WELLCOME PRIZE ESSAY for 1934.

By RICHARD SCOTT.

"AN HISTORICAL SURVEY REGARDING THE FUNCTIONS OF THE PANCREAS".

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The pancreas has two chief functions viz. the production of an alkaline juice which, by virtue of its enzymes, performs the greater part of the process of digestion, and secondly, that of pouring into the blood stream the hormone insulin, which is absolutely essential for carbohydrate metabolism. Strictly speaking then, this essay should embody only the history of the discovery of those two functions and matters of anatomy, biochemistry of digestion, isolation of the various enzymes, and of the hormone should be set aside as irrelevant. I have, however, included some data of this nature for the sake of coherency, and also with the hope of making the essay more readable. I must confess that I have been torn between the Scylla of wanton brevity and the Charybdis of irrelevant detail with what result the reader will soon discover.

I propose to discuss the matter roughly under the following headings:

1. The gradual evolution of the appreciation of the importance of the pancreatic juice in digestion. - The earlier work, up to and including Claude Bernard.

2. The work of the German Schools (especially Kuhne) on the three enzymes.

3. The Mechanism of the Pancreatic Secretion.

4. The discovery of the presence of an internal secretion of the Pancreas.

5. The allocation of this hormone to the islets of Langerhans.

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I.

The earlier work.

The ancients were well aware of the position of the pancreas and of its glandular nature. It is referred to by Herophalus who was the great anatomist of his day (circa 300 B.C.) and taught at the famous school at Alexandria. This was the man who gave the name to the duodenum. Names for the gland in his day were "Pancreas" and "Callicreas" - Greek words which describe its flesh-like composition. Galen in "de usu partium" is very obscure about the gland. From Galen's time (200 A.D.) for a period of about 1500 years there was no advance in physiology or anatomy. People trusted Galen more than their own eyes, and it was not till Paracelsus (1490-1541) and Vesalius (1514-64) had questioned his authority, the former in physiology and the latter in Anatomy, that we could hope to have any advance in our subject. It was not so much the actual work of those men, but the inspiration of their methods, which helped to establish physiology as a rational science. Paracelsus was followed by Van Helmont (1577-1644). This man really started the great work on the chemistry of digestion. His 'Six Stages of Digestion' are well known. The second stage took place in the duodenum, but he knew absolutely nothing of the pancreatic juice, as Wirsung had not yet discovered the duct. He did/
did a great deal, however, to show the importance of ferments.

The first great advance came from the School of Francis de la Boe or Slyvius, at Leyden. In 1642 the duct of the pancreas and its opening into the duodenum had been described by John George Wirsung. The discovery was also claimed by his pupil Maurice Hofmann. There seems to have been some heated discussions on this matter and Wirsung was shot when entering his house one night after a quarrel (the legend states) about the discovery of the duct. Claude Bernard, lecturing on this subject seems to have been intrigued by the zeal of those men for their work, and amusingly compares the physiologist of the 'old days' with his apathetic students:

"Nous constatons de nouveau ici que les découvertes anatomiques et physiologiques suscitent aujourd'hui moins de passions".

Wirsung had made little use of his discovery but a pupil of Sylvius - Regner de Graaf (1641-73) a youth of 23 made an investigation of the pancreatic juice. He published his work ("Disputatio medica de natura et usu succi pancreatici") in 1664. He inserted a cannula in the shape of a quill into the pancreatic duct of a living dog and studied the properties of the liquid so obtained. He describes his previous unsuccessful attempts and how he finally succeeded in obtaining as much as a whole ounce of juice in 7 or 8 hours. This fistula experiment was never repeated for about 200 years when Claude Bernard took it up.

De Graaf's examination of the juice was very cursory.
Extracts from de Graaf’s "Opera Omnia" 1677.

P. 553.

The action of the pancreatic juice:

"Effervescentiam excitari ex Succi Pancreatici aciditate, 
& Bilis sale volatili, ac fixo obundantis concursu, tanto 
liberius afferere audemus; quia hactenus nullum vidimus 
exemplum spiritus acidi cum sale lixivo concurrentis 
absque contingente effervescentia etiam satis manifesta, 
dummodo sublata sine impedimenta.

In Bile utrumque salem reperiri probat nobilissimum atque 
insigne veritatis Medicæ instrumentum Chymia, cujus 
beneficio salem volatilem cum spiritu acido effervescentem 
& salem lixiviosum idem opus longe manifestius a bsolventem, 
separare possimus."
The report on examination of the juice of a sailor, describing how the sailor met his fate and how ultimately de Graaf examined his pancreatic juice by taste.

"Rationibus atque auctoritatibus statim allatis sequens addemus experimentum, quod in hominibus naturalem Succi Pancreatici aciditatem mirum in modum confirmat: anno 1666. dum in Academia Andegavensi commoraremur, Nauta 30. circiter annorum, vir boni habitus, &, in quantum ex adstantibus potuimus intelligere, optime sannus, navicula sua Sub antiquo ponte, supra Moenam fluvium posite transire nitens erecto naviculae suae malo trabem e ponte detrusit, qui in corpus ejus incidens illico hominem interfecit, cujus Cadaver statim ad Nosocomium delatum fuit, ubi illud adhuc calens cum D. Crosnier, ejusdem Nosocomii Chirurgo, aperuimus, in eoque Succum Pancreaticum collegimus, quem variis curiosis gustan dum exhibuimus, qui illum acidum judicarunt, quantum vero ad nos attinet, libere profitemur nos nunquam in canibus aciditatem magis gratam reperisse."

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This consisted chiefly in tasting it. He found it "sometimes insipid, at other times acid or rough, often salt, but most frequently acid salt". He persuaded himself that the juice was acid. On this observation is based the whole of the teaching of the Sylvius School on the action of the juice. This is somewhat surprising as the chemical differentiation between acid and alkali was established at that time, chemistry being in the ascendancy, and Sylvius was one of the leading authorities of his time on the subject. Sylvius knew the bile was alkaline and thought that the bile and pancreatic juice, mixing in the duodenum, produced an effervescence and so chyle was produced. The discovery of the lacteals had not been long known and it was thought that after this 'chylification' the whole of the matter was absorbed into the lacteals and so to the blood. Sylvius had the fixed idea that effervescence of a purely chemical nature and fermentation were identical processes. He dismissed the finding that there is no effervescence on mixing pancreatic juice and bile, in vitro, because of the absence of the heat of the "very warm viscera".

This great role in digestion, attributed to the pancreas was not to remain long unchallenged. J.C. Brunner published in 1682 "Experimenta Nova Circa Pancreas". In this he described how he had removed practically the whole of the pancreas several times and had kept the animals alive for a considerable time. The animals seemed quite well and he says that de Graaf and Sylvius must have been wholly wrong in attributing the importance which they/
they did to the digestive powers of the pancreas. Later, at Heidelberg in 1687 he described the glands of the duodenum known by his name. Peyer had written in 1677. So the pendulum swung back from the pancreas and more weight was now given to the glands of Brunner and the lymphoid patches of Peyer. The stomach now became the chief organ of digestion.

The following (18th) century added very little to our knowledge of the pancreas. Boerhaave, also of Leyden, did something for the work. The ideas of acidity and alkalinity were now becoming more definite and in his "Institutiones Medicæ" published in 1708, he expresses astonishment that Sylvius could ever have thought the pancreatic juice acid. He also distinguished between the chemical fermentation of Sylvius and true fermentation, such as that of wine. His views were held for a long time, but we still find little of note in the writings of the great physiologist Haller, who stated in 1757, in his "Elementa Physiologiae":

"A part at least of the usefulness of the pancreatic juice will be to dilute and soften the cystic juice .... so that this mixes better with the food. Whence you may explain the hunger of the animals from which the pancreas has been removed, attributing it to the reflux of a sharper bile into the stomach".

He adds:

"There may be other functions of the liquid not as yet known to us".

Reaumur followed Haller and so the whole of the importance of digestion was focussed on the stomach for the rest of the century.
No real systematic work was done on the pancreas after the short lived prominence given it by the School of Sylvius, until the master mind of Claude Bernard tackled the subject in 1846. Various people were working, however, in different parts, and, on before going to Bernard's work, I shall briefly indicate how miscellaneous data had been published before that date.

Asch in 1756 examined the pancreatic juice under the microscope and found it full of little globules. This was possibly fat. Horne repeated the observation in 1780. Plenck in 1794 and Fordyce in 1791 stated that the pancreatic juice and the saliva were similar in all respects. Magendie (one of Bernard's teachers) early in the 19th century found the pancreatic juice to be alkaline and that it was coagulated by heat.

Later Leuret et Lassigne got pancreatic juice from a horse and stated it to be the same as saliva.

Corvisant tells of earlier workers who knew that the pancreatic juice could emulsify fat and that it digested proteids. He says:-

"Eberle ayant découvert, en 1834 que le liquide du pancréas a pour fonction d'émulsionner les corps gras, rien ne fut plus inattendu que ce qui Purkinje et Pappenheim affirmèrent en 1836, savoir, qu'ils avaient encore retiré du pancréas un liquide doné de la propriété de dissoudre les aliments albuminoides eux-mêmes".

Tiedmann and Gmelin had also hinted at a function of the pancreas re protein digestion but they had a rather fanciful idea that the pancreas added nitrogen in the form of casein to the food.

M./
M.P. Berard refers to their work and derides their theory:

"M.M. Tiedmann et Gmelin professent que le suc pancréatique, riche en matériels azotes, contribue à animaliser les matières alimentaires et à favoriser leur assimilation; ils pensent que cette action est due surtout au mélange des principes azotés du pancréas sur les substances introduites dans le tube digestif. Ce qui prouve, suivant ces auteurs, que les substances azotées sont absorbées avec l'aliment qu'elles modifient, c'est que leur proportion va en diminuant du haut en bas dans le tube digestif".

In 1845, the year before Bernard began his work Bourchardt et Sandras had shown in a Paris publication that the pancreatic juice produced sugar from starch paste.

We therefore see that in 1846 there was practically no distinction made between the saliva and the pancreatic juice. At the same time the collected bibliography shows that each of the three actions of the juice had at least been hinted at, at various times in the 19th century though in a very obscure manner. It was therefore left to Claude Bernard to lay bare, in one clear and logical step, the threefold action of the pancreatic juice. This he did in an exceedingly brilliant manner using an improved form of de Graaf's technique and going on at the same time to lay the foundations of modern experimental physiology.

It is rather interesting to note that it was a mere accidental observation, and an erroneous one, which started Claude Bernard on his valuable work on the pancreatic juice. He had in the course of an experiment in 1846, introduced fat into the stomach of a rabbit and had observed that the material was not modified/
A rough photographic impression of the Claude Bernard's

Leçons de Physiologie
Éxperimentale -

Appliquée à la Medicine.

Faites au College de
France.

Paris 1855.

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A Photographic copy of the
Portrait of Claude Bernard.
from
Michael Foster's
"Claude Bernard".
modified until it had reached a much lower part of the intestine than a like change occurs in the dog. He began working on the pancreatic juice in that year and published his famous 'Memoir' in 1848. This was followed in 1856 by his "Lecons de Physiologie Experimentale".

He completely reviewed the knowledge of the pancreas of his day and comments especially on the work of Tiedmann and Gmelin and of Leuret et Lassigne. The latter had obtained the juice from a horse by means of a cannula in the duct - but they had failed to differentiate the properties of the juice from those of saliva. Bernard used the technique of de Graaf with improvements and used dogs for his experiments. After describing its chemical and physical properties he went on to show the action of the juice on foodstuffs. His first great step was to show that the pancreatic juice not only emulsifies fat as Eberle had indicated in 1834 but that it saponifies them, producing fatty acids. He did not associate the act of emulsion with that of saponification and though he was the discoverer of the latter process he seems to have thought that the former was far more important. He regarded emulsification as the result of a ferment of the intestinal juice - "ferment emulsif".

He next showed that starch, giving a blue colour with iodine and no reaction with "le tartrate cupro-potassique" (Fehling's Solution) on being acted upon with pancreatic juice very soon was changed to sugar, losing its blue reaction and reducing the copper solution.

Finally/
Finally Bernard showed the importance of the juice with regard to nitrogenous bodies. He showed that the pancreatic juice could dissolve proteins in the presence of bile but thought that it had no action when alone. He sums up in 1856:

"Le suc pancréatique alcalin agit sur toutes les matières de l'estomac:

1°. il emulsionner les matières grasses et les rend apte à être absorbées;

2°. il transforme le fécule en sucre.

3° Enfin, il agit sur les matières azotées, soit sur celles qui n'avaient pas été dissoutes par le suc gastrique, soit sur celles qui, après avoir été dissoutes par ce fluide ont été précipitées de nouveau dans le bile".

It will be noticed that Bernard rather erred in failing to stress sufficiently the proteolytic action of the pancreatic juice. This was, however, soon put right in a mastery work by another Frenchman, Lucien Corvisart who published a pamphlet on this subject in 1857. It was called "Sur une fonction peu connue du Pancreas. La Digestion des Aliments Azotés". He gave up the fistula technique and reverted to the use of an extract of the gland, which had been used by the workers of the 19th century before Bernard.

He took a dog and tied the duodenum at both ends to eliminate gastric juice. He introduced nitrogenous food and found some of it had dissolved after 18 hours, when the animal was killed. He repeated the experiment having first washed out the duodenum and tied the bile duct. He got the same result and so the bile was excluded. To demonstrate this more clearly he obtained pancreatic juice by chopping up the/
A Photographic impression of the title page of the work referred to on the opposite page viz.

"Sur une fonction peu connue

Du Pancreas

La digestion des aliments azotes.

Expériences paralleles sur la digestion gastriques et intestinale. Inductions cliniques

par

LUCIEN CORVISART.

Paris

1857 - 1858."
the gland and filtering off the uncontaminated juice. The thus obtained 50 c.c. of juice. To this he added "40 grammes d'albumine lavée que le suc gastrique n'avaient pas digérés" and stewed for 5 hours at 40° C. He found that practically the whole 40 grammes had dissolved.

He states that the pancreatic juice is every bit as proteolytic as the gastric.

"Le suc pancréatique transforme exactement comme le suc gastrique, le blanc d'oeuf en albumin peptone. Les deux nutriments venus de l'albumine paraissent identiques, malgré la différence des agents digestifs auxquels ils doivent naissance".

We see therefore that 1846 works a great advance in our knowledge of the pancreas. Claude Bernard could say with truth that the physical and chemical properties of the pancreatic juice were not at all fixed, and that its functions were in no wise understood, when he began working in 1846. Yet in the course of about ten years practically the whole basis of our conception regarding the use of the juice in the economy of digestion, was firmly established. This is a great tribute to Bernard and to the idea which he brought into physiology that

"Ce n'est pas en portant de l'anatomie d'un organe que l'on peut songer à en déduire les fonctions, mais que c'est au contraire en se plaçant au point de vue physiologique et en poursuivant un phénomène dans les différentes phases qu'il subit au contact de l'organisme".

II.

The threefold action of the pancreatic juice being now well established/
established, it is not surprising that the minds of physiologists began to enquire into the nature and mode of action of the ferments concerned. Among the most outstanding of these men were Kuhne, Heidenhain, Sheridan Lea, Harris, Gow, Roberts and Langley.

The term 'enzyme' was actually coined by Kuhne in a publication at Heidelberg in 1879.

The real work on the pancreatic enzymes dates from this period. Kuhne demonstrated the presence of the enzyme trypsin and named it in 1877. He also eliminated the possibility of bacterial fermentation by checking this with Salicylic acid and was the first to carry out aseptic digestion. He cleared the way for the study of the products of tryptic digestion.

In consequence of the growing knowledge of the nature of the pancreatic enzymes we consequently find improved technique for the extraction and separation of the enzymes. Kuhne and Chittenden in 1878 elaborated the method of autodigestion. The trypsin digests away the protein of the pancreas extract and is then precipitated with ammonium sulphate. V. Wittich used glycerin extracts from the gland in 1869.

Various degrees of success were also claimed in separating the ferments from the pancreatic juice. Thus Danilewski, a pupil of Kuhne obtained an extract free from lipase, and separated and prepared from it solutions having only proteolytic or only saccharolytic properties. This was in 1862. Cohnheim in 1863 isolated/
isolated the Saccharolytic principle. Roberts described in 1880 how he obtained amylase extracts with dilute alcohol.

I shall now state briefly what was known about these enzymes in relation to the three big classes of foodstuffs:-

1. Amylase:
   We have seen that Bourchardat et Sandras showed that pancreatic juice produced sugar from starch paste. Musculus followed and did much to show that this was due to an enzyme and was not quite analogous to hydrolysis by mineral acids. He showed in 1860 the nature of the balanced action which stopped when the proportion of dextrin to grape sugar was a constant figure. Knowledge of physics and chemistry had rapidly advanced and Fehlings test and measurements of optical activity were fairly exact. So that Mering and Musculus were able in 1877 to show that the sugar formed by amylase was identical to the sugar maltose described by O'Sullivan in 1872. Nasse and Brucke were able in 1877 to speak of 4 stages of hydrolysis by amylase, viz. Starch → Maltose and Erythrodextrin. The latter he also converted into maltose.

Meltzer worked on the conditions of optimum activity of amylase and showed in 1894 that it had definite limits of reaction beyond which it could not act.

2. Lipase:
   Nencki worked on the enzyme and showed that as the process of fat splitting could not be due to bacteria, nor was it obtained after boiling the extract, it must be due to an enzyme. (1886) Rockford at Cambridge in 1891 demonstrated the rapidity of action of this enzyme.

3. Trypsin.
   We have already referred to the demonstration of the presence of this enzyme by Kuhne in 1877. This author also discovered the important difference in peptic and tryptic digestion which were thought by Corvisant to be identical. Kuhne digested peptones with trypsin. Roberts of Cambridge published a paper in 1881, showing the variation in the action of trypsin for different temperatures and showed that/
that its activity increased up to 60° and that if the temperature was increased above this point it was rapidly killed. Kuhne demonstrated that trypsin must have an alkali medium. Boas and Meltzer showed also the limits of trypsin with regard to neutral or faintly acid media.

We therefore see that towards the end of the 19th century our knowledge of mechanism of the function of the pancreatic enzymes was rapidly approaching our present day standards. A milk curdling enzyme was added to the list by Roberts in 1879. Halliburton wrote of this enzyme in 1896.

It is interesting to note in passing that the human pancreatic juice has been examined by various workers and compared with that of experimental animals. De Graaf records that he examined the juice of a sailor who had died suddenly, and had found it tasted exactly like the juice of the dog. Herter collected juice from a duct enlarged due to carcinoma of the duodenum in 1880. Nor is the pancreas without its homologue of Alexis St. Martin, as Zawadski reported on a case which had a permanent fistula after removal of a pancreatic tumour in 1891. He found all three enzymes present. Bidder and Schmidt estimated the yield of pancreatic juice for a man at 175 grammes per diem.

III.

We shall now turn to the history of the discovery of the mechanism of the pancreatic secretion. The first to observe the gland during secretion were Kuhne and Sheridan Lea. They described/
described the zymogen granules seen under the microscope and noted their disappearance during secretion. The fistula experiment was revived in order to study the mechanism of secretion. Heidenhain used the technique of Bernard. Bernstein opened the duct and connected it with the wall of the abdomen. Heidenhain also evolved the idea of resecting the piece of gut where the duct enters, suturing it together again, and then bringing the piece of mucus membrane to the surface. Thus a permanent fistula was obtained. Pavlov improved on this by cutting out only the small quadrilateral piece of intestine which contained the ampulla of the duct.

Claude Bernard had mentioned in his 'Memoirs' that a flow of pancreatic juice was provoked by the introduction of ether into the stomach or intestine. This was attributed to a nervous reflex and Heidenhain began work on it. He concluded that this was a reflex and succeeded in producing a flow of juice by the stimulation of splanchnic nerves. He also got this result by stimulation of the medulla in 1875. Bernstein had shown that stimulation of the central end of the vagus inhibited the secretion in 1869 and Pavlow confirmed this in 1878. The great School at St. Petersburg now took up the subject. Pavlow found that prolonged stimulation of the peripheral end of a cut vagus produced a flow of juice.

In the course of his work Pavlow showed that the maximum flow of pancreatic juice occurs 3 hours after food and demonstrated the/
ERNEST H. STARLING, C.M.G., F.R.S.
Born 1866. Died 1927.

(Photograph by Professor H. S. Raper.)
the causal relationship between the passage of food through the pylorus and the secretion of pancreatic juice. Wertheimer of Lille in 1899 and Popielski (a pupil of Pavlow) followed up this cue and showed that secretion of juice was due to the introduction of acid into the small intestine and was absolutely unaffected by the division of both vagi, by division of the spinal cord, or by excision of the splanchnic nerves. They therefore rejected the old idea of a long reflex arc, and suggested that there must be a local reflex with a centre in the coeliae plexus. Wertheimer, however, came very near to discovering the truth of the matter, as he knew that the intensity of reaction varied directly with the proximity of the loop of intestine, into which the acid was introduced, to the duodenum, and further showed that injection of acid into the blood had no effect on secretion of the pancreatic juice. The crucial step was taken in January 1902 by Bayliss and Starling. They prepared a bitch for the experiment by 18 hours starvation. The nerve masses around the superior mesenteric artery and coeliae oxis, were removed and both vagi were cut. A loop of jejunum was cut and tied at both ends. It was carefully dissected out so that it was attached to the body only by its blood vessels. The secretion of the pancreas was recorded by means of a cannula. 20 c.c. of 0.4% HCl were introduced into the duodenum. There was a well marked increase in secretion. A similar response took place on introducing the acid into the enervated loop of intestine. Hence there must have been a chemical/
chemical messenger to the pancreas via the blood. Yet acid injected into the blood produced no effect, so the epithelial cells must hold the key to the mystery. These were extracted with HCl and the extract injected. A good response was obtained. The active principle was called by these workers "Secretin" and thus was a great advance made. Bayliss and Starling also showed that Secretin exists preformed in the alimentary mucosae in a proportion which diminishes as we go distal to the duodenum.

Later it was shown by J. Mellanby that bile is also involved in the production of secretin, and that a very powerful type of secretin was formed in the presence of bile salts as well as acid. Mellanby also pointed out that the nervous mechanism provided the enzymes while the hormone provided the alkaline fluid mainly, of the pancreatic juice.

One more discovery remains to be mentioned before we leave this section of the essay, i.e. that of trypsinogen. This was due to Heidenhain in 1875. He called the substance Zymogen. Delezenne also collected trypsinogen. Chepowałnikov, working in Pavlov's laboratory discovered that a drop of succus entericus greatly increased the activity of trypsin and so enterokinase was discovered.

Bayliss and Starling showed that trypsin was not a compound of trypsinogen and enterokinase but that the latter is essentially an enzyme.

We shall now leave the external secretion of the pancreas and/
and consider next the discovery of an internal secretion, tucked away, in the economy of nature, albeit for years to the despair of numerous physiologists, in the midst of this busy gland.

IV.

The clinical condition of diabetes was known to the ancients but it was not till the end of the 19th century that the condition was associated with the pancreas. This was demonstrated by the famous experiment by the German workers, V. Mering and Minkowski in 1899 when they removed the pancreas and produced Glycosuria and all the symptoms of diabetes mellitus. De Dominicis arrived at the same result independently, in the same year but interpreted it quite erroneously. The pancreas had already been removed by Brunner as long ago as 1680. He noted that the animal passed more urine than normal and had a voracious appetite but he thought this was due to the sharp bile, unmodified by the pancreatic juice. He makes an amusing reference to a dog thus depancreatized, which caused some trouble by molesting its former master, a butcher, for food. After the experiment of Mering and Minkowski the work went ahead rapidly. R. Lepine confirmed their results in the same year. In 1892 Lanceraux and Thirloix caused the acinar cells to atrophy (this had been done in 1872 by Schiff by injection of paraffin, with no obvious deleterious effect). They then showed that the atrophied gland when grafted subcutaneously prevented the onset of diabetes, but that/
that if the graft was removed, the condition supervened. E. Hédon in 1893 showed that this was true for grafts of portions of the gland. So the field was cleared for E.G. Laguesse to suggest in 1893 that an internal secretion was present in the pancreas which prevented the onset of diabetes. Schafer confirmed these results and said in an address to the British Medical Association in 1895:

"... in connection with the manner in which the pancreas prevents excessive production of sugar within the body - this effect must be produced by the formation of some material secreted internally by the gland, and probably by the interstitial vascular islets, and this internally secreted material profoundly modifies the carbohydrate metabolism of the tissues."

We have shown how the internal secretion of the pancreas was demonstrated and it is interesting to note that the rapidly growing subject of Pathology had contributed something to this discovery. Thus Cawley in 1788 demonstrated pancreatic damage in a post mortem of a diabetic case. Much later Frerichs and Rokitansky noted a pathological condition of the pancreas in diabetes. Bourchardat in 1846 and Lancereaux in 1877 had suggested the importance of the gland in diabetes but no attention was paid of this until the discovery of Mering and Minkowski.

I now propose to sketch briefly the story of how the function of secreting insulin was finally allocated to the cells of the islets of Langerhans. The literature on this subject is enormous and I can only try to pick out such parts as are relevant to the subject on which we are writing.
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SIR EDWARD ALBERT SHARPEY-SCHAFFER

Professor of Physiology, 1899-1933
The islets of the pancreas were discovered by Langerhans in 1869. The earlier workers considered these to be collections of lymphoid tissue but Laguesse 1893, Harris and Gow 1894, and Schafer, and Diamare 1895, corrected this view. Laguesse in 1893 was the first to point out that the islets were the seat of the formation of the internal secretion. He was wrong, however, in supposing that the acinar cells could take up the function of islet cells. Hansemann the pathologist went to the other extreme and postulated in 1894 that the acinar cells were the seat of carbohydrate control. The bulk of the work which followed this, in support of the insular theory was due to Laguesse, Schafer, Bensley, Lane and Opie with their co-workers. We may remark here again, that "Mortui vivos docent", as much of the earlier work was done by pathologists. Thus Shulze having in 1900 demonstrated the islets in the fibrosed mass of Hédon's experiments, we find that Opic and Ssobolew in 1901 wrote on pathological conditions of the actual islets in cases of diabetes. Sauerbeck in 1904 and Heilberg and Weichselbaum in 1911 followed up this line of research.

The next great step was taken by R.R. Bensley when he introduced the method of staining the islet cells by intra vitam stains. He published a paper on this subject in 1911. M.A. Lane had shown in 1907 that two types of cells are to be differentiated/
differentiated, viz. Alpha and Beta cells according as they contain Oxyphil or Basiphil granules respectively. The islets were now recognised on positive criteria and not on the absence of Zymogen granules as before. This discovery was soon brought to bear upon the insular theory.

Allen and Homans began working on a new line of research, in 1913. They extirpated sufficient of the gland to produce diabetes then, waiting till the condition was well advanced, killed the animal and examined the remaining islets, using Bensley's new technique of staining. Thus Homans found in 1915 that the Beta cells were those most affected. Next came the isolation of insulin from the islets cells. Scientists had been working for over a quarter of a century on this isolation. This is probably an ironical pun on the part of nature.

It is interesting to note that de Meyer in 1909 was the first to use the term 'insulin'. Schafer used the term in ignorance of this fact in 1916 and it was again adopted, apparently independently by MacLeod in 1922. Banting had used the term 'iseletin'.

Whereas the isolation of insulin by Banting and Best in 1922 was the first proof that the islets secrete this hormone, it has been shown that the acinar tissue does not entirely atrophy after ligation of the duct and the final demonstration was due to Wilder and his collaborators (Allan Power and Robertson) in 1927. They reported a case of spontaneous hyperinsulaemia occurring in a medical practitioner due to carcinoma of the islets. They observed the Beta cells in the various metastases in many of the organs/
A copy of illustration opposite P. 25 of J.J.R. MacLeod's monograph "Carbohydrate Metabolism and Insulin" 1926.

The original photo illustrates the pathological condition of the islets seen after partial extirpation of the pancreas. C.f. the reference to Allen and Homans on opposite page.

(Facing p. 20).
organs of the body. These were extracted and were shown to contain insulin by injection into a rabbit. This work was confirmed by Thalkimer and Murphy in 1928 and by MacClenahan and Norris, also by Howland in 1929. We thus see that a very certain knowledge has grown up that the islets of Langerhans are the seat of elaboration of insulin. I have referred to the isolation of insulin as a proof of this theory and I shall now briefly sum up the history of this isolation at the risk of straying from the actual title of the essay.

VI.

The story of the isolation of insulin makes very interesting reading, and has been so fully written on by Schafer, MacLeod and others that I feel like a cheap and tawdry imitator in attempting even a brief outline of the history. There are, however, many points well worth noting in this throbbing story of struggling and failure. So many came so near to the goal - so many fell by the wayside - so many extraneous influences, so many accidents - fortuitous and otherwise. It is interesting to note how the chaos of 1914-18 comes into our story. There must be many who believe that had this period of upheaval, adding though it did, in an inestimable degree, to our knowledge of Surgery and allied subjects, definitely delayed the arrival of insulin. Murlin and his collaborators, Paulesco and others had to leave the laboratory while success was practically in sight. So many workers, too were/
were labouring on this one subject, simultaneously, in the various centres, that it is difficult to assess the true value of this work, and further to arrange their findings in chronological order. There can be no doubt that Banting and Best were definitely the first to put in our hands, the syringe which was to make all the difference to the diabetic patient, but who can truly weight up such anomalies as the work of Professor E. Gley, to whom I refer below?

Professor Schafer in his address to the British Medical Association in 1895 refers to the work of Valli and of Sandemeyer. The former claimed to have caused disappearance of glycosuria in experimental animals by injecting an emulsion of the pancreas intravenously. Schafer points out at this early time that toxic symptoms were sure to supervene from such an emulsion and this is really a prophetic epitome of the results of workers for the following 20 years. Sandemeyer had failed to relieve diabetic symptoms by feeding the fresh gland. Minkowski had failed in 1892 with an emulsion of the gland. Soon after this, however, Capparelli, using extracts with isotonic saline, claimed to clear up glycosuria in depancreatised dogs. The next man to report positive results was Aussi in 1895 who noted an improvement on giving raw pancreas to a dog and was so bold as to carry out his experiment on a human case. He reported successful results but this is doubtful in the light of our present knowledge of insulin. Lepine, Hedon and Hougouneng all reported negative/
negative findings. They used glycerin extracts mainly. In 1898 just before the end of the century Blumenthal almost succeeded. He used alcoholic extracts of the expressed juice. He also used his injections on patients. He definitely helped the diabetic conditions but his preparation was unfortunately too toxic.

Lepine opened the new century with the work of extraction but he failed to get any lasting results. He himself says

"Mais les résultats n'ont nullement réponse aux espérances, ce qui peut s'expliquer à l'aide de diverses hypothèses."

Zuelzer used alcoholic extracts - a method which even at that time had already proved advantageous. He reported in 1908 on eight patients whom he injected intravenously with this extract. He was able to diminish ketonuria and glycosuria and also reported a marked clinical improvement. His process however had to be given up owing to rigors and other toxic symptoms which supervened. Forschbach in 1909, working in Minkowski's clinic, tried out similar preparations and had to give them up owing to their high toxicity. J.J.R. MacLeod refers to this work and states:-

"The elusive pancreatic hormone came very near to being caught through Zuelzer's researches, and it is probable that insulin would have been really bottled up at this time had more attention been paid to a study of the effects of the extracts on laboratory animals, rather than diabetic patients".

Themanyfold generations of cats, dogs and rana temporaria, which were to perish before this happy result was obtained would make the heart of the anti-vivisectionist quiver with righteous indignation/
indignation - fortunately, for his piece of mind's sake, he is not unduly given to dabbling in the literature of physiological research.

For the sake of preserving chronological order I must now refer to a paper read at a meeting of the Societe de Biologie held in Paris 1922. This is referred to in MacLeod's Book "Carbohydrate Metabolism and Insulin" P. 68. The paper had been deposited in a sealed package in 1906. It was the work of Professor E. Gley. This worker followed up the researches of Laguesse and believed the islets to be the seat of production of the anti-diabetic principle. He also believed that the failure of extracts up to date was due to the toxic effects of other substances besides the active principle. He therefore proceeded to extract the fibrous masses left behind after glands had been caused to atrophy - and found that such an extract was extremely efficacious in bringing back to normal health, dogs which had been experimentally depancreatised. He also states in the paper, his intention of preparing the extract in a suitable form for administration to patients - but this work he had to lay aside because of other researches. This is really a remarkable paper and of its authenticity there seems to be no doubt. One cannot help wondering how far we would have been ahead today with those extra ten years with insulin, which, evidently, we might so easily have had.

A great deal of work was done about this time to show that
the pancreas did not contain an anti-diabetic hormone and its
great toxicity on injection was repeatedly demonstrated. But
such work merely helped on the work of isolation. Thus Leschke
and Cohnheim pointed out the great toxicity of the pancreatic
enzymes and this gave E.L. Scott the idea of preventing the action
of these enzymes on the anti-diabetic principle. He failed
however to cause the gland to atrophy by ligation of the ducts.
He published the same year, however, a series of positive results
on extraction of the whole gland with alcohol and ether (1912).
But the results were so doubtful that he gave up the work.
Murlin, Kramer and Sweet followed Scott. They used concentrated
saline extracts and claimed positive results. They also combined
their extraction experiments with heart transfusion experiments
to estimate the glucose consumption of the heart. Their methods
were full of promise but they had to give up owing to the war.

The war was also responsible for cutting short the work of
N.C. Paulesco of Bucharest. He probably came nearest of all to
stealing a march on the Toronto workers. He extracted the fresh
gland with sterile water - ice cold, and the extract was given
intravenously. He showed that in dogs suffering from severe
diabetes - his extract could bring down sugar in the blood and
in the urine, ketone bodies in the urine, excessive urea in the
blood and urine. He had to abandon his work in 1916 owing to
the German invasion of Roumania. His researches were published
in August 1921 and were completed by Gley.
The Hero Who Found Insulin

By

George Malcolm Thomson

There are three characters in this story. You have heard of the first and the last—I just throw out the back of the stomach, a flat, busy gland whose main occupation in life is pouring digestive juices into the duodenum.

I said "main occupation." Not so long ago they would have said "sole" occupation; which is the point of the story. It is called pancreas. It is also called the fat charwoman.

The second character is the sinister disease, diabetes. It is a disease of people who lead sedentary lives, eating and drinking too much. Like the Nazis, it has a special dislike for Jews. One American in every hundred has it.

This is the young diabetes: the body no longer burns sugar, its chief fuel. For some reason or other the pancreas cannot convert its sugar into heat and power and nourishment. The engine slows down, runs to a standstill. The body wastes, muscles shrivel, growths break out, and energy fades.

The man who has diabetes suffers from thirst. He is always hungry, and he cannot be appeased, and from a thirst that cannot be quenched. And all the time the urine in which he accumulates like syrup in his veins.

There was no cure for diabetes. There isn't now. The treatment used to be a careful regulation of the diet in order to curb the fire in the body as low as possible. It kept some people alive for a few years, or for two years by starving them.

The story of diabetes is a tragedy. But this story I am telling you now has a glorious ending.

The story of Frederick Grant Banting, the young Canadian doctor from the backwoods. He is the hero of the story—a hero without heroes.

Banting was not a brilliant student. He was a plodding chap. But when he made up his mind about a thing he was great.

He went to France with the Canadian Army. And was wounded in the forearm.

The doctors wanted to amputate: told him it was the only chance of saving his arm. They'd be needing it," said Banting. He kept the arm.

And he needed both and all his determination when he settled in London, Ontario, as a surgeon. Patients did not flow into his consulting rooms; the new young physician with the long, bony face and pinces-nez did not have the name of the man who demanded in London, Ontario.

Anyhow, he made four dollars in the first year. He could live pretty hard, but he could not live on a dollar a week because it was in the Western Ontario Medical School. It puzzled him, and he had always been trying to find some relief for the human body under his care.

Banting knew all about the classical experiment of those Germans, Metting and Minckus. In 1884, the experiment which showed that when you removed a dog's pancreas it died of diabetes. He knew that Langenang, another German, had stood in the pancreas which seemed to do nothing at all for their living.

And now here was this chap, Moses Banting, saying—what? That when the pancreas is shut off by years against problems which this young man did not know existed.

"No doubt, he had a hunch. But if a medical school were to open the doors of its laboratories to a busy, busy fellow of a laboratory, and ten dogs, and an assistant, a medical student named Charles Best.

Banting sold up at London, Ontario, and plunged into the

The daily dose that defeats diabetes.

(RIGHT: DR. FREDERICK GRANT BANTING)

MEN AGAINST DEATH—VII. From "Daily Express"

9/12/23.

The Voice Of The People is on Page Seven.
We now come to work of F.G. Banting and C.H. Best who worked in MacLeod's laboratory at Toronto. Professor J.J.R. MacLeod was at this time a great authority on Carbohydrate metabolism. Toronto seemed suddenly to spring up as the nerve centre of the insulin seeking world. All the laboratories were switched over to this work and there were innumerable men on the job. Practically endless literature has streamed from the Toronto press, so that it is extremely difficult to say exactly who did certain parts of the work - there was certainly a truly co-operative effort, and the result was - insulin. It is not without significance that the University awarded the Cameron Prize to both MacLeod and Banting - the former in 1923, the latter in 1927. Banting gives a very entertaining account of the isolation in the address delivered on this occasion. I shall briefly refer to it here.

The author tells how he began work on the 16th May 1921 in MacLeod's laboratory. An article in the Journal of Surgery Gynaecology and Obstetrics by Baron, had drawn his attention to atrophy of the pancreas after ligation, or blockage with a stone, of its duct. He made up his mind to extract this residue. Having obtained the facilities for the experiment he began the work in MacLeod's laboratory with Best for an assistant. He used freezing brine for the purposes of extraction and succeeded in July 1921 in bringing down the blood sugar of a depancreatized dog with this extract. He then sought other means than ligation of getting rid of/
of the acinar part of the pancreas. He exhausted the gland of Zymogen granules by continuous injection of secretin then extracted. This gave good results but was obviously unpractical, yet it gave weight to the insular theory. He then turned to the extraction of foetal pancreases - bearing in mind the finding of Ibrahim who pointed out in 1909 that insulin occurs in the pancreas of a 5 months foetal calf at which time the Zymogen granules have not yet formed. Successful extracts were made from these but these were insufficient for clinical work. He had found that the active principle could be extracted and was not destroyed, by alcohol and acetone. So an efficient method of extraction was evolved whereby the adult pancreas could be extracted and the extracts contained no ferments.

On 11th January 1922 the first patient was treated at Toronto and the chapter was closed.

J.J. Collip and Best worked on methods of refining the extract and finally crystallised it. Manufacturing chemists were called in, clinics were established and post graduate classes were begun. And so our subject has marched right out of bounds, and we can only pursue it further in vast literature of Therapeutics Clinical Medicine and Pathology.
VII.

I should like in conclusion to deal in a few words, with the history of our knowledge of the mechanism of insulin secretion. The mechanism of insulin secretion is still a matter of great controversy but there are one or two names associated with this work. G.A. Clark writing in the Journal of Physiology of 1924 finds that parasympathomimetic drugs cause an increase in insulin secretion. The vagus therefore is secretory to the islets. He has also pointed out that some of the vagus fibres are inhibitory to the islets. Two names are associated with crossed perfusion experiments, these are Stoub and La Barre. They have shown that increase in blood sugar acts as a stimulus to the islets. Thus if a dog A has its blood vessels anastomosed with a dog B and B is depancreatized, then injection of sugar into A causes a fall of blood sugar in B. J.J. MacLeod in a Lecture to the Royal College of Physicians in London in 1930 stated that the islets are under a chemical rather than a nervous control and that changes in the blood sugar act as hormones.

Various workers have pointed out the relationship between the islets and the other ductless glands. Thus among the first to show the relationship between adrenalin and insulin were Eadie, F.M. Allen and MacLeod. While J.H. Burn in 1923 showed that extracts of the posterior lobe of the pituitary were antagonistic to insulin. Friedman and Gothesman showed in 1922 that removal of the thyroid in depancreatized dogs causes a fall in blood sugar even/
even without the administration of insulin.

Here I must write 'Finis'. I can only claim to have pecked here and there a few intellectual crumbs of our vast knowledge of the pancreas. I have attempted to make the review purely an historical one and to mention in chronological order some of the more important steps, which have been taken in the past in this most interesting branch of research. My field of vision is much too microscopic to have attempted any critical assessment of the various findings. Many details I have omitted, partly through ignorance, and partly with a view to making the broad outlines stand out more clearly. It is interesting to note how incomplete even our present day knowledge of the pancreatic functions are. Our various journals are full today of new findings on the function of the pancreas. I take as an illustrative example the recent work which has demonstrated the relation of the pancreas to growth and such a clinical entity as Diabetic Dwarfism. We can ill afford to laugh at the absurd hypotheses of de Graaf and Sylvius. These were truly remarkable men for their time.

I have enclosed a cutting from a recent copy of one of our daily papers. It demonstrates very well the great increase of interest of the laity in medical matters. This is probably due to our present day efficiency, armed with telephone, wireless and photography, incirculating information of all kinds. The excellent resources for intercommunication between men of Science have added greatly to our rapid advance in Medicine. How much further/
further ahead we would have been today if Claude Bernard had been able to give a series of broadcasts on the "Le suc pancreatique" from Poste Parisienne every Tuesday evening! How exciting too, to read in the Sunday papers of the morbid details of the murder of Wirsung, or of the caustic remarks of Vesalius anent Galen's knowledge of anatomy!

The writing of this essay has afforded me the greatest pleasure. I humbly appreciate the honour of living for a brief spell the experiences of that staunch army of determined men. It has more than amply rewarded my feeble effort of enquiry, to be privileged to be reactionary along with Paracelsus, to have dissected out the Pancreas with de Graaf, to have boldly ventured forth with Sylvius, to have timidly peeped into the laboratory of Bernard, to have listened to the clear ringing prophetic words of Schafer, and to have taken part in the tremendously exciting chase for insulin by the workers of this century. Such intimate glimpses into the minds of these great men leave a very lasting impression which will persist long after the details of the actual experiment are forgotten. They are a lasting treasure which cannot be taken away - an inspiration. We shall be refreshed with the poet when

"-- They flash upon the inward eye
Which is the bliss of solitude".
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(8) Starling gives a complete account of this subject in the "Mercers' Company Lectures on Recent Advances in the Physiology of Digestion", which were published in 1906.


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The/
The books chiefly used, other than those already referred to above were "Claude Bernard" and "History of Physiology" by M. Foster. Very good references are to be found in connection with the work of Kuhne and his contemporaries in Schaefer's "Textbook of Physiology" 1898. Vol. II. 'The Endocrine Organs' by the same author was also found to be very helpful.

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"The Work of the Digestive Glands" by Pavlov (translated) 1910; and The Volumes of the Journal of Physiology also supplied much detail.

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