decreased the glycosuria of completely depancreatized dogs and alleviated diabetic symptoms. Gley's report indicated his intention to isolate the active

[100] My account of Sobolev is taken from an appreciation by Cornelia van Beek, 'Leonid V Sobolev, 1876–1919', *Diabetes*, 1958, **7**: 245–8. His thesis was published in 1901 and a condensed version of 33 pages appeared in German a year later. Ill health forced him to resign from his post in the Department of Pathology in 1912 and in 1919 he died in a mental hospital.

[101] Peyton Rous, 'An inquiry into certain aspects of Eugene L Opie', *Arch. Path.*, 1942, **34**: 1–6. For a synopsis of Opie's life, see Joseph Hughes, 'Eugene L Opie', *Diabetes*, 1958, **7**: 496–9.

[102] E L Opie, 'On the relation of chronic interstitial pancreatitis to the islands of Langerhans and to diabetes mellitus', *J. exp. Med.*, 1901, **5**: 397, *idem*, 'The relation of diabetes mellitus to lesions of the pancreas; hyaline degeneration of the islands of Langerhans', *J. exp. Med.*, 1901, **5**: 527.

[103] Osler, op. cit., note 25 above, 5th ed., 1903, p. 326.

[104] For example F Taylor, *The practice of medicine*, London, J & A Churchill, 1898.

[105] Cushny, op. cit., note 61 above, pp. 690–1. This paragraph appears unchanged in all subsequent editions of the book up to the 6th in 1918.

anti-diabetic principle, study its action and see if the extracts could be used on man, either subcutaneously or by mouth. For unknown reasons he did not pursue his ideas.[106]

In 1903 John Rennie reported in the *Quarterly Journal of Microscopical Science* that the islets of teleostean fishes were independent of the pancreas proper and many species had a relatively large principal islet. Working in Aberdeen with Thomas Fraser, Rennie was able to get large supplies of islet tissue from the fishmarket to give to diabetic patients.[107] The first, an 18-year-old boy, was treated in November 1902 with an average of 0.57 grams of islet tissue daily by mouth. No real benefit resulted and he died in March 1903. Four more patients were treated, usually with islets macerated in a mortar, digested for some time at 40°C and then taken by mouth. However, between 9 and 14 October 1904 the third patient, a 44-year-old man, was given a filtered extract by hypodermic injection. The dose was usually one-fifth of a gram but this route was abandoned because of the reaction it caused. The only indication of this was that on the fourth day "his circulation was disturbed. His evening pulse 104". His urine volume and excretion of sugar were unaffected, and Rennie and Fraser concluded either that they had not given enough islet substance (a maximum of 4 grams a day for one week) or that the metabolism of cold blooded fish might differ from that of mammals. Twenty years later, a year after the discovery of insulin, the *Lancet* suggested that Rennie might have been successful had there been some simple method of estimating the blood sugar.[108] The standard Bertrand method, used up to about 1910, required 50–100 ccs of blood which was defibrinated by stirring in an evaporating dish as it was drawn from the vein. The blood was then heated and a deproteinized filtrate prepared. Then followed preparation of a cuprous oxide precipitate which was washed and weighed.[109] A method described by the Professor of Physiology in Dundee in 1896 took at least one hour for each determination and demanded meticulous laboratory technique.[110] It would have been totally impractical for use in patients even if hospitals had had a chemical laboratory. As endpoints, clinicians were therefore obliged to use subjective feelings of the patient, weight and the volume of urine and its sugar content.

In 1906 Georg Zuelzer, a young physician in Berlin, took pancreata, tied off the ducts, removed the whole organ, squeezed out the juice, precipitated the proteins with alcohol, and administered the alcohol-free extract subcutaneously and intravenously.[111] Over the next three years he treated eight patients and, in his published report, concluded that his extract eliminated the excretion of sugar and ketone bodies without any change in the diet.[112] Zuelzer's extract, patented as Acomatol, was tested in Minkowski's clinic by Forschbach

[106] Gley's communication is described in 'Action des extraits de Pancréas sclérosé sur des chiens diabétiques', *Société de Biologie. Comptes Rendus*, 87 (Dec. 1922). Accounts in English can be found in J P Hoet, 'Gustave Edouard Laguesse: his demonstration of the significance of the islands of Langerhans', *Diabetes*, 1953, **2**: 323, and Bliss op. cit., note 1 above, pp. 170–1. Depositing sealed envelopes at learned societies was common in France as a way of establishing priority for a discovery.

[107] J Rennie and T Fraser, 'The islets of Langerhans in relation to diabetes', *Biochem. J.*, 1907, **2**: 7–19.

[108] 'Biochemistry and medicine', *Lancet*, 1923, **ii**: 791–2, p. 791.

[109] W C Stadie, 'Obituary of Henry Rawle Geyelin', *Diabetes*, 1957, **6**: 291–2.

[110] E Waymouth Reid, 'A method for the estimation of sugar in blood', *J. Physiol. Lond.*, 1896, **20**: 316–21.

[111] Bliss, op. cit., note 1 above, pp. 29–33; K H Mellinghoff, *Georg Ludwig Zuelzers, Beitrag zur Insulinforschung*, Dusseldorf, Michael Triltsch, 1971.

[112] G Zuelzer, 'Über versuche einer specifischen fermentherapie des Diabetes', *Z. Exp. Path. Ther.*, 1908, **5**: 307–18. When Zuelzer's first paper appeared the editor stated in a footnote that he had withheld publication for three years at the request of the author. Apparently Zuelzer asked for this delay in the hope of being able to report a non-toxic extract (Pratt, op. cit., note 2 above, p. 286).

on three dogs and three humans but, although confirming that it suppressed glycosuria, he felt that the side effects, especially fever, were so severe that it would be impossible to use therapeutically.[113] Zuelzer continued his experiments until 1914 when he was called into the army. In retrospect, one might conclude that his failure to produce a therapeutically active extract was mainly due to lack of a powerful backer whereas the failure of Ernest Scott was due to a powerful professor who thwarted him.

Scott was a reticent man and what we know about his experiments in Chicago in 1910–11 comes from a paper by his pupil Dickinson Richards, the 1956 Nobel Laureate in Medicine or Physiology[114] and a privately printed book by Scott's second wife.[115] Scott went to the University of Chicago in 1908 to work with the newly appointed Professor of Physiology, Anton J Carlson (1875–1956), who appears to have been uninterested rather than actively antagonistic to his work.[116] Scott believed that the digestive enzymes of the pancreas destroyed its internal secretion[117] and first ligated the ducts to atrophy the acinar tissue. When this failed he extracted fresh pancreas with sand and warm alcohol. His extract produced a significant drop in glycosuria and in the dextrose:nitrogen ratio in three out of four dogs. The conclusions he drew *in his thesis* were:

1st, there is an internal secretion from the pancreas controlling the sugar metabolism.
2nd, by proper methods this secretion may be extracted and still retain its activity.
3rd, this secretion is easily destroyed by oxidation or by the action of the digestive enzymes of the pancreas.
4th, the secretion is insoluble or nearly so, in strong alcohol but is readily soluble in acidulated water.
5th, the failure of previous workers to procure satisfactory results was due to their not preventing oxidation or the action of the digestive enzymes.[118]

As Richards pointed out, these conclusions were clear, unequivocal and, in the light of Banting and Best's work, correct.[119] Unfortunately, by the time Scott's paper was published, a sentence had been inserted warning that *"It does not follow that these effects are due to the internal secretion of the pancreas in the extract"* (my italics).[120] What Scott's wife described as "that damning sentence" was almost certainly inserted by Carlson, who in 1917 wrote:

The endeavour to determine how absence of the pancreas causes diabetes is practically a record of repeated failures. The leading idea in all this work has been the internal secretion theory . . . [but] . . .

[113] J Forschbach, 'Versuche zur Behandlung des Diabetes Mellitus mit dem Zuelzerschen Pancreashormone', *Deutsch. Med. Wschr.*, 1909, **35**: 2053.

[114] D W Richards, 'The effect of pancreas extract on depancreatised dogs: Ernest L Scott's thesis of 1911', *Perspect. Biol. Med.*, 1966, **10**: 84–5.

[115] A H Scott, *Great Scott: Ernest Lyman Scott's work with insulin in 1911*, Bogota, New Jersey, Scott Publishing Co., 1972.

[116] Scott, according to his wife (A H Scott, ibid., p. 6), said that Carlson had wanted him to work on a different problem but "I had come with my own problem, to find out something about diabetes which killed young men in their prime". Mrs Scott compares Carlson ("a recent Swedish immigrant") unfavourably with her husband ("a fourth-generation Ohio farm boy").

[117] The belief that the pancreas contained a "powerful ferment" which would destroy the hypothetical internal secretion was a widespread misapprehension. As early as 1875 Heidenhain had shown that extracts of fresh pancreas have no proteolytic activity and in 1902 Delezenne found that trypsinogen is only activated when it comes in contact with the succus entericus (Batty Shaw, op. cit., note 55 above, pp. 173).

[118] Scott's thesis (No. T-10553) was submitted to the University of Chicago in 1911 and obtained by Richards in 1965.

[119] Richards, op. cit., note 114 above, p. 85.

[120] E L Scott, 'On the influence of intravenous injections of an extract of the pancreas on experimental pancreatic diabetes', *Am. J. Physiol.*, 1912, **24**: 306.

the possibility that the work of the pancreas in maintaining normal sugar metabolism consists of detoxification processes must always be kept in view. The fact that even temporary glycosuria is not induced in normal animals by diabetic blood does not render the detoxification hypothesis untenable.[121]

After moving to Kansas, Scott continued his interest in the internal secretion of the pancreas and in 1912 visited J R Macleod (then Professor of Physiology at the Western Reserve University, Cleveland) who was "not interested, he just shrugged it off".[122] Although he later shared the Nobel Prize for the discovery of insulin, Macleod's reaction is not surprising because as late as 1921 he was, like Carlson, ambivalent about the role of the pancreas, writing:

> the removal of some hormone necessary for proper sugar metabolism is, however, by no means the only way in which the results can be explained, for we can assume that the pancreas owes its influence over sugar metabolism to some change occurring in the composition of the blood as this circulates through the gland—a change which is dependent on the integrity of the gland and not on any one enzyme or hormone which it produces.

To Macleod, either view was tenable and the only experiment which would be decisive was to see if replacing the hypothetical hormone restored normality. He concluded that:

> there is no evidence that the blood of a normal animal, even when it is from the pancreatic vein, contains an internal secretion that can restore to a diabetic animal any of its lost power to utilise carbohydrate.[123]

Undoubtedly, this message came across loud and clear to Scott but in retrospect he attributed his failure to being forced to use as his endpoint Lusk's D:N ratio[124] rather than blood sugar which, since, it needed 20 ccs for each measurement, for a thirty-six hour experiment virtually involved exsanguinating even large cats.[125] In a letter to the *Journal of the American Medical Association* in 1923 Scott disclaimed any part in the isolation of insulin but suggested that the discovery of the curative power of "insulin" had been open from January 1912 to anyone who cared to repeat and extend his work.[126]

How the hypothetical hormone worked was of course a matter of conjecture but one suggestion, associated particularly with Otto Cohnheim, was that it might activate a ferment

[121] A L Carlson, 'The endocrine pancreas and its contribution to the sex life of women', *Surg. Gynaec. Obstet.*, 1917, **25**: 283–93. This curiously titled paper is, apart from the final 1½ pages, a review of attempts to resolve the enigma of pancreatic diabetes. Commenting on his own pancreatectomy experiments in pregnant dogs, Carlson said, "This absence of diabetes may be due either to the pancreas hormones of the fetus passing into the mother's blood or to some detoxicating action on the part of the fetal pancreas".

[122] Scott, op. cit., note 115 above, p. 28.

[123] J J R Macleod, *Physiology and biochemistry in modern medicine*, 3rd ed., London, Henry Kimpton, 1921, p. 714.

[124] The D:N ratio or relation between urinary excretion of dextrose and nitrogen was introduced in 1904 by Graham Lusk (1886–1932), who concluded that in the severest diabetic the ratio was 3.65:1. By this was meant that on an exclusively fat:protein diet 3.65 grams of dextrose appeared in the urine for 1 gram of nitrogen. In other words, 60 per cent of the protein burned by the body appears in the urine as sugar; see E P Joslin, *The treatment of diabetes mellitus*, Philadelphia and New York, Lea and Febiger, 1917, pp. 131–2. Joslin did not find the D:N ratio helpful and pointed out that after fasting the D:N ratio completely disappeared when the urine became sugar free. "It is thus", said Joslin, "hard to understand how a patient one day fails to burn the protein of an ox and on the next day burns his own body protein with ease".

[125] E L Scott, 'The relation of pancreatic extract to the sugar of the blood', *Proc. Soc. exp. Med. Biol.*, 1913, **10**: 101–3.

[126] E L Scott, 'Priority in discovery of a substance derived from the pancreas, active in carbohydrate metabolism', *J. Am. med. Ass.*, 1923, **81**: 1303–4.

in muscle. Cohnheim reported that the combination of pancreas and muscle extract had a marked glycolytic action and, as this occurred in a cell free fluid, it must, he thought, indicate a glycolytic ferment in the muscle which was activated by the internal secretion of the pancreas.[127] In 1911 Henry Sewall, Professor of Medicine in the University of Denver, reported his own experiments with muscle and pancreatic extracts by mouth.[128] Four patients, all beyond middle age, were treated with what Sewall admitted was "essentially beef soup" and three appeared to derive some benefit. Then in December 1909 he treated a 7-year-old girl first with a simple beef infusion (juice by mouth) and then with a mixed beef-pancreas preparation made by soaking "about six ounces of ground fresh beef pancreas in one quart of water acidulated with 1 dram of dilute hydrochloric acid". He established to his own satisfaction that a sequence of beef followed by pancreatic juice could abolish glycosuria for up to three weeks and greatly increase carbohydrate tolerance. Unfortunately, fresh pancreas was difficult to obtain and most unpalatable, so Sewall tried a proprietary pancreatic preparation, "Holadin", and a glycerine extract of fresh pancreas. The results were disappointing, as were further attempts to treat the girl with beef and pancreas juice. Sewall wondered whether frequent administration of beef juice had led to formation of an antienzyme but found it hard to reconcile such an explanation with the physiology of carnivorous animals.

Interestingly, it was only when Sewall's paper was in press that his attention was drawn to "the brilliant lectures delivered by T Lauder Brunton nearly forty years ago".[129] Sewall referred only to the work of Mervyn Crofton,[130] Lecturer in Special Pathology at University College, Dublin, who, believing that pancreatic extracts were destroyed by acid in the stomach, gave a 13-year-old diabetic girl insoluble capsules containing a proprietary pancreatic product, Fairchild's Holadin.[131] This was followed by a "remarkable reduction in the quantity of urine" for the two months the capsules were given. Then, thinking the pancreas had recovered sufficiently to stand an additional stimulus, Crofton gave a tablet of secretin three times a day to "help the damaged pancreas do better work". Crofton's interest was vaccine therapy and, according to him, Almroth Wright had suggested that the pancreatic lesion might be due to "an acute or subacute microbial inflammation which may subside and leave behind a greater or less degree of fibrosis."[132] On this basis Crofton

[127] O Cohnheim, 'Ueber Kohlehydratverbrennung. 2. Mitteiling. Die aktivierende Substanz des Pankreas', *Zrschr. f. Physiol. Chem.*, 1904, **42**: 401–9.

[128] H Sewall, 'Is there a specific treatment for diabetes mellitus?' *Am. J. med. Sci.*, 1911, **142**: 313–28.

[129] Brunton, op. cit., note 26 above, p. 223.

[130] William Mervyn Crofton studied medicine at the Royal University in Dublin where a lectureship in special pathology was created for him. He later became an immensely successful private practitioner in London. His son describes him as a man of great ability and originality who had too much self-confidence. "He only had to think of an interesting new theory and it became correct".

[131] W M Crofton, 'Pancreatic secretion in the treatment of diabetes', *Lancet*, 1909, **i**: 607–9, p. 608. Holadin is described in the 1913 *Medical Annual* (p. 223) as an extract of pancreas from which all the proteins and external ferments have been removed.

[132] For example, W M Crofton, 'Some cases of vaccine therapy', *Br. med. J.*, 1908, **ii**: 877, in which he suggested that the ordinary practitioner could manage well without measuring the opsonic index. Vaccine therapy had a tremendous vogue at this time, mainly as a result of the work and entrepreneurial activities of Almroth Wright at St Mary's Hospital Medical School. The previous year Wright had given a very long address to the Royal Society of Medicine on 'Vaccine therapy: its administration, value, and limitations' (*Lancet*, 1910, **ii**: 863–74). See also Michael Worboys, 'Vaccine therapy and laboratory medicine in Edwardian Britain' in *Medical innovations in historical perspective*, ed. J V Pickstone, Basingstoke, Macmillan, 1992, ch. 5:

suggested that the ideal treatment for acute cases would be a specific serum or for more chronic cases a vaccine. When he put forward his ideas at a meeting of the Royal Academy of Medicine in Ireland in 1911 he received a hostile and sceptical reception.[133]

In 1912 Murlin and Kramer in New York had the idea of combining duodenal mucosa and pancreas and extracting the two together in the hope that secretin might be an adjuvant. When their extract was given to a diabetic patient subcutaneously it diminished the excretion of sugar. In March 1913 they made a new extract which completely eliminated glycosuria in a depancreatized dog but their professor convinced them that this was because the kidneys had been damaged by too much alkali.[134] In 1914 Raulston and Woodyatt tried to treat diabetes with blood transfusion, without success.[135]

On the eve of the First World War the average doctor could have read a huge variety of conflicting accounts about the cause of diabetes and the relevance of the pancreatectomy experiments of the previous twenty years. The London physicians Garrod[136] and Hale White[137] inclined to the polyglandular doctrine of the Vienna School in which diabetes was thought to be due to a loss of balance between the thyroid, pituitary and chromaffin system on the one hand and the pancreas on the other. Garrod concluded that:

> Many organs take part in the regulation of carbohydrate metabolism . . . The displacement of one prop may endanger the equilibrium of the whole fabric . . . We are justified in regarding the normal metabolic level as maintained by the balance of a number of mutually controlling forces . . . While it is true that in some cases of diabetes the nervous system is evidently at fault, and that in others the thyroid, the pituitary or the pancreas is the seat of the disease, in the great majority of cases which we encounter in practice we can find no indication of the underlying lesion on which the metabolic derangement depends.

Nevertheless, others were sure that there must be a human equivalent of the type of diabetes produced by pancreatectomy in animals and that this was caused by absence of an internal secretion. In his 1913 book, Artur Biedl wrote that all the known facts about pancreatic diabetes pointed unequivocally to suppression of an internal secretion which normally played a decisive role in carbohydrate metabolism, although he noted that "the brilliant results expected of organotherapy have been conspicuously absent in pancreatic diabetes".[138] The author of another contemporary monograph on internal secretions, Wilhelm Falta was also certain that the insular apparatus produced a hormone which was carried to the liver in venous blood. He described a patient fulfilling all the conditions of a physiological experiment—a man with obstructive jaundice, steatorrhoea and gross hydrops of the gallbladder (due to carcinoma of the pancreas) who had five 100 gram glucose tolerance tests without developing glycosuria. To Falta this proved that the internal and external secretory elements of the pancreas were independent and his explanation of the failure to isolate the internal secretion was that, unlike that of the thyroid, it was not stored.[139]

[133] 'Royal Academy of Medicine in Ireland: section of medicine', *Lancet*, 1911, **i**: 1009–10.

[134] J R Murlin and B Kramer, 'A quest for the anti-diabetic hormone 1913–1916', *J. Hist. Med.*, 1956, **11**: 288–98.

[135] B D Raulston and R T Woodyatt, 'Blood transfusion in diabetes mellitus', *J. Am. med. Ass.*, 1914, **62**: 996–1000.

[136] A E Garrod, 'Lettsomian Lectures on Glycosuria', *Lancet*, 1912, **i**: 483–8. Archibald Garrod (1857–1936) introduced the concept of inborn errors as a result of his studies of alkaptonuria in 1899.

[137] W Hale White, 'An address on glycosura', *Lancet*, 1914, **i**: 367–73.

[138] Biedl, op. cit., note 47 above, p. 423.

[139] W Falta, *The ductless glandular diseases*, trans. M K Myers, Philadelphia, P Blakiston's Sons, 1915, p. 501. Wilhelm Falta (1875–1950) was assistant to Carl von Noorden. See note 142 below.

Even those who believed in an internal secretion were depressed about the possibility of isolating it. According to Frederick Allen[140] the reasons were: (i) the complete disappointment from organotherapy, (ii) repeated failures to find pancreatic lesions in diabetic necropsies, and (iii) the differences that were more and more insisted on between human diabetes and that following pancreatectomy in dogs.[141] The result, according to Allen, was "a period when few persons were willing to affirm that diabetes is regularly and fundamentally a pancreatic disorder". In a 1915 review article von Noorden discussed the evidence (which in his view was overwhelming) that the source of the hormone which promoted carbohydrate metabolism was the islets of Langerhans, and concluded:

> I have advocated the point of view that in every case of real diabetes, there is a functional breakdown of the pancreas. Since then, after von Mering and Minkowski had demonstrated this supposition by the discovery of experimental pancreatic diabetes, nearly all modern investigators have come to the same conclusion, some earlier, some later . . . the intensity of diabetes is inversely proportional to the total quantity of Langerhans islands present in good functioning condition.[142]

The therapeutic conclusion drawn by von Noorden was the same as that reached by Allen in the USA[143] and George Graham in England;[144] food, and particularly carbohydrate, stressed the ailing islands of Langerhans and led to a downward spiral of increasing glandular fatigue. The solution was to give the diabetic as little carbohydrate as possible. The results of starvation treatment appear to have been so relatively satisfactory, at least to some clinicians, as to push into the background the search for a cure. In 1915 Eliot P Joslin[145] wrote eulogistically that the advance in treatment during the past year had been greater than any since Rollo's time[146] and that "at one stroke the patient is delivered from medicines, patent or otherwise, sham kinds of treatment, gluten breads and in 99 cases out of a 100 of alkalis". Most English physicians were equally enthusiastic, although after the introduction of insulin they were readier to admit how awful the starvation treatment had really been. For example in 1927 Hugh Maclean, Professor of Medicine at St Thomas's Hospital, wrote:

[140] F M Allen, 'Investigative and scientific phases of the diabetic question; their probable relations to practical problems of clinical medicine', *J. Am. med. Ass.*, 1916, **66**: 1525–32. Frederick Madison Allen (1876–1964) worked at the Rockefeller Institute and in 1913 published *Studies concerning glycosuria and diabetes*, Boston, W M Leonard, 1913.

[141] As late as 1921 J J R Macleod claimed that diabetes in the pancreatectomized dog was unaccompanied by any of the classical symptoms seen in the clinical condition. Macleod, op. cit., note 122 above, p. 710.

[142] C von Noorden, 'The pancreas', *The Practitioner*, 1915, Jan-June, 221–46. Carl H von Noorden (1858–1944) was famous for his oatmeal diet for the treatment of diabetes. His best known book was *Diabetes and its treatment*, the 1st edition of which came out in 1895 and the 8th in 1927.

[143] F M Allen, E Stillman and R Fitz, *Total dietary regulation in the treatment of diabetes*, New York, The Rockefeller Institute for Medical Research, Monograph No. 11, 1919.

[144] G Graham, 'The Goulstonian lectures on glycaemia and glycosuria', *Lancet*, 1921, **i**: 1059–65.

[145] E P Joslin, 'Present day treatment and prognosis in diabetes', *Am. J. med. Sci.*, 1915, **150**: 485–96. E P Joslin (1869–1962) was believed during his career to have seen over 50,000 diabetic patients. The first edition of his famous textbook, *The treatment of diabetes mellitus*, was published in 1916. See obituary notice *Br. med. J.*, 1962, **i**: 729–30.

[146] In 1797 John Rollo, an Edinburgh physician, advocated an animal diet including such items as "fat and rancid old meats", the end result of which was a reduction in carbohydrate and calorie intake. See Alexander Marble, 'John Rollo', *Diabetes*, 1956, **5**: 325–7.

In many cases the diabetic treatment was so severe that the patients could not be induced to continue with it. Some of them quite frankly stated that they preferred death to the physical agony which they endured.[147]

It was presumably the scepticism of some clinicians about the starvation "cure" which led to continuing attempts to isolate the internal secretion.

In 1915 Israel Kleiner at the Rockefeller Institute, New York, reported that, when intravenous glucose was mixed with an emulsion of pancreas, diabetic animals handled the sugar normally, whereas without, disposal of glucose was extremely slow.[148] In 1919 Kleiner published the results of intravenous injection of his extract in sixteen depancreatized dogs. In most there was a substantial reduction in blood sugar between 60–90 minutes after injection. In a representative experiment (LP72a) a blood sugar of 331 mg/dl fell to 140 at the end of the 78 minute injection period and was still low 90 minutes later. Submaxillary gland extract was ineffective, as were spleen and muscle extracts. Kleiner concluded that the temporary effect of his extract in dogs might be duplicated in man and might be useful in emergencies. He also noted that it was simple to make and did not have any toxic consequences, but he worried that the effect might be species specific.[149] Others do not appear to have shared this concern, presumably because extract of animal thyroid was effective in man.

Work very similar to that of Banting and Best was carried out by the Romanian physiologist and physician Nicolas Paulesco (1869–1931). Paulesco's interest in diabetes began when he worked with Lancereaux in Paris at the turn of the century when he had begun work to isolate and study the internal secretion of the pancreas.[150] This lapsed until 1916, when he found that an aqueous extract injected into a diabetic dog gave immediate, if temporary, relief of symptoms. His work was interrupted by the war but when he resumed in 1920 he showed convincingly that his extract lowered the blood sugar in both diabetic and normal dogs.[151] In his first experiment he injected the extract into the external jugular vein and over one hour the blood sugar fell from 140 to 26 mg% (7.7 to 1.4 mmol/l) and the dog died of hypoglycaemia. When he gave the extract subcutaneously there was too much local irritation to consider using it in human beings.

How widely was Pancreatic Organotherapy used?

Between 1910 and 1921 clinicians and physiologists were unanimous that attempts to cure severe diabetes by feeding or injecting pancreatic extracts had failed. Nevertheless, there is evidence that these treatments were often used as a desperate last resort. Cobb, in a book on organotherapy for general practitioners, recommended pancreas extracts because:

[147] H Maclean, 'The results of insulin therapy in diabetes mellitus', *Br. med. J.*, 1927, **ii**: 1015–19, p. 1015.

[148] I S Kleiner, 'Retention in the circulation of dextrose in normal and depancreatized animals and the effect of an intravenous injection of an emulsion of pancreas upon this retention', *Proc. Natn. Acad. Sci.*, 1915, **1**: 338–41.

[149] I S Kleiner, 'The action of intravenous injections of pancreas emulsions in experimental diabetes', *J. biol. Chem.*, 1919, **40**: 153–70. Kleiner's contract at the Rockefeller Institute was terminated by F M Allen in 1919 on the ground that there was no future in this sort of research.

[150] N C Paulesco, *Exposé des titres et travaux scientifiques du Dr Paulesco*, Paris, 1899.

[151] N C Paulesco, 'Recherches sur le rôle du pancréas dans l'assimilation nutritive', *Int. Arch. Physiol.*, 1921, **17**: 85–109. See also I Murray, 'Paulesco and the isolation of Insulin', *J. Hist. Med. Allied Sci.*, 1971, **26**: 149–57.

It is quite possible that such preparations will turn the scale in favour of the patient, while if left solely to the conservative method of withholding carbohydrate food it might turn in favour of the disease. Such therapy as is offered by extracts of the pancreas is rational and harmless . . .[152]

Organo-therapeutic preparations were widely advertised in medical and pharmaceutical journals. In 1913 the British Organotherapy Company Ltd offered "Modern and scientific organotherapy products (which) are being extensively prescribed in conditions, having as their origin, degeneration, metabolic disorder, imperfect functioning, auto-intoxication, fatigue and exhaustion".[153] As well as diabetes, other conditions in which their compounds were employed with "exceptional success" were exophthalmic goitre, rheumatoid arthritis, osteoarthritis, disseminated sclerosis, locomotor ataxia and heart and blood vessel degeneration. This company was still advertising its products in 1922, when it could supply soluble gelatine capsules containing extract of parathyroid, thyroid, thymus, prostatic, placenta, splenic, pancreatic, gastric mucosa "or any combination thereof".[154] These could also be supplied in ampoules for hypodermic injection. For glycosuria the company advertised Eukinase, "a scientifically prepared product containing the entire condensed duodenal juice in a dry state and in an active and unalterable form". In 1920 G W Carnrick Co. offered Trypsogen, described as "an accepted medication in diabetes mellitus and glycosuric conditions" and said to be a combination of enzymes of the islands of Langerhans with trypsin, amylopsin, and minute doses of gold and arsenic bromides.[155] Seven years earlier this preparation had been recommended in the *Medical Annual*.[156] As late as 1923 Brown-Séquard's orchitic fluid was still on the scene: John Morgan Richards and Sons Ltd were importing from Denmark "Spermin Liquidum, DMK", for which the indications were weakness due to arteriosclerosis, anaemia, diabetes, impotence, tabes dorsalis and neurasthenia (Figure 2).[157]

After 1922 pancreatic extracts for diabetes disappear from the advertisements. There are none in a list of thirty-four gland products available from Parke Davis & Co.[158] and neither is pancreatic extract advertised by Duncan, Flockhart & Co.,[159] who, like Parke Davis, still produced combinations of thyroid, pituitary, ovarian and orchitic tablets ("Tetraglandine"). The justification for pluriglandular preparations was that cells would select the hormones they needed and discard the rest.[160]

[152] I G Cobb, *The organs of internal secretion: their diseases and therapeutic application (a book for general practitioners)*, London, Ballière, Tindall & Cox, 1917 (1st ed.), 1918 (2nd ed.). Ivo Geikie Cobb obtained his MRCS, LRCP from St Thomas's Hospital in 1910 and MD (Brussels) in 1912. As far as I can tell he never held hospital appointment in England but his continuing interest in the wilder shores of endocrinology is shown by the publication in 1947 of the 3rd edition of another book, *The glands of destiny: a study of the personality*, an attempt to prove that personality depends on the mix of hormones. This was extended to historical characters, so that "in his prime, Henry VII was an anterior-pituitary personality but the last few years of his life were marred by the gradual eclipse of all his endocrine glands" (p. 9).

[153] The British Organotherapy Co. Ltd., advertisement, *Medical Annual*, Bristol, John Wright & Sons, 1913, p. xiii.

[154] The British Organotherapy Co. Ltd., advertisement, *Medical Annual*, Bristol, John Wright and Sons, 1922, p. xxxiii.

[155] G W Carnrick Co., advertisement, *Medical Annual*, Bristol, John Wright and Sons, 1920, p. xiv.

[156] *Medical Annual*, Bristol, John Wright and Sons, 1913, p. 649.

[157] John Morgan Richards and Sons Ltd., Advertisement, *Medical Annual*, Bristol, John Wright and Sons, 1923, p. xxix.

[158] Parke, Davis & Co. advertisement, ibid., p. xxxv.

[159] Duncan, Flockhart & Co., advertisement, ibid., p. xxii.

[160] R G Hoskins, 'Some principles of endocrinology applicable to organotherapy', *J. Am. med. Ass.*, 1922, **79**: 104–6.

MEDICINAL SPECIALITIES

Regd. TRADE MARK.

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COPENHAGEN. DENMARK.

TABL. GLANDULÆ THYREOIDEÆ, D.M.K.

Physiologically Standardised under the Control of Prof. Dr. Med.h.c. C. O. JENSEN, Univ. of Copenhagen.

SUPPLIED IN THREE STRENGTHS:

No. 1.	No 2.	No. 4.
Each Tablet cont. 100 H.U.	Each Tablet cont. 200 H.U.	Each Tablet cont. 400 H.U.

INDICATIONS: Myxœdema, Cretinism, Lupus, Psoriasis, Chronic Eczema, Goitre, Ichthyosis, Enuresis.

ORIGINAL BOTTLES containing 50 and 100 Tablets each.

TABL. GLANDULÆ MAMMÆ, D.M.K.

1 TABLET = 4·25 FRESH GLAND.

INDICATIONS: HYPOGALACTY, METRORRHAGIA, MENORRHAGIA, UTERINE FIBROMATA.

In ORIGINAL BOTTLES containing 100 Tablets.

TABL. OVARIÆ, D.M.K.

1 TABLET cont. 0·32 gram Dried Gland = about 2 gram fresh Gland.

INDICATIONS: AMENORRHŒA, DYSMENORRHŒA, MENORRHŒA, OLIGOMENORRHŒA, INFANTILISM, ARTIFIAL and NORMAL CLIMACTERIC, CHLOROSIS, HAEMOPHILIA.

In ORIGINAL BOTTLES containing 50 and 100 Tablets

SPERMIN LIQUIDUM, D.M.K.

Original Bottles cont. 30 c.c. = the Hormones of 2 Testicles.

INDICATIONS: Weakness due to ARTERIOSCLEROSIS, ANÆMIA, DIABETES, IMPOTENCE, TABES DORSALIS, NEURASTHENIA.

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Figure 2: Advertisement for organic fluids from the 1923 *Medical Annual*. In the year that insulin was marketed in England, testicular fluid is still being advertised for diabetes.

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In a 1922 paper Mackenzie Wallis, Chemical Pathologist at St Bartholomew's Hospital, claimed to have isolated the internal secretion in 1919 in a form suitable for oral administration.[161] He reported three patients and wrote that those who did best were between the ages of ten and twenty. One case in which we know it was used in addition to "various forms of pancreatic and hepatic extracts, intestinal antiseptics, raw meat juice and externally applied oil" was a girl who developed diabetes at the age of four in 1918 and who, after five and a half years of dietetic treatment, weighed only 28 lbs and could only tolerate 364 calories a day. She began insulin treatment in October 1923 and was at once transformed.[162] That organotherapy was commonly used as a last resort in desperate cases up to 1922 is shown by a diabetic patient who wrote to *The Times* in 1923 saying, "I was a bit of a sceptic about insulin. One hears of a number of sensational recoveries . . . I had tried two pancreatic preparations and both had failed".[163]

That pharmaceutical companies continued to advertise organotherapy products for diabetes and other diseases between 1889 and 1921 suggests a market for their wares. Who prescribed these products is unknowable, but it was presumably what academic critics called a credulous profession.[164] At a time when doctors faced fierce competition from irregulars, the pressure for optimistic prescriptions was very high. Organotherapy had however brought the emerging science of endocrinology into disrepute. A persistent critic was Swale Vincent. In his 1922 Arris and Gale Lecture he said:

> Manufacturing druggists are not the only, nor indeed the chief offenders in this matter. They after all only push upon the market what they are likely to be able to sell and their prospect of sale depends on the recommendation of physicians . . . The medical press is crowded with articles on the alleged benefit of organic preparations. The majority of these contributions can only be described as utter nonsense, and are only fit, as indeed they are frequently destined, to serve the cause of advertisement.[165]

One of the most foolish organic preparations, according to Vincent, was a combination of dessicated pancreas, tonsil and duodenal mucosa to be taken by mouth for diabetes.[166] In retrospect Brown-Séquard was blamed for the drought which descended on clinical endocrinology for nearly thirty years and it was claimed that any young doctor showing an interest was naive and gullible or, worse, a gold-digger and quack.[167]

A Force of Magical Activity

The conclusions of the first paper from Toronto on the newly discovered insulin were that:

> (1) blood sugar can be markedly reduced even to the normal values, (2) glycosuria can be abolished, (3) the acetone bodies can be made to disappear from the urine, (4) the respiratory quotient shows

[161] R L Mackenzie Wallis, 'The internal secretion of the pancreas and its application to the treatment of diabetes mellitus', *Lancet*, 1922, **ii**: 1158–61.

[162] W H Passmore, M O Raven, 'A case of protracted childhood diabetes mellitus arrested by insulin', *Lancet*, 1924, **i**: 896–7.

[163] 'A patient's point of view', *The Times*, 7 Aug. 1923.

[164] H Cushing, 'Disorders of the pituitary gland', *J. Am. med. Ass.*, 1921, **76**: 1721–6.

[165] Vincent, op. cit., note 45 above, p. 319.

[166] S Vincent, *Internal secretion and the ductless glands*, 3rd ed., London, Edward Arnold, 1924, p. 442.

[167] H Lisser, 'The Endocrine Society: the first 40 years (1917–1957)', *Endocrinology*, 1967, **80**: 5-28.

evidence of increased utilisation of carbohydrates, (5) a definite improvement is observed in the general condition of these patients and, in addition, the patients themselves report a subjective sense of wellbeing and increased vigour for a period following the administration of these preparations.[168]

These conclusions were amply confirmed by other North American physicians in the latter half of 1922 and by the British physicians who took part in the Medical Research Council trial before insulin was released for general use in Britain in April 1923.[169] A patient writing to *The Times* described it as a force of magical activity[170] and the pharmacologist Arthur Cushny, who at the turn of the century had complained about haphazard use of the hypodermic syringe, described the results as brilliant.[171] Yet insulin was expensive[172] and, since it had to be given by injection, inconvenient. Proponents of oral organotherapy made one last stand. In March 1925 Dr Hollins of Chesterfield wrote that "the use of raw fresh gland has yielded such striking results during the $2^1/_2$ years I have been using it that I think they are worth recording". Hollins claimed that raw pancreas rendered the urine sugar free within twenty-four hours, lowered the blood sugar and cleared ketones from the urine and was free from what he called the grave risks attendant on the use of insulin. Two patients were briefly described but in other cases ("about six in all") the same excellent results had been obtained and one woman who had been started on insulin by "an over-zealous house physician" felt less well than she had on raw glands. To the objection that eating raw gland was loathsome, he retorted "patients inform me that it forms quite a delicious meal especially when taken with lettuce".[173] Two weeks later Dr Robertson Young wrote to say that in 1895 he had written his Glasgow MD thesis on the treatment of diabetes by raw pancreas.[174] Strangely, his method of administration was identical to that of Hollins, even to mixing it with lettuce! Dr Dunn of Uppingham described the effect of raw pancreas on a 21-year-old man and concluded that Dr Hollins' discovery "is of even greater practical importance than insulin, as it brings the treatment within the range of the mass of people whereas insulin is only for the few".[175] Several physicians wrote to the *British Medical Journal* that they had tested raw pancreas under controlled conditions in hospital, with negative results.[176] Dr R D Lawrence tested it on himself (an insulin-dependent diabetic) and concluded that it was ineffective. In fact, said Lawrence,

> I found raw pancreas so horrible as to prefer a dozen injections a day, if necessary, and I am sure that its continued use would have made me unable to eat much else—thus providing a simple method of introducing nausea, starvation, and undernutrition into the treatment![177]

[168] F G Banting, C H Best, J B Collip, W R Campbell, A A Fletcher, 'Pancreatic extracts in the treatment of diabetes mellitus: a preliminary report', *Can. med. Ass. J.*, 1922, **12**: 141–6, p. 146.

[169] 'Some clinical results of the use of insulin: a report to the Medical Research Council', *Br. med. J.*, 1923, **i**: 737–40.

[170] 'A patient's point of view', *The Times*, 7 Aug. 1923.

[171] Cushny, op. cit., note 61 above, 8th ed., 1924, p. 542.

[172] When it first came on the market in April 1923 100 units cost 25 shillings. By April 1924 the cost had fallen to 6s.8d. per 100 units and by 1929 to 2s.0d. J Liebenau, 'The MRC and the pharmaceutical industry: the model of insulin', in J Austoker and L Bryder (eds), *Historical perspectives on the role of the MRC*, Oxford University Press, 1989, p. 175.

[173] T J Hollins, letter, *Br. med. J.*, 1925, **i**: 503-4.

[174] R Robertson Young, letter, ibid., p. 632.

[175] William Dunn, letter, ibid., p. 680.

[176] G A Harrison, letter, ibid., 760–1; P J Cammidge, letter, ibid., p. 805; G Graham, letter, ibid., pp. 859–60.

[177] R D Lawrence, letter, ibid., p. 1108.

In conclusion it can be seen that the *Lancet*'s question about the thirty year gap after Minkowski's work was tendentious. It implied that there was a simple and obvious solution to the problem of diabetes, if only clinicians and physiologists had not been so blinkered. In fact, it is quite clear that pathological, physiological, clinical and therapeutic evidence was seemingly open-ended. Almost any piece of evidence from any of these domains could be contested with counter-evidence with almost unfailing consistency. Observers regularly reported failure to replicate results published by others. None of this is surprising. In an era in which standard techniques were only just being created either in the clinic or in the laboratory, untranslatable practices and knowledge were bound to produce highly contestable local accounts.

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