WELLCOME PRIZE ESSAY

1934.

"AN HISTORICAL SURVEY REGARDING THE FUNCTION OF THE Pancreas".

DAVID H. LEES.
"Some bold adventurers disdain
The limits of their little reign,
And unknown regions dare descry."

Be it spoken as parallel or metaphor our subject embodies
its truth. Medicines' past can speak of heroes as great and
spirits as bold as any other sphere of life. That this can be
said of the little field we now explore is truly significant.

The quiet, efficient and brilliant research of numerous
men rewarded by a knowledge and power of isolation of two
essentials of biological functions - that is the statement of
truth. Treatment of diseases and substitution of deficiencies
are based on the knowledge of mankind.

We cannot but realise the inadequacy of any attempt at a
gesture of admiration by our humble selves. Let us go
with our heroes, share in the disappointments they met, exult
with them in their triumphs and be everlastingly honoured by
the pleasure of their delightful company.

By etymological reasoning it would appear that the
pancreas (\textit{πανκρέας}) was first known and recognised by the
Greeks in classical times, and that moreover it was regarded
as having been an organ with a flesh like consistency (\textit{κρέας}).
That the organ had been observed long before that time, there
is, however every possibility. Three men's names are associat-
ed with the gland in pre-Galenic times. Hérophile, who studied/
studied at Alexandria, had full cognisance of its position and glandular nature. Claude Bernard mentions Hérophile in this connection, adding that Eudémus thought that the gland excreted a substance like saliva into the intestine, and he further points out that Rufus of Ephesus recognised the pancreas as an organ or viscus.

Galen was obviously at a loss as regarded its function and speaks in a very obscure and guarded manner in his treatise "de usu partium". When we consider how great was the reliance on, and belief in Galen's work in all branches of medicine in succeeding centuries, it is not surprising that the "dark ages" saw no further development in investigation of function of this gland, and historians at the beginning of the seventeenth century hazard a description of the gland which betrays an ignorance of the gland which is hardly rivalled by the descriptions of the ancients themselves.

The first half of the seventeenth century saw the foundation of the Van Helmont or Chemical School of thought, the discovery of the microscope and the coming into prominence of Sylvius and his pupils. In relation to the pancreas the microscope did not manifest any discovery at this time - the only record is that Malpighi had looked at it in his investigations on the liver.

Van Helmont had arrived at that stage of investigation when he perceived the complexities of digestion but did not know/
know whence they came. He observed the change of the acid chyle to a salt nature, but in ignorance plunged into a fantastic theory based on chemical and spiritual imaginings. It was about this time, too, that Aselli made his erroneous statements, describing as the pancreas a group of mesenteric ganglia peculiar to the dog (1627).

In 1614 there was born Sylvius de le Boe, or Dubois, or in Latin, Franciscus Sylvius. He took his degree at Dusseldorf, studied at Amsterdam and was later made professor of Medicine at Leyden (1658). Sylvius is everywhere regarded as Van Helmont's successor. In as much as he took the chemist's point of view he was, but was in other respects he was totally different. Sylvius was, above all, a brilliant expositor; he cast off all the spiritualistic ideas that pervaded medicine in his day, and "trod the path of the most naked materialism". It is a tribute to Sylvius' great personality and teaching genius that we think of him in connection with discoveries made regarding the pancreas in his time, despite the fact that it is really to his pupils that we ought to ascribe the actual findings.

Priority in discovery of the pancreatic duct has been attributed to different men but most historians are agreed that John George Wirsung, a Bavarian, and pupil of Sylvius who later held the Chair of Anatomy at Padua in the middle of the seventeenth century, actually found it. According to Bernard, one/
Maurice Hoffmann, a pupil of Wirsungs, discovered the pancreatic duct in a cock in 1642 and that he furnished the opportunity for Wirsung's discovery of the duct in man in the same year. How Wirsung imparted the knowledge to his friend Riolan in 1643 by sending him a diagram on leather, how this diagram and copies of it got hopelessly mixed up, and how the tragi-comedy ended in Wirsung's assassination is described very wittily by Bernard, who does not let slip the opportunity of having a little joke at the expense of his pupils by remarking on the "lack of enthusiasm nowadays". That Hoffmann claimed the discovery as his own is pretty certain, but whether he had a vivid imagination or merely regretted of his former generosity is difficult to say. We may take it, I think, that the duct was discovered by the man whose name it bears. Wirsung too, seems to have observed the pancreatic juice but did not pursue the subject.

Sylvius, meantime, had been speculating on the discovery of his pupil, he recognised the possibility of another digestive juice and the discovery of another pupil of his was soon to lend him further food for thought.

Regner de Graaf was born in 1641 and studied under Sylvius at Leyden where while still twenty three years of age he investigated the pancreatic juice and published his "Disputatio medica de nature et usu succi pancreatici". In this tract he describes how after several unsuccessful attempts at/
at obtaining the juice he got the right method. De Graaf's record of his examination of the juice is very meagre. He did not do any chemical tests but relied on his sense of taste. He found that the qualities of the juice varied; it was insipid, sometimes acid or rough, often salt, but most frequently acid-salt. Dr Graaf records that he had the opportunity of examining the pancreatic juice of a sailor who died suddenly, and he found, presumably by gustatory examination, that it was identical in its properties with that of the dog.

Dr Graaf having thus persuaded himself that the pancreatic juice was acid, Sylvius accepted this fact and put forward a new theory of digestion - the use of the pancreatic juice, he asserted, was "to effervesce, to ferment, with the bile". That De Graaf the pupil of this famous man should have reiterated his views is not surprising but the whole matter shows how completely Sylvius and his school identify physiological fermentation with chemical effervescence. That the bile and pancreatic juice when mixed outside the body did not effervesce they pointed out was due to an unsuitable temperature. Despite all the clear-cut ideas of the effects of pancreatic juice and bile, Sylvius was not clear as to how it promoted digestion. De Graaf says that the action was to attenuate the mucous membrane of the intestine and allow of easier absorption, and to assist also in the separation of the useful from the useless parts of the food, but how this latter is effected, even he is not very clear.
But Sylvius and Dr Graaf, though they did mistake the nature of the action, yet by their recognition of the importance of the pancreatic juice, anticipated by some two centuries the work of Claude Bernard. The discoveries and theories of Sylvius were, however, soon destined to lose much of the popularity they had gained.

Jean Conrad von Brunner was born in 1653. He studied and graduated at Strassburg and after travelling in Holland France and England was elected professor of Medicine in Heidelberg. In 1682 he published his "Experiments Nova circa Pancreas", embodying results of work he had begun ten years before. He had succeeded in removing nearly the whole pancreas from dogs and keeping the animals alive for a considerable time afterwards. The animals on recovery from operation - and most of them did recover - in no way suffered in health. One he describes as eating, drinking, and running about as usual, well nourished and with no upset of digestion. Obviously, says Brunner, Sylvius and De Graaf were wholly wrong in attributing the importance they did to the pancreatic juice - for the duct and nearly the whole gland had been removed in these dogs, yet they digested as usual.

In the light of the connection between extirpation of the pancreas and glycosuria made known by modern researches, the additional observation of Brunner is interesting. Having first removed the spleen, and later the pancreas he says "It was/
was especially to be seen that the animal made water very frequently, and that he was very thirsty, drinking largely of water in proportion to the discharge of urine". But Brunner observes that Malpighi had noticed a similar result after ligature of the vessels of the spleen.

One cannot but wonder what Malpighi considered the vessels of the spleen, and it seems surprising that someone did not see any significance in these two operations.

With Brunner and Peyer's discoveries the short lived glory of the pancreatic juice raised up for it by Sylvius and de Graaf passed away. The minds of syphsiologists went back to the older view that the stomach was the chief seat of digestion.

And now we pass to a century which saw very little advance in knowledge of the pancreas. Theories were put forward but had nothing to support them, in fact, the whole century went to prove the maxim: -

"Errors like straws upon the surface flow:
He who would search for pearls must dive below."

From this we must only exempt two men - Boerhaave and pupil van Haller. The trouble was as has been said, lack of experimental work.

Clopton Havers, appropriately enough, ushered in the century with what the witty Bernard calls a marvellous theory of digestion. Boerhaave was born in 1668 and was called to the Chair of Medicine at Leyden in 1701, where he had a distinguished/
distinguished career. So highly was he valued that he was provided with a laboratory to satisfy his wishes. There he carried out his researches, applying an excellent knowledge of chemistry, physics, anatomy and physiology to his experimental work. Boerhaave expressed his wonder that Sylvius, who knew what an acid was, should ever have thought that the pancreatic juice was acid. He further antagonised the fermentation idea of digestion—it was more, he said, a solution, and in this idea von Haller supported him. Von Haller having pointed out that the ideas of Sylvius and De Graaf were no longer held goes to find basis for a new theory in the fact that he found that the pancreatic and bile ducts had a common orifice. "All these things being considered", he says, "a part at least of the usefulness of the pancreatic juice will be to dilute and soften the cystic juice .......... so that it mixes better with the food". —thus he explains the hunger of depancreatized dogs as being due to the sharpness of the bile. He ends by saying, prophetic of the work of Bernard a century later, "There may be other functions of the liquid still unknown to us".

After this time numerous small points were mentioned and many false theories propounded. Bryan Robinson in 1752 and George Heuermann in 1755 attributed much importance to the pancreatic juice and the latter discovered that there were two ducts of the organ, but opening at a common orifice. In
1756 Arch, and in 1780 Home, examined the pancreatic juice microscopically and described globules. In 1891 Fordyce made some chemical study of the gland but found nothing new. In 1794 Jacob Plenck analysed the pancreatic juice and the saliva and found them similar in their properties. The anatomists and pathologists also made erroneous contributions regarding the function of the pancreas at this time.

Thus we have come again to the beginning of a new century - it is a new era in discovery of pancreatic function. The eighteenth century according to M. P. Beard saw the birth of the erroneous view that the pancreatic juice moderated the activity, diminished the acidity and concentration of the bile.

"But now the hand of Fate is on the curtain and gives the scene to light".

In connection with the pancreas, Claude Bernard is, I think the outstanding physiologist. He had a very clear picture of what was done in this direction before his time, did brilliant research work in his own time, and propounded theories that were later universally accepted. At the beginning of the century and just before Claude Bernard's time, Tiedemann and Gmelin had the idea that the pancreatic juice was rich in nitrogenous materials and that it converted and favoured the assimilation of foodstuffs. The addition of the nitrogenous parts from the pancreatic juice to the foodstuffs was supposed to make the food absorbable. Bernard admits that he is rather at a loss to understand how the supply/
CLAUDE BERNARD.

"ἀνήρ, καλός καὶ ἄγαθος"
supply of constantly disappearing nitrogenous substance was to be kept up. And so Bernard introduces himself:

"D'apres tous ces travaux, vous voyez, messieurs, que les proprietes du sur pancreatique n'etaient nullement fixees et que ses usages n'etaient pas connus lorsqu'en 1846, nous fumes conduit a etudier le role du sue pancreatique par la circonstance survante .........."

How the romantic life of Claude Bernard began and his earlier work we unfortunately cannot mention here but we will stop his earlier life and join him where he presents to the Societe Philomatique in 1848 the first account of his work. When Bernard commenced his work on pancreatic juice, knowledge of this subject was of the scantiest. Muller and Beaumont were doing theis work on the stomach, the bile was receiving some attention, but the pancreas had up till this time been passed over almost in silence. The excellent researches of Hiedemann and Gmelin contained all that was known with certainty relative to the changes which the chyle undergoes in the intestine. But that we have already referred to.

Valentin in 1844 not only inferred that the pancreatic juice had an action on starch but confirmed his view by actual experiment with juice expressed from the gland. Eberle in 1834 had suggested that the pancreatic juice had some action on fat, indeed Cavisart goes as far as to say:) "Eberle ayant decouvert en 1834, que le liquide du pancreas a pour fonction D'emulsionner/
d'emulsionner le corps gras," but then continues "rien ne fut
ne fut plus inattendu que ce que Purkinje et Pappenheim,
affixmerent en 1836, savoir qu'ils avaient encore retiré du
pancréas un liquide doué de la propriété de dissoudre les
aliments albuminoides eux-mêmes." Thus it would seem that
Bernard was unlike his contemporaries and immediate predecessors - he relied on experiment, stated theories only when he
had foundation for every statement, and it is on this that
rests the value of his work. Bernard at one stroke made clear
the three-fold action of the pancreatic juice. He showed how
it on the one hand emulsified, on the other hand, split up
into fatty acids and glycerine the enutral fats discharged from
the stomach into the duodenum, he clearly proved that it had a
powerful action on starch, converting it to sugar, and lastly
he laid bare its remarkable action on proteid matter. He
describes how the stomach action on proteids is only a prepara-
tory one, and how the pancreatic juice and the bile together
act on the proteid matter, that the pancreatic juice cannot
alone do this unless the food has been previously subjected to
the action of the bile. Bernard in his experimental work
took a hint from Blondlot who in 1843 had introduced the
artificial gastric fistula, and perfected the pancreatic fistula
of Regner de Graaf, who as we have seen, did the experiment in
1662. Bernard made the operation really practicable and useful.
For his brilliant work in experimental Physiology he was
awarded/
awarded the prize for that subject by the Académie des Sciences in 1850. Claude Bernard died in 1878—his name will never die.

Lucian Corvisart, a countryman of Bernard now takes the stage. Corvisart, in his writings was almost contemporary with Bernard. How much he learned from the latter we do not know, but he thought along the same lines, confirmed many of Bernards discoveries, and, in one detail shows where Bernard was mistaken. Corvisart enclosed in a part of duodenum some white of egg and observed the digestion that followed when the pancreatic duct was open and when the bile duct was open and closed. He points out the fallacy of Bernard’s view that bile was a necessary factor in proteid digestion. Corvisart puts aside the De Graaf experiments as being of no true value in research, and experiments with chopped-up infusion of pancreatic gland. That the action of the gastric and pancreatic juices on proteid materials are identical is the conclusion he reaches in his work, and that the pancreatic juice at body temperature has a powerful digestive action on proteids which requires no supplementing.

And so we reach that stage when it is no longer possible to base our survey on men or the life of one man. So numerous do the writers in this field become that it is possible to trace the discovery of facts alone, to appreciate the advances made by some, and for interests sake to notice the mistakes of others. That interest which must necessarily be lost may be/
be reawakened in part by taking as basis to a conception of the most pleasant associations of these men's lives, a survey by necessity sacrificed on the altar of brevity. Each could equally well have said of himself "Nihil Medicinae alienum a me puto", but we will consider them only in the light of the contribution to knowledge of pancreatic function.

Since the researches of physiologists during the remainder of this century were directed to a fuller knowledge and better understanding of the enzyme properties of the pancreatic juice, and since moreover that knowledge was only obtained after many wanderings, it is in the interests of clarity to reproduce here a part of the classification of enzyme from Schaffer's Text-Book of Physiology, 1902.

Following on the work of Pelletier in 1844, "il est transformé le suc de la jupe" of the pancreatic juice in his "Memoire sur le suc du foie..." He..."brevity.

**SCHAEFFER'S CLASSIFICATION:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Name</th>
<th>Digestive Fluid</th>
<th>Concise Description of Specific Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastatic</td>
<td>Amylopsin</td>
<td>Pancreatic Juice</td>
<td>Converts amylopectin (starch and glycogen) into dextrin, maltose and trehalose, accompanied by a trace of glucose.</td>
</tr>
<tr>
<td>Proteolytic</td>
<td>Trypsin</td>
<td>Pancreatic Juice</td>
<td>Converts proteins into albuminogen, peptones, and amino acids.</td>
</tr>
<tr>
<td>Sterolytic</td>
<td>Steapsin</td>
<td>Pancreatic Juice</td>
<td>Splits up rennet jelly into fatty acid and glycerin.</td>
</tr>
</tbody>
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Following on the work of Valentin in 1844, "Le transforme la
fécule en sucre" says Claude Bernard of the pancreatic
juice in his "Mémoire sur le pancréas et sur le rôle du suc
pancreatique 1856". Of Corvisort's knowledge of the carbo-
hydrate digesting power of the pancreatic juice we have seen
proof. Bouchardat and Sandros had before this (1895) showed
that the pancreatic juice dissolved starch paste and formed
sugar, an action which they attributed to the amino-acids.
Had they omitted the product of their imagination and stood
by the findings of their experiments, Claude Bernard would
perforce have surrendered to them much of his honour. It is
easy to look back and say to these men of 1875

"μη νιν τά πόρρω τῇ γυναῖς, μένεις σκόπει"
Musculus in 1860 showed, in Paris, that saccharification was not complete and estimated the proportions of the products of digestion as 1 part of sugar to 2 of dextrose. Sheridan Lea contended that 85% went to sugar - this in 1890, and towards the end of the century Musculus and Gruber maintained that after five days action of diastase, dextrin was still present.

While attributing to Eberle, on the authority of Corvisart, the discovery of the action of pancreatic juice in the digestion of fats a further reference to Bernard's work "Du suc pancréatique will serve to show the authoritative opinion at that time. Thus Bernard says of the juice "Il emulsionne les matières grasses et les rend après à être absorbées." Bernard did not associate the formation of the emulsion with the production of fatty acid. Although he recognised the saponifying action he did not consider it of so much importance as the formation of emulsions in the intestine and he speaks of the "ferment emulsif". In 1868 Khüne pointed out that emulsive power does not depend on alkalinity. Rachford in 1891 corrected many mistakes when he pointed out that in favourable cases the action of bile and Hydrochloric acid could produce enough fatty acid to form an emulsion at room temperature in 2 minutes. - this is the fact which misled Bernard. The slower action of pancreatic extracts and the fact that fistula - collected juice has been less emulsive power and is poorer in protein led many false conclusions at this time. Rachford reports in the Journal of/
of Physiology in 1891 his observations. The activity is greatly increased by the presence of bile and also by Hydrochloric acid. The action is very fast and occupies no more time than any other stage of the digestion. Basing his ideas on the work of Abelmann in 1890, Minkowski a year later declares the emulsive power to be due to a proteid.

Schaf er in his "Text Book of Physiology 1898" sums up the position very clearly. He admits that little is known of the pialyn, he recognises that it is destroyed by boiling, it is less stable than the other enzymes and is therefore susceptible to the action of acids; and that since it acts in the presence of antiseptics, bacteria are not concerned. "It is now certainly known", he says, "that fatty acids are always found in the intestine after fat ingestion, but an emulsive ferment is no longer believed in. The rapidity of fresh pancreatic juice in forming fatty acid is remarkable".

"Purkinje et Pappenheim affirmerent en 1836 savoir, qu'ils avaient encore retiré du pancréas un liquide doué de la propriété de dissoudre les aliments albuminoides eux-mêmes." So states Corvisart in his "Collection de mémoires sur une fonction peu connue du pancréas, la digestion des aliments azotés". Paris 1857". It is not clear whether Corvisart saw in Bernard a dangerous rival, or bore him any grudge, but I cannot but think that he goes out of his way to drive Bernard of distinction in this case it does appear that Bernards many instances. However, /work was anticipated. Of Bernard's false theory of bile being necessary for proteid digestion and
of Corvisart's correction of this I have made mention.

Corvisart's views on the proteid digesting power of pancreatic juice were at first denied, but Meissner in 1859 and Danilowski two years later confirmed the views.

Külne besides confirming Corvisart's results but himself made very important advances. He named the proteolytic enzyme of the pancreatic juice "Trypsin" and he was the first to obtain a satisfactory extract. He showed that although trypsin is precipitated by excess of salicylic acid, smaller quantities of that substance do not stop the action of the enzyme, while they do stop the growth of organisms - Kolbe had previously shown the latter fact - thus he was able to evolve a method of antiseptic digestion.

These are the main points in the discovery of the true functions of the pancreatic juice in its enzymatic capacity. It has not been possible to even compromise chronological order and maintenance of readability, but I would ask to be allowed to treat of the latter half of the nineteenth century as a period recognising it as a time at which so many new ideas were expressed and so many conflicting opinions held that it is advisable only to dip into the literature of the time. I would try to give due prominence to what was of worth and of the rest - "Gracem est non protest legi".

As early as 1847, a sugar got from starch paste by the action of malt extract had been described by Dubrunfaut.

O'Sullivan/
SIR EDWARD ALBERT SHARPEY-SCHAPE
Professor of Physiology, 1899-1933

"Quicquid aget, quoque vestigia vertit Componit furtem, subsequiturque decor"
O'Sullivan, rediscovered and exhibited it in 1872, giving to it the name "Maltose". Mering and Minkowski followed this up by showing that this maltose was exactly similar to the substance produced by the action of malt diastase or Amylopsin on starch paste. Numerous theories as to the stages in carbohydrate digestion were then put forward. Additional findings regarding the enzyme itself and its method of extraction were published simultaneously with those regarding its active diastatic function. Liversedge in 1874 suggested a diastatic Zymogen or precursor of the enzyme but Garnge pointed out just after this that micro-organisms were not eliminated from this experiment. Schafer at the end of the century (1898) states that it is very doubtful if there is any precursor of the enzyme. Roberts (1881) stated that pancreatic diastase converted 400000 its weight of starch into maltose and dextrin. Schafer stated that the rate of conversion increased with the temperature up to 30°C. Between 30°C and 15°C it is at a maximum, over 45°C the action slows down proportionately and at 60°C or 70°C the enzyme is destroyed. Amylotropin was found to act best in neutral or slightly acid medium and Melzar stated that .01% hydrochloric acid was most suitable. Schafer states that the pancreatic juice is more diastatic than saliva according to some writers of that time, but he points out that there was not much foundation for this view as diastases could not be isolated.

Paschutin in 1873 recommended extraction by sodium carbonate and sodium bicarbonate, of the fat splitting enzyme, and Grutyner immediately followed him by announcing his glycerin-sodium extra carbonate method.
Of extraction Schafer says "However extracted it must be taken from a fresh gland and not from one which has stood over a day .......... for thereby acid reaction would be destroyed". this he states in his Text Book of Physiology (1898). Concerning rapidity of action and suitable medium it was known at this time that rapidity of action increased with rise of temperature so that at 38°C the action was twice as fast as at 18°C and moreover that a neutral medium provided the best facilities for its action and that 25% sodium carbonate medium slowed the action.

Danilowski had in 1962 obtained a pancreatic extract which did not give the usual proteid reactions but in 1876 Kühne was successful and he named the proteid digesting enzyme "Trypsin". Roberts in 1881 stated that he found tryptic activity to increase with temperature up to 60°C and then it rapidly fell, the action ceasing between 75°C and 80°C. Kühne was puzzled by the fact that pepsin and hydrochloric acid destroy the digestive powers of trypsin - the attributed the action to the pepsin. Boas closely followed him by shewing that it might well be the acid alone and Melzer (Jahrg. Discuss, Erlangen 1894) showed that most of the destruction was due to the acid alone.

Such, then, are the salient features of half a century of research by numerous workers. Kühne, of whom more will be said later, was the outstanding figure, and he stands out
as a shining light among a constellation of lesser stars. It calls to mind a passage from Hazlitt who observed that "One age is employed in building up an absurdity and the next exhausts all its wit and learning, zeal and fury, in battering it down, so that at the end of two generations you come to the point whence you set out and have to begin again". Shall we substitute "decades" for "generations" and further say......"when the dogma is stripped of all its mystery and intolerance, and reduced to common sense, no one appears to take any further notice of it".

That there can be obtained from the pancreas a substance from which the proteolytic ferment can be derived but which does not itself possess proteolytic powers was shown by Heidenhain in 1875. This substance he called "zymogen" and the name "Trypsinogen" was later given to it. Heidenhain with Kühne was one of the really outstanding physiologists of this time. His contributions to knowledge of the pancreas are considerable, but as his more brilliant researches were concerning gastric digestion we will not attempt an appreciation of his life but merely state the conclusions from his work. In differentiating trypsin and its enzymogen he draws attention to the following facts:--

I. Trypsinogen is soluble in glycerine. Thus it is, that glycerine extracts of the pancreas have no fermentative action, but if the extract be dissolved in 1% caustic soda and distilled water, fermentative power is restored.
2. Inactive glycerine extracts of pancreas, treated with oxygen and Sodium Carbonate are rendered active. Simultaneously if oxygen be taken from the active extract, the inactive form results.

Podolinski in 1876 showed that platinum black rendered the inactive extract active. According to Kuhne, Zymogen was converted to trypsun by heating it with alcohol. Schafer at the end of the series points out that active Acetic Acid (1%) makes with the glycerine extract of pancreas a very active ferment.

Round about 1890 some very interesting work was done in extraction of pancreatic enzymes and trypsin was very fully investigated. The general method of preparing pancreatic extracts was with water if the solution was for immediate testing. Wittich in 1869 introduced the glycerine extract method. How lipase was extracted has been mentioned. As regards amylase - Roberts made an extract with dilute alcohol in 1880, this following Grutzmer's method for the comparison of diastatic and fat splitting powers of pancreatic extracts in 1876. Kuhne did most of the work on trypsin extraction. It occurred to him in 1878 that since trypsin digests albumoses to peptones, it should be possible to obtain a precipitation by saturating with Ammonium Sulphate - thus he got his extract. Much work was done at this time in the German school at Weisboden, and Hammersten in 1895 propounded the method of tryptic extraction by water and 0.1% ammonia. Roberts put forward/
forward various views while working in London in 1891 - he extracted by various methods viz:-

1. Water and Chloroform  
2. Water, Boracic Acid and Borax.  
3. Sodium Chloride  
4. 25% Alcohol

Schafer writing in 1898 was rather baffled by the "metacasein" reaction of Sir William Roberts. Roberts noticed that under the influence of extracts of the pancreas, caseinogen, before it is clotted by the milk curdling ferment of the gland, passes through a stage in which it is coagulated by heat. This was termed the "metacasin" reaction by Roberts in 1879 and mentioned again in 1891. Edkins (Journal of Physiology, Cambridge and London 1891) showed that Kuhne's purified Trypsin also produces "metacasein" in an early stage of its action, though it does not produce coagulation of milk. Thus Schafer says in 1898 - it does not appear to be due to the simultaneous development of acid produced by the fat-splitting enzyme.

Long before Corvisart's time the question of what medium the pancreatic juice acts best in, was under dispute. Corvisart himself is his "memoirs sur une function peu connue du pancreas, la digestion des aliments azotés " 1857 says "Les physiologistes se sont peu accordés sur le reaction propre au doudeum, les uns le disent acide, les autres alcaline". Following on experiments he concluded that the pancreatic juice "conservait toute sa vertu, toute sa liberté d'action dans un milieu alcalin/
The accumulation of knowledge regarding the carbohydrate digesting function of the pancreas has been traced up to Mering and Minkowski's time. Almost a year later (1875) Musculus and Gruber pointed out that although maltose was the chief result of anlyotropic digestion, yet small traces of grape-sugar were formed. The first stage of this digestive process came to be accepted as a change from starch to soluble starch - the time required was two minutes and the product gave a blue colour with iodine. In 1877 Nasse described the second stage - from soluble starch to maltose and dextrin which gave a red color-

**CARBOHYDRATE DIGESTION**

From Schafer's Text Book of Physiology:

<table>
<thead>
<tr>
<th>Stages</th>
<th>+ Iodine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Soluble Starch</td>
<td>1 Red - Blue</td>
</tr>
<tr>
<td>2 Erythrodextrin</td>
<td>2 Red</td>
</tr>
<tr>
<td>3 β - Achromedextrin</td>
<td>2 No colour</td>
</tr>
<tr>
<td>4 α - Achromedextrin</td>
<td>2 do.</td>
</tr>
<tr>
<td>5 β - Achromedextrin</td>
<td>2 do.</td>
</tr>
<tr>
<td>6 Maltose</td>
<td>2 do.</td>
</tr>
<tr>
<td>7 Grape Sugar</td>
<td>2 do.</td>
</tr>
</tbody>
</table>

A stage of Erythrodextrin to give no colour with iodine, and to reproduce. Again Biology" for tables that is a pleasant sensation, perceiving how vague

"of such herc for what we found when the sun in the sea heavily dips".
The accumulation of knowledge regarding the carbohydrate digesting function of the pancreas has been traced up to Mering and Minkowski's time. Almost a year later (1875) Musculus and Gruber pointed out that although maltose was the chief result of anylotropic digestion, yet small traces of glucose-sugar were formed. The first stage of this digestive process came to be accepted as a change from starch to soluble starch - the time required was two minutes and the product gave a blue colour with iodine. In 1877 Nasse described the second stage - from soluble starch to maltose and dextrin which gave a red coloration with iodine. This dextrin was called Nasse's Dextrin, later Grassmayer's dextrin, later Bondonneau's dextrin, and Brucke wound up the series by calling it Erythrodextrin. A third stage came to be recognised - that of Erythrodextrin to maltose and a further dextrin which gave no colour with iodine the names given to it I will not attempt to reproduce. Again I refer to Schafer's "Text book of Physiology" for tables that make the action clear at a glance. It is a pleasant sensation, searching the literature of the world, perceiving how vague are the notions, and returning to our Alma Mater - to see a teacher of ours at one stroke make clear a problem that mystified a world.

"Of such heroes few shall be found when the sun in the sea sinks stormily and the state's prow heavily dips".
A consideration of pancreatic function must necessarily include Starlings work on secretion, but as a preliminary to this it will elucidate matters much to survey briefly the history of the function of the gland. Bernstein in 1869, and later Afanarsieau and Pavlov (1878) said that stimulation of the central end of the vagus and of the sensory nerves in general gives inhibition of pancreatic secretion if the nerves denham said this was due to heidenham got secretion by stimulating and when secretion was in progress noticed that pilocorpine caused pavlov in 1893 noticed that atropine and he attributed to the vagus gland - since by experiment he of that nerve. Heidenham's works success in his experiments and questionable. Pavlov was very all the problems of secretory to a reflex through the cortex, nervous system and travelling or sympathetic. The importance of this long reflex, from the intestine to the central nervous system and back along the vagus or splanchnics was later questioned ed by Wertheimer of Lille and Popeliski a pupil of Pavlov's in 1899. Wertheimer records his results in the "Comptes rendus" of
of 1889 and Popilski in "Pfluger's Archives". Both these men showed that the secretion of pancreatic juice, evoked by introducing acid to the duodenum was unaffected by division of vagi, sympathetics, splanchnics or the spinal cord. They propounded the theory that a local reflex started in the mucous membrane of ganglion cells now took up the question of everything but blood stimulation with acid.

that the injection of acid occurred to Starling and his co-workers to be able to solve them all, more or less satisfactorily."

His findings were:

1. Acids, simply excite the pancreatic gland and therefore the stomach contents activate the gland by being acid and entering the duodenum.
2. Starch does not augment the total secretion of pancreas, but increases its content of amylolytic ferment.
3. Fat is an excitant of pancreatic secretion and increases amount of fat-splitting ferment.
4. Sleep does not hinder pancreatic secretion.
5. Pressure excites only, but is unimportant.
6. Water is an independent excitant.
7. Solub or tincture and alkaline salts of alkaline inhabit the pancreas secretion.

This hydrolysis theory was questioned, since substances other than acids could give a secretion (Bernard used ether and oil was quite...
of 1889 and Popiński in "Pfluger's Archives". Both these men showed that the secretion of pancreatic juice, evoked by introducing acid to the duodenum was unaffected by division of vagi, sympathetics, splanchnics or the spinal cord. They propounded the theory that a local reflex started in the mucous membrane of the gut and travelled to the collections of ganglion cells in the pancreas. Bayliss and Starling now took up the question. They exposed a part of gut, derived it of everything but blood supply and got a secretion of juice by stimulation with acid. Since Wertheimer had previously shown that the injection of acid to the blood did not give a secretion it occurred to Starling and his colleagues that the layer of epithelial cells between the lumen of the gut and the blood must have some significance. Consequently they extracted the cells with acid, filtered it and injected it into the blood - a secretion of juice resulted. An even greater flow of juice was obtained by introduction of the acid to the lumen - this substance was therefore formed by the action of and on the cells. Starling gave to it the name "Secretin". He describes its characters briefly - not a ferment for not destroyed by boiling, diffuseable, soluble in alcohol or alcohol and ether, and can be got by simply boiling the tissue with water, but this extract is not active, and thus Starling was led to observe the presence of this "prosecretion" as he called it, which by hydrolysis was converted to secretion. This hydrolysis theory was questioned, since substances other than acids could give a secretion (Bernard used ether and oil was quite/
"Sapocrinin" which
oil on the mucous
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quite active in evoking a flow of juice). "Sanocrinin" which Fleig suggested was formed by the action of oil on the mucous membrane does not differ, according to Starling, from secretion except in its mode of origin.

The actual changes in the gland substance need not concern us here. It is enough to state that Barcroft after many observations described the action of the gland as being very similar to the salivary gland. Kuhne and Sheridan Lea described the histological changes and appearances during secretion.

That the existence of a precursor of trypsin in the pancreas was recognised by Kuhne, Heidenham and Langley and that they gave to it the name "trypsinogen" we have already seen. Pavlov accepted this - only modifying his predecessors views by stating that a good deal of trypsin itself could be obtained from the pancreas.

Chepowalnikow, who worked in Pavlov's laboratory found that a drop of intestinal juice or extracted membrane from the intestine, if added to the pancreatic juice, increased the proteolytic powers enormously. His conclusion was that a ferment contained in the succus entericus had the power of transforming trypsinogen to trypsin and to it he gave the name "enterokinase". Dèle Chasse followed him up by showing that pancreatic juice collected by a cannula in the pancreatic duct had no proteolytic activity at all. Thus it was made clear to both workers that only trypsinogen existed in the pancreas and that it must come in contact with the intestine and be subjected to the/
the action of enterokinase before it took on its trypsin form. This discovery throws rather an interesting side light on methods of collecting juice by fistulae. The seemingly compromising actions of Pavlov's samples of juice have their explanation in a consideration of the method of collection of the juice.

Of Pavlov's statement that Chelowalnikow's enterokinase was "the ferment of ferments" of how it was questioned by various workers before Boyliss and Starling made it manifestly plain that Pavlov was correct and ending that chapter of research with:

"Τούτο ἐκέινο τῷ τῆς παροίμίᾳ"

- of that little need be said. It is sufficient that Délézanne, and later Destre and Stassano (Archives internat de Physiol. Vol.1 p. 86 1909) held the view that there was a proportion between the enterokinase and the trypsinogen and they gained the support of Metchnikow and Erlich in suggesting an analogy in the Amboceptor and the complement in the destruction of red blood corpuscles by foreign sera. Starling proved by experiment that there was no relation at all in the proportions of trypsinogen and enterokinase and that Pavlov was correct.

In a consideration of the adaption of the pancreatic juice to the nature of the food and its relation to nervous control of the pancreas we need not go further back than Pavlov, for before that the nature of pancreatic juice itself was not clear.

Pavlov and his pupil Varilieff held the view that the pancreas/
pancreas had a marvellous qualitative adaptive power. Walther was even more emphatic in this view and Bainbridge "confirmed" it. When we also have Weinland for the affirmative it took much courage on the part of a Frenchman, Bierry, to dare state that there was no adaptation, but in support of the saying that "Right is might" Plummer and Popeils supported Bierry's statement. Since it is only in recent years that a nervous or psychic factor concerned in pancreatic secretion has been recognised, the champions of the adaptation principle had to find explanation of these changes in the "secretin" mechanism of Starling.

Though much still remains to be recounted of the investigations in this field of pancreatic research a more important problem now concerns us, and it may be left to the text books of to-day to give details of further discoveries as regards the enzymatic properties of the juice.

So we have an alpha superimposed on an omega. While the final details of the knowledge of pancreatic secretion were being cleared up a totally new field of operation was opened up. For the initiation of this new conception of pancreatic function we must pay to the anatomists our compliments.

It has been said that "the slow advance and perpetual interpositions of impediment is a salutary check to the rashness of innovation and to hazardous experiment...." The interpositions were, it must be admitted, faithfully supplied by the comparative anatomists at the end of the nineteenth century. The/
The endless experiments of numerous workers on almost every type of animal under the sun, and their observations on these make dreary reading, and contribute but little to the knowledge of pancreatic functions.

Langerhans in 1869 first discovered and described the islets of tissue in the pancreas which later came to bear his name. He did not venture any theory as to their function, remarking simply that there was a close relationship between the islets and the nerves and nerve ganglia. The view that the islets were simply lymphoid cell collections was put forward successively by Lea and Khune (1882). Sokoloff (1883) Krause (1884) and Ellenberger (1887). The fallacy of this view was later pointed out by Laguesse (1893), Harris and Gow (1894) Gianor (1895) and Schafer (1895) and Gentes in 1901 made this point clear, by showing that the islets were not hypertrophied in leucaemia like ordinary lymphoid tissue. Thus the islets came to be regarded as epithelial cells with little difference from the acinar tissue of the gland. Indeed it was the view of Harris and Gow (1894) and of Giannelli and Giacomini (1896) that they secreted a diastatic enzyme or at least a co-enzyme which met another enzyme to form trypsin. This latter co-enzyme Sajous as late as 1904, suggested, had its origin in the spleen. The absence of ducts in the islet tissue discounted these views. Lewaschew (1886). Tschassowinkow (1900) and Mankowski (1900) maintained that the islets were acini that had undergone change - probably exhaustion - but the/
the persistence of blood vessels and nerves was irreconcilable with this. Gianelli (1899 and 1902) and Oppel (1900) suggested that the islets were vestigial remnants of a tissue with secretory functions in primitive animals which has been replaced in higher animals by acinar tissue. Laguesse showed that this was not the case and that acini are more rudimentary than islets.

Diamare first took the view that islet tissue is not developed from completely developed pancreatic secreting tissue and denied the interchange of state between islet and secreting tissue, and vice versa. In this view he was supported by W. A. Heigurg (1906) Kuster (1907) Wiechaelbaum and Kyrtle (1909 Bensley (1911) Schafer (1912) and Homans (1913) - the contention of these men was that if diabetes were due to deficiency of islets, then new islets could be developed from secreting tissue and so diabetes would cure itself - but this does not happen. This idea was endorsed by Rennie.

The fact that in some animals a fine branching cord connects the alveoli and the islets seems to lend support to the view that the islets grow out from the budding ducts like the alveoli of the secreting gland was suggested by Schafer.

The further fact concerning the anatomy of the islets may be rapidly summed up (1) Clark using Bensley's intra-vitam staining methods calculates that there are ½ to 1½ million islets in the pancreas.

(2) Lane, Bensley, Saguchi and others recognised two types of cells/
cells in the pancreas - the $\alpha$ cells and the $\beta$ cells - the $\alpha$ cells were oxyphil and insoluble in alcohol the $\beta$ cells were basiphil and soluble in alcohol. Some cells had no obvious granules.

(3) Kuhne and Lea (1882) described the capillary network - its completeness and close connection with the islet cells. Schafer later saw in this relationship a reason for believing that the secretion of the islet tissue went direct to the blood.

(4) Gentes (1902), Pensa (1905) and de Castro (1923) observed the good nerve supply of the islets and the button-like extremities of the nerves.

(5) S. W. Britton (American Medical Journal 1925) says that the right vagus when stimulated caused a decrease in blood sugar. Stimulation of the left vagus or of the sympathetic did not give similar results.

It is infinitely more interesting and pleasant to deal with things mellowed by the hands of time. Especially could this be said of history in our time - The records of investigation on pancreatic function in the eighteenth or even the nineteenth century have merit alone as their criterion of survival; tried and tested theories only reach us and the march of progress is well defined. Not so in the present century. Recording of their results, no matter how ridiculous they may be, is within the reach of all, and a separation of the grain from the chaff is consequently no easy matter.
J. von Mering and Yinowski’s experiment of 1889 is the beginning of a subject on which the literature is enormous. Every man of science or medicine seems to have considered it his duty to give a view on diabetes and the pancreas - and this is a fact that must be taken into consideration, that research work except in a few instances, had its beginnings in the investigation of diabetes and thence focussed on the pancreas, rather than otherwise. This being the case, I propose to take the very unorthodox step of using as my background diabetes, and by a consideration of the theories held regarding its aetiology in relation to the pancreas - to throw them into relief the investigations on and true functions of the pancreas.

The theories of aetiology of diabetes could be classed as:

1. "Extraneous" hypothesis.
2. Acinar hypothesis.
3. Islet hypothesis.
4. Acino-Insulor hypothesis.

of the first little need be said. Bernard’s pancreatectomy operation cannot be connected with this disease, and he himself localised the diabetic control in the lungs. Joseph Hart Myers in 1779 writing in his "Dissertatio Medica inauguralis de diabete" makes no mention of the pancreas and attributes the causes mainly to the kidneys.

T. Cawley (London Medical Journal 1788, 9, 286) reported a case of diabetes seen at post-mortem showing marked pancreatic damage "The pancreas was full of calculi which were firmly impacted/
impacted in its substance...... the right extremity of the pancreas was hard and appeared to be "he writes. Whether there was some malignant condition of the islets is uncertain but he laid the foundation of the view that the pancreas was concerned in diabetes - naturally it was to the acini that he referred in talking of the pancreas. Bourchardat (Nouvelle mémoire sur glycosurie en diabète sucré, Suppl à l'ann de méd Paris 1896 p. 209) and Lancereaux (Bull. Acad. de méd 1877 6 1215) gave some slight support to the acinar theory. Frediche found that 20% of diabetic cases had obvious changes in the pancreas and Rokitansky put the number down at 13 out of 30. Hansemann (1894) was the last champion of the acinar hypothesis. He laid much stress on "granular atrophy" of interacinar tissue, maintaining that this was the most important lesion in diabetes.

The operation of van Mering and Minowski set pancreatic investigation back on the rails. They found that the de-pancreated dogs showed sugar in the urine in 4 - 6 hours reaching a maximum in 24 hours, and the dogs died in 4 weeks time. These facts were published in 1889 and Minowski described the operation in 1893. de Dominicis (1889) arrived at the same result of pancreatectomy, but did not draw the proper conclusions. R. Lepine (1889) and E. Gley (1901) repeated and confirmed the operation, the latter modified it by tying the veins to the organ and so producing diabetes. Mering and Minowski further found that ligation of the pancreatic duct did not/
secretions. The evidence of this is complete....." he explains that pancreatectomy causes damage by removal of the internal secretion, and adds "...... cases of glycosuria occurring in the human subject were frequently associated with disease of some kind of the pancreas".

He goes on to quote Freich's and Hekitansky's figures, mentions Bernards pancreatectomy experiments and leads up to Mering and Minowskie's classic experiment of 1889. He points out that Schiff had blocked the pancreatic duct with paraffin and no diabetes was obtained, so that the important substance was not in the secreting part of the gland. Finally he mentions Hédon and Thiroloix's operations - the gradual removal of the pancreas and the grafting experiment, and draws the conclusion that the supply of the substance is to the blood direct, and he ends up by saying of the islet tissue ......"it is, I think, fair to assume that the pancreas mainly owes its function as an internally secreting organ, at least as far as regards the prevention of diabetes, to this tissue which is apparently peculiar to it amongst secreting glands". It is perhaps a little unfair to Minowski, who published a very concise account of his operation and views on diabetes, to consider Schafer's theory first, but we will now consider the points Minowski made before going on to follow up the insular theory to its zenith of popularity. Minkowski takes a very similar line of argument to Schafer. He agrees with Thiroloix that there is no connection between external and internal secretions/
secretions of the pancreas, and concludes that the pancreas secretes into the blood something that influences the utilisation of sugar, although he does not agree with R. Lépine that this something has a glycolytic power. His theory may be put thus:

(1) Glucose is converted to glycogen in the presence of an internal secretion. The conversion of fructose is not dependent upon the presence of this internal secretion.

(2) Glucose is free in the blood and the tissues are acted on by the internal secretion to make them form attachments with the glucose.

To continue the story of the development of the insular theory of diabetes. It was frequently noticed that the islets showed degenerative change in diabetes. This was noticed by E. L. Coie (1901) M.B. Schmidt (1902) L. W. Srovelen (1901 and 1909) and later by Weichselbaum, Strange, Kyrtle and J. Homans.

Pfluger's and Hédon's theories in 1907 and 1910 respectively that the anti-diabetic function of the pancreas is controlled by a nerve plexus in the duodenal wall was quashed by Minowski's removal of the head of the pancreas and duodenum without diabetes resulting, and subsequently removing the rest of the gland with ensuing diabetes.

Following Knowlton and Starlings Heart-Lung experiments of 1912, MacLeod and Pearce in the following year made investigations on the action of the internal secretion on glucose and/
and fructose and came to the conclusion that fructose utilising power remained longer than glucose - utilising power. Verzar in 1913 came to the same conclusion. Thiroloix and Jacob (1912) noticed that prolonged carbohydrate feeding caused diabetes and F. N. Allen attributed this to the excessive and prolonged strain leading to breakdown of the internal secreting mechanism.

J. de Meyer (Arch. di fixol, VII, 1909) was the first to give the name "Insulin" to the secretion of the islet tissue of the pancreas.

The acino-insular hypothesis throws no light on pancreatic function so that it needs mention only to excuse its presence here. Laquesse (Revue générale d'historologie, le pancreas 1906), we saw already, adhered to the "balancement" theory. Lombroso (1910), Rutmann(1905), Karakascheff (1906) give it their support. Herxheimer believed that when the islet tissue is injured, the internal secretion is supplied by the islets (1905). S. Saguchi (1920) an American and C. Seyfarth (1920) a German, have given the theory their support and at the present time Shields Warren has leanings towards this view (The pathology of Diabetes Mellitus 1930).

To biochemists the attempted and successful methods of extraction of insulin must be of engrossing interest, but to the comparatively uninitiated, figures only serve to weary. I will refer to these methods and attempts at extraction only in so far as they provide a very accurate barometer of scientific
scientific belief and investigation on the pancreas at this time.

A debt of gratitude is due to those who isolated and those who all but isolated the pancreatic hormone, but a far greater debt is owing to the men behind the scenes, who kept the great possibilities before the laboratory men, and when they seemed to have lost all hope, supplied new material for them to work upon. I refer to Laguesse, Diamare, Hédon and Schafer.

The literature on this subject of insulin extraction is enormous, and it is only possible to select the names of a few more famous men and hope that fame to genius:

"Like a gate of steel,
Fronting the sun, receives and renders back
His figure and his heat."

Minowski is again a pioneer. He first made the attempt at extraction and use of the hormone in 1892, but with no beneficial effects. Capparelli followed and claimed to have reduced glycosuria in dogs by administration of the extract. Ausset in 1895 recorded good results by giving raw pancreas, and Borrman confirmed his statements. Since these extracts were all given by mouth it is not surprising that Vanni and Burzagli found reason to deny the claims. The last two years of the century saw the climax of "the first fine careless rapture." Hougouneng and Doyen, Hédon and Lépine all made their contribution. Lépine used intravenous injections of normal lymph
The daily dose that defeats diabetes.

(Right) DR. FREDERICK GRANT BANTING.

“άλλ’ ὑστερον μὲν ἡλθον, ἐν καὶρω ημῶς.”
view that the alkali was the beneficial agent. N. C. Paulesco of Bucharest commenced work in 1916. He named the substance "pancreine" and obtained the best results of any workers so far, but his operations were upset by the German Invasion in 1916. E. Gley puts forward a claim to having anticipated the idea of Banting and Best by 16 years, but this claim has not been popularly accepted.

It is to Banting and Best, the Toronto workers, that we owe the isolation of insulin and the use of the hormone in treating diabetes as a practical possibility. The fact that Zuelzer, Scott, Murlin, and Paulesco came so near to discovering a method of extracting the hormone does not detract from the brilliant work of Banting and Best. Professor F. G. Banting, as he later became, and Charles H. Best, working in Professor J. J. R. Macleod's Laboratory in Toronto published their findings in 1921. In connection with this work, Professor Macleod was awarded the Cameron Prize in 1923, and Professor Banting received a similar mark of honour in 1927 from the University of Edinburgh.

Professor Banting's Cameron Prize lecture delivered in Edinburgh on October 30th 1928 makes clear the details of his discovery, the relative importance of the findings of various workers, and may eventually be taken as a reliable survey of a period in the history of the pancreatic function which is elsewhere complicated by a complexity of doubtful records. The
lecture is a delightful little story of boyish enthusiasm, inevitable setbacks, and the triumph of will power and tenacity over seemingly insurmountable obstacles. The story is that of the last step in pancreatic investigation leading to the knowledge of the gland which we possess to-day.

In the course of his lecture, after paying his compliments to the senate and thanking Professor Barger for his invitation to come to Edinburgh, he proceeds to an account of his early life. The hopelessness of his practice, his desire to obtain his fellowship degree in Edinburgh, and his ensuing studies are related. Banting relates how he knew of the Islets of Langerhans, of Wering and Minowski's classical experiment and his reading an article by Moses Baron in a Journal of Surgery which stated that when the pancreas is shut off by a gall-stone, its cells degenerate although the islet cells do not. Thus at the age of twenty-nine he seized upon this idea, consulted his colleagues and superiors, but got little support and so he went to Toronto to see Macleod. His spirits were a little damped by his reception, and it was only with difficulty that he obtained the use of Macleod's laboratory, an assistant, and some dogs to work on. The ups and downs I will not attempt to relate but will make brief mention only of the events which led to the isolation of insulin:—vizt:-

(1) The ducts of the pancreas were ligated and the extract obtained from the degenerated residue which contained the islets. This extract was injected intravenously and a fall in blood sugar/
sugar in depancreatised dogs was noted. He attributes E. L. Scott's failure to incomplete degeneration of the gland acini.

(2) Banting had the idea of getting rid of the toxic effects of pancreatic juice by exhausting the secretory function by injection of secretin before removal of the gland - the results were very satisfactory.

(3) He seized upon Laguésse's idea of new born animals having more islet tissue. The extracts were obtained at the abbatoir from Calves' (foetal) pancreas and the results were even more encouraging.

(4) Extraction of the hormone from the adult beef was now attempted on the principle of Zuelzer (1908) and Forschbach (1909) and by a special process was very successfully accomplished. Alcohol extracts which were later rid of alcohol by the distillation invacuo were used.

Thus was the story completed. Treatment of human diabetes was instituted and was a success. This was the climax of Banting and Best's labours in 1921.

J. J. R. Macleod now took the matter on hand. His whole laboratory was working on Insulin and its purification. Collip successfully tried a method of refining the product, but Best was more successful still. The giving of Glucose for overdosage with Insulin was discovered by the Toronto school. The unit of Insulin was defined and Insulin became a commercial preparation. Banting had wished to call the hormone "Isletin" but Macleod would not hear of this and for the/
the third time it was named Insulin. The establishment of a Clinic in 1922 for the treatment of Diabetes and the inauguration in Toronto of a Post-Graduate Course on Diabetes and Insulin treatment—Banting's cup of happiness overflowed. Here indeed is a story that would hold children from their play and draw old men from the chimney corner.

The Great War is an immovable barrier in the swathe mown by the scythe of time. Beyond it is a great field of interest, loving hoarding its secrets in books, and the sharing of these secrets is the inestimable privilege of the student of history. On this side is a seething mass of humanity. History cannot and does not exist. The War itself is as yesterday. Facts are cruelly put, theories propounded to serve their day. A consideration of pancreatic investigation shows that it has not escaped the change—time will mellow and some day history will, we hope, and know, result. Thus I propose to close my survey with the recognition of Banting's work—a gift from history which brings a boon of health and happiness to our present day.

I would only mention recent facts where they have put "finis" to the theories we have seen, or indicate whence may spring new knowledge of the pancreatic function, which may not yet be realised. The case of R. M. Wilder, F. N. Allen, M. A. Power, and H. G. Robertson, described in the Journal of the American Medical Association 1927. 89. 378. and which showed hyperinsulinism/
hyperinsulinism due to cancer of the islets clinches the insular theory of diabetes. Similar cases noted by Thalhimer and Murphy (1928) by Maclennahan (1927) and by Howland (1929) lend additional and irrefutable proof. Starling's acceptance of Roberts' "Metacasein" reaction, being due to trypic activity, is very satisfying. Mellanby's theory of the importance of diet in pancreatic secretion and his recognition of a psychic factor controlling enzyme formation, opens fields for new research.

From Pathology, from Physiology and from a knowledge of the evolution of knowledge concerning the pancreas will spring a new fount of ideas to be received by future geniuses and adapted to the benefit of man.