Theories of Carbohydrate Metabolism and Diabetes Mellitus, together with a Statistical Investigation into the Mortality of the Disease in Scotland from 1875 to 1910.

Thesis by

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It is curious to reflect that diabetes was known as a distinct disease characterized by thirst, polyuria and loss of flesh, centuries before its cardinal sign—the specific change in the composition of the urine—was noted. Celsus and others at the beginning of the Christian Era so described it, and Aretæus wrote of it under the name of diabetes, although it was only in the last century that diabetis mellitus and diabetis incipidis were clearly distinguished and accepted as separate and distinct affections.

As far as is known, Sushruta, an Indian physician, was the first to be aware of the change in the composition of the urine. It is not surprising that the discovery of its sweet taste in this disease should have been made first by an Indian physician, since, judging from the reputed relative prevalence of the disease...
at the present time, he must have had many more opportunities of observing it than his Western contemporaries.

It was not until the publication of the "Pharmaceutice Rationalis" of Thomas Willis in 1674 that glycosuria became a clinical entity and one stated to be found in all cases of diabetes. So far as present-day medicine is concerned, then, the discovery of glycosuria was not made until 1674.

The next discovery was made by Matthew Dobson of Liverpool, who, in 1776, not only obtained the sugar from the urine by evaporation, but also detected the sweet taste of the blood serum of a diabetic patient, and thus discovered hyperglycoceuria. He also noted the sweetish odour of diabetic urine, a phenomenon we now know to be due to the presence of acetone, and named acetonuria.

It was not until 1807 that Chevreul proved the sugar present in diabetic
urine to be glucose. Before the latter event — in 1796 — the dietetic treatment of the disease was introduced by John Rollo. The introduction of chemical tests for glucose in the urine came later, Frommer's test being introduced in 1841, Moörie's in 1844, and Fehling's quantitative method in 1849. The detection of the disease in its early stages was thus facilitated and now no disease is better known. Its causation, however, amidst the multitude of theories — and they grow more numerous every day — put forward to account for it, it remains as obscure as when Celsus first described it, or perhaps we should say, as when John Rollo introduced his dietetic treatment in 1796, for surely that was a great advance in treatment and pointed the way of subsequent research. Many theories then have been advanced to explain the disease, and it is to examine some of the more recent of these in a critical manner, and to
submit some ideas of the author's, together with statistics showing its mortality rates in Scotland from 1875 to 1910 as shown by the Registrar-General's returns, that this thesis is written.

It might perhaps be well not to begin by attempting a definition of the disease, since, until its cause is agreed on, no definition can be generally acceptable; and if, as many contend, the disease may be due in different cases to different causes, no definition can be generally applicable. The author, however, believing as he does, that the disease known as diabetes mellitus, whatever may have been the cause of its onset, is always ultimately due to one cause, and in order to make his position clear at the outset, may state that an attempt will be made to prove that diabetes mellitus is – the disease due to the
partial or entire absence of effective pancreatic internal secretion. The signs and symptoms of the disease, when it is not being appropriately treated, vary with the amount of effective pancreatic internal secretion available and are in inverse proportion to its amount. These signs and symptoms are hyperglycaemia, glycosuria, polyuria, polyphagia, thirst, vomiting etc. making up a definite clinical picture.

It will be noted that the word 'effective' is used in speaking of the pancreatic internal secretion. This is important, for it is quite possible to conceive of the pancreas being normal and producing its normal secretion, but, if this secretion is diverted from its normal function - it might be by combination with a toxin generated in the intestine by bacteria, or by abnormal metabolic processes - it will become
ineffective for its special duties.

The absence or diminution of effective pancreatic internal secretion thus may be, and probably in the majority of cases is a phenomenon secondary to another morbid condition.

In 1875, Rouchardat suggested that diabetes was due to disease of the pancreas and today many competent observers are of the same opinion. If this were always true, one would expect all cases dying of diabetes mellitus and coming to post-mortem examination, to show evident disease of the pancreas, microscopic if not macroscopic. Even Dupic however has been compelled to admit that in a number of cases dying of diabetes mellitus, or dying from intercurrent disease while suffering from advanced diabetes mellitus, have shown no macroscopic or microscopic evidence.
of pancreatic disease. It is true that more refined methods of examination are showing a larger proportion of cases with pancreatic abnormality; there still remain however many cases showing no recognisable pancreatic changes. This finding renders it necessary, in order to account for the disease, to fall back broadly speaking, on one of two hypothesis. Those who believe that diabetes mellitus is always due to disease of the pancreas maintain that disease of that organ may be present, although not demonstrable by our present methods and apparatus. The second hypothesis - and the number of its adherents seems to be ever on the increase - is that the disease is not always due to pancreatic disease, but also may be caused by disease or other abnormal condition of other organs. The position taken up by the
The author of this thesis is that while the disease in some cases may be initiated by abnormality of other organs, the fatal progressive disease denominated diabetes mellitus, is ultimately caused and invariably accompanied, by absence or diminution of effective pancreatic internal secretion. As has been suggested above, pancreatic internal secretion may be rendered ineffective without the pancreas being diseased.

What the author considers to be the function of this secretion will appear later, and, since that the pancreas has an internal secretion concerned in carbohydrate metabolism has been doubted by some and altogether denied by others, it is necessary, in the first instance, to place on record briefly the fact relied on to prove its existence. Laguness was the first to suggest that the pancreas had an internal...
secretion concerned in carbohydrate metabolism, the absence of which causes hyperglycemia and consequent glycosuria, and the available evidence for its existence is as follows:

1. Extirpation of the pancreas (in dogs and other mammals) causes hyperglycemia and glycosuria—it invariably does so. Boxa and neto's case proves that in the human being the same result is met with, when the destruction of the pancreas by disease is complete or almost complete.

2. a. Foschbach conclusively proved by his experiments with parabiotic dogs, one of which had been deprived of its pancreas, with resultant slight glycosuria only, but on separation developed diabetes—that the pancreas does supply a secretion, the absence of which causes hyperglycemia and glycosuria.

b. Hédon inserted a portion of
the pancreas of a healthy dog into
the circulation of the spleen of a
diabetic dog. The sugar almost
disappeared after some hours, to
return again after the connection
between the two animals was severed.
Heidou also found that if the
blood from the pancreatic vein
of a normal dog was injected
into a mesenteric vein of a
diabetic animal, the excretion of
sugar fell for a time almost
to the normal amount (3)
3. Partial extirpation of the pancreas
is not followed by hyperglycemia
and glycosuria.
4. If the gland is removed in
three pieces on different occasions,
the above phenomena do not occur
until after the removal of the last
piece.
5. If a fragment of the pancreas
is engrafted into another part of
the body without interference with
its blood connections, and the
remaining part of the pancreas ablated, hyperglycemia and glycosuria do not occur until the grafted fragment disappears or is removed, when diabetes occurs as surely as if the whole gland had been removed at once.

That injury of the solar plexus is not the cause of the diabetes following extirpation of the gland is proved by Minkowski's experiment of transplanting the descending portion of the gland into the subcutaneous tissue of the abdomen, allowing it to become engrafted there, severing the nervous connections of the graft and then removing the intra-abdominal portion - no diabetes resulted.

These various facts appear to the writer to prove indubitably that the pancreas does furnish an internal secretion which in some way does prevent hyperglycemia and glycosuria.
The exact source of this secretion is still a matter of dispute, but the evidence that it is supplied by the so-called 'Islets of Langerhans' is very strong. That it is not supplied by the digestive juices poured into the intestine by the pancreatic ducts is proved by the fact that if these juices are run off by a pancreatic fistula, diabetes does not occur, although wasting does. The ducts also have been obliterated by various substances without the occurrence of glycosuria. It would seem that the secretion is poured directly into the circulation.

Regarding the 'Islets of Langerhans' it seems to be agreed that an accurate histological description of the appearances seen in a normal pancreas in the great majority of cases is: the islets are formed of small groups of polygonal cells surrounded by a fine capsule.
which separates the cells from the surrounding acini. These groups of cells are richly supplied with blood by means of a copious network of capillaries. So pronounced is this feature that the islets have been spoken of as "pancreatic glomeruli." Other glands known to produce an internal secretion are similarly richly supplied with blood. These structural facts seem to the author to be of much importance, since they do not support the theory of a rapidly changing kaleidoscopic picture, such as those who urge that the islets are mere transformations of acini would appear to imagine.

These islets also, are practically always - as far as can be demonstrated - independent of the duct system of the gland and appear to be much more resistant to morbid changes than the acinar
portion of the gland.

Those who urge that the islets are not independent structures but merely transformed acini, have practically no evidence to put forward for their belief except occasional microscopic appearances that might be post-mortem changes. It is stated that pancreatic growth is a function of the islets, that the islet stage represents an internal secretory stage as opposed to an acinous or external secretory stage; and that these stages alternate with the same group of cells. This seems improbable and is certainly not paralleled in the performance of any other known human organ.

It is stated further that the cell islets are produced as the result of extreme activity of an acinar portion of the gland and practically represent exhausted acinar cells.

To these exhausted cells is
ascribed the function of providing one of the most important secretions in the body (Starling). This is hardly reasonable, but it indicates the straits to which the adherents of this theory have been reduced.

From the evidence adduced it would seem to be quite clear that the pancreas produces a secretion having for its function the regulation or control, in some manner, of the carbohydrate metabolism of the body.

Whether or not this secretion is produced solely by the 'Islets of Langerhans' is still 'sub judice', but the available evidence that it may be so, is very strong.

Assuming an internal secretion to be proved, how can we explain in terms of a common denominator, the causation of all cases of hyperglycaemia and glycosuria, including the grave disease diabetes mellitus? The greatest obstacle to the acceptance of any one
of the many theories that have been advanced, has been the inability to explain all cases in terms of that theory.

One matter which, to the author, appears to be of the utmost importance is the determination of the form in which the carbohydrate traverses the circulatory system. This question, so far as we are concerned, practically resolves itself into a determination of one of two theories. Does the carbohydrate traverse the circulatory system in the small molecular form of free glucose or in a combined form giving a larger molecular value?

The glycogenic theory is, that all carbohydrate ingested passes to the liver through the portal vein as glucose. The glucose thus conveyed to the liver is there transformed into glycogen. This glycogen is re-transformed into glucose as required, and paid out into the circulation as such.

According to this theory then, not
only does the carbohydrate traverse the circulatory system in the small molecular form of free glucose, but to the liver is assigned the all important function—all important, that is, to the holders of the glycogenic theory—of controlling and regulating the amount of sugar in the blood.

The great and life-long opponent of this theory was Pavy, who contended that carbohydrate did not traverse the circulatory system in the small molecular form of glucose. He supported his contention by irreproachable experimental work and proved that free glucose in the blood was excreted by the kidneys more or less in proportion to its amount in the blood. That glucose, as Pavy contended, is a constant constituent of the urine, is no longer denied, although a fierce and often bitter fight was fought before the fact was admitted.

Pavy believed that glucose was
metabolised at the seat of absorption in the intestine, by the lymphoid cells into protein and by the epithelial cells into fat. Any glucose not so assimilated passed by the portal vein — as glucose — to the liver, where it was transformed into glycogen, the circulation thus being kept free of any excess of free glucose. Perty does not clearly explain, so far as we have been able to ascertain, in what form the liver sends out its carbohydrate when its glycogen store is called upon for a supply, nor the mechanism of the process. He clearly does not believe that the glycogen is transformed into glucose and carried through the circulatory system in that form. He must have believed it to be carried as "a carbohydrate assimilated by synthesis into protein," in other words, that in the liver a process occurs similar to that which he believes to occur at the seat of
absorption. Thus, "Whether or not the linking-on operation in the construction of protein in the villi is related to that concerned in the production of glycogen in the liver it is impossible to say, but, as a matter of fact, the latter is as much the result of a building-up process as the former, and it is possible in both instances that the issue may be brought about by the same instrumentality."

If he believed this in regard to the building up of glycogen, he probably believed it also with regard to the transformation of glycogen into "a carbohydrate assimilated by synthesis into protein." Pavy's view that carbohydrate does not normally traverse the circulatory system in the small molecular form of glucose is making headway and is held by the writer.

Regarding this point the opinion of von Noorden may be quoted. "It used to be thought that the sugar
circulating in the blood existed either in a free state or in solution, but this view must probably be withdrawn, in favour of the hypothesis, that the greater part if not the whole of the sugar exists in a loose combination with other substances."

The experiments of Kolisch and Steykal point to the same conclusion, and these authors came also to the conclusion that urine sugar corresponds in quantity to that found in the blood—a fact that still seems to be disputed by some investigators.

To the mind of the writer however, the whole glycogenic theory, involving as it does, the passage of carbohydrate as free glucose through the circulatory system, and its utilisation as such by the tissues, and the erection of the liver to the position of high priest controlling the destinies of carbohydrate...
metabolism has been destroyed by
the results of recent successful
Eck-fistula operations.
The operations referred to were
performed by Bernheim and Voegtlin
of John Hopkins University and
are supported as to the conclusions
drawn from them by similar
successful experiments previously
carried out by Filippi.
In an Eck-fistula dog the liver
is practically excluded from the
circulation, since the portal vein
is anastomosed to the inferior
vena cava and the hepatic artery
brings only a small quantity of
blood to the organ. Some of the
animals lived for as long as ten
months and on an ordinary mixed
diet showed no urinary abnormalities.
It is apparent that if glucose
- as such - normally entered the
portal circulation from the intestine,
and was intercepted and converted
by the liver into glycogen, and
subsequently paid out from the liver in suitable quantities, and this is the glycogenic theory, then when the liver does not intervene between the portal and the systemic circulation - as it does not intervene when the Eck fistula has been made - there ought to be, there must be, hyperglycemia with consequent glycosuria.

It is not so.

The utmost that can be said is that the glucose tolerance is only slightly decreased. (Filippi)

"In our experiments we could confirm the view expressed by Filippi. With the exception of a few animals which were fed on large amounts of milk (800 c.c. to dogs weighing 8 Kgs.) no sugar could be detected in the urine." (Bernhein and Voegtlin.)

These experiments prove that utilizable carbohydrate does not traverse the circulatory system as
free glucose, since there is no liver to intercept the glucose and keep the circulation free from sugar, an essential dogma of the supporters of the glycogenic theory. These experiments are crucial and put out of court—once and for all—the importance ascribed to the liver, and consequently to glycogen formation in the liver, in carbohydrate metabolism. The liver, so far as carbohydrate is concerned, is a mere store and its storage functions can probably be assumed at need by other organs, for Filippi was actually able to demonstrate in some cases, that the muscles of *Eck fistula* dogs contained more glycogen than those of normal control animals. The experiments of Bamber, Sachs and Strauss on frogs deprived of their liver prove how little it has to do with carbohydrate metabolism. Strauss' conclusions
may be quoted: "The importance of the liver in preventing the appearance of sugar in the urine, when a large quantity of carbohydrate is rapidly administered, in human beings and in frogs, can be only wholly insignificant if the functions of the body are not being otherwise disturbed at the same time." 8)

The known facts in connection with liver diseases are also all in favour of the above view. Grave disease of the liver is seldom accompanied by derangement of carbohydrate metabolism. This is a very well known fact, in spite of which the importance of the liver to carbohydrate metabolism is tenaciously clung to by many observers, who seem to be obsessed by this idea, although hard put to it to explain how it is that the liver may be extensively diseased, may be - as
in acute yellow atrophy—almost disorganised, and yet no apparent disturbance of carbohydrate metabolism occur.

To refer once again to Bertheim and Voegtlin's paper, a case reported by Schulz and Müller is quoted by them. In this case a patient had, near the hilus of the liver, thrombosis of the portal vein, in which there was complete obstruction. Superficial compensatory circulation was fully established. At the autopsy no anastomosing vessels were found between the portal system and the liver.

The patient came to the clinic suffering from severe ascites, but otherwise in good condition. The fluid was removed every two weeks. The nutritional condition was perfectly normal as shown by the weight. This case, in that the liver was cut out so far as the portal circulation was concerned, was a modified
Eck fistula operation performed by disease in a human being. Glycosuria is not noted as occurring, nor would we expect it to in view of the experiments quoted above.

In his book 'Disorders of Metabolism and Nutrition' von Noorden writes:

"For the flow of sugar brought to it by the portal vein, the liver serves as a large and capacious reservoir. Almost all sugar is in the first instance retained here and deposited as glycogen in the liver cells. By this means the entire vascular system beyond the liver is protected from an excess of sugar. It is only very slowly and gradually that the sugar passes on from the liver, and it does so exclusively in the form of glucose. The process is so slow that even after a heavy meal of carbohydrate food, the amount of sugar is not appreciably increased in the arteries and veins of the body."

It seems to the writer that all
this is abundantly and conclusively disproved by the results of the Ehrlich fistula operation. The above pronouncement of von Noorden's also seems curiously at variance with that quoted on page 19 of this thesis.

As against this view also is Cammidge's statement that "the amount of glycogen in the liver depends largely on the intake of food, but never exceeds 150 grams (about 5 ounces) and as this only disappears after several weeks starvation, it cannot account for the whole of the sugar which is absorbed in a short space of time when a meal rich in starch and sugar is taken. It is therefore assumed that the excess passes through the liver and is laid down in the muscular and other tissues, also in the form of glycogen, thus accounting for another 150 grams. Even if the whole of the glycogen in the liver..."
muscles and other tissues of the body, and the sugar in the circulating blood, which is about 10 grams (½ ounce) or less, is allowed for, they do not still represent the whole of the carbohydrate that may be absorbed. It is consequently supposed that the balance enters into the constitution of the proteins, nucleo-proteins, and albumenoids, from which a carbohydrate has been obtained on treatment with an acid; it is probable also that a certain proportion may be turned into fat.

Even therefore if it were allowed that free glucose traverses the portal vein and is transformed into glycogen in the liver, it is apparently absolutely compulsory to admit that only a comparatively small quantity of the ingested carbohydrate can be accounted for in this way. This in turn makes it necessary to admit that
Ingested carbohydrate is disposed of in a form other than that of glucose, by other channels and methods, else the circulation must become flooded with sugar which would make its appearance in the urine. Since, then, it has to be admitted that some carbohydrate must traverse the circulation in a combined form, it seems illogical to deny that all utilizable carbohydrate does so, when that view explains all the difficulties attendant on the other theory, and raises no difficulties of its own.

von Noorden is clearly of opinion also that the diminished capacity of the organism for glycogen formation is the cause of the disease. He writes: "Disturbances in the function of the pancreas markedly diminish the glycogen storing capacity of the liver. This is one of the cardinal phenomena of true diabetes mellitus."
of the organs to form glycogen explains almost all the peculiarities of diabetic glycosuria. "...." The protoplasm is not able to assimilate the free hexatomic sugar in the blood and in the cells. Glycogen must first be formed (by polymerisation) .... It may be asserted with perfect confidence that the diabetic - in a degree corresponding with the severity of the disease - has lost the power of utilising carbohydrate. .... "The most important peculiarity of the diabetic condition consists in the loss of the capacity of those organs whose normal function it is, namely liver, muscles, and perhaps with certain restrictions, glands - to perform the function of taking from the blood the therein circulating glucose - largely derived from the ordinary carbohydrates of the food - and of storing it up as glycogen. So comparatively the same extent as they have lost this faculty so have
they also lost that of burning off the carbohydrates. For the natural fuel of the cell is not glucose but glycogen.

The above extracts have been given in extenso since they clearly show that if von Noorden accepted the theory now put forward by the writer, that - in the absence of effective pancreatic internal secretion - glycogen cannot be formed - a simple explanation will have been furnished of the difficulties of which he is so conscious.

The loss of the power of glycogen formation thus becomes - not the cause of the disease - but the result of the lack of effective pancreatic internal secretion; which latter is the true cause of diabetic mellitus. Glycogen is not the natural fuel of the cell; it is merely a storage form of carbohydrate, readily available in case of need. That glycogen formation is in abeyance in the absence of...
pancreatic internal secretion is proved by the small quantities found in depancreatized animals.

The rapidity also with which sugar appears in a diabetic, with a previously sugar-free urine, after the administration of carbohydrate, gives support to the same idea, since the transformation into and from glycogen must take on appreciable interval of time.

Most authors who hold by the glycogenic theory and contend that carbohydrate is paid out by the liver as glucose, also believe that free glucose is used up as such by the tissues. Even those who admit that carbohydrate does not traverse the circulatory system as free glucose believe it to be used up by the tissues as free glucose. Von Noorden obviously does not belong to this group since, as quoted above, he categorically states: "the natural fuel of the cell is not glucose but glycogen." Yet glycogen
is an insoluble substance.

It may be stated at once that it has never been proved that the tissues are able to utilise free glucose.

The conclusions drawn from the experiments of Knowlton and Starling, and which seemed to prove that free glucose plus an extract of the pancreas was used up when perfused through an isolated diabetic heart, have been unreservedly withdrawn by Patterson and Starling.

There are many arguments against this conception, one of the most effective being that while it has never been proved that the diabetic organism does not utilise carbohydrate, many considerations lead to the conclusion that it cannot utilise carbohydrate presented to it as free glucose. In other words, free glucose is unutilisable carbohydrate, so far as the tissues are concerned.

The writer frankly accepts this
proposition and states unequivocally that free glucose is unutilisable carbohydrate and that, in normal conditions, free glucose in the blood is— for the most part— waste product.

If the tacking—on of glucose to its carrier was all that was defective, the glucose would still reach the tissues and be utilised, although owing to its presence in the blood in a free state, much of it would rapidly filter off with the urine.

Were this the whole trouble, it is obvious that the malnutrition resulting could be prevented by an increased ingestion of glucose or other carbohydrate. Clinical experience, however, proves that this method of treatment invariably prejudices the course of the disease, and indicates that the fault is not a mere matter of the carrier of carbohydrate in a small molecular form,
but proves that carbohydrate in that form is not utilised.
In advanced diabetes mellitus the blood is loaded with glucose, which is obviously not utilised, since the body wastes under such conditions. The experiments of Baumgarten, 22 of Verzar and of Murkin confirm this statement for depancreatised animals.

Pavy's theory that glucose is assimilated in its passage through the intestine and passes to utilisation in the tissues, seems to the writer to involve an unnecessarily complicated metamorphosis and one that would require to be repeated in the liver on the transformation of glycogen into transportable carbohydrate, and also to be repeated in the reverse direction at the seat of utilisation in the tissues.

The writer's idea, is that the process is not an assimilation
in the usually accepted sense of the term, but a loose tacking on of carbohydrate to protein, so that a large molecule is formed, thus preventing excretion by the kidney. That is all that is necessary and does not imply that the carbohydrate forms an integral part of a stable compound, but that it is merely tacked on for purposes of transport and is easily detachable where and when needed. The form in which the carbohydrate is tacked on to protein (through the instrumentality of the pancreatic internal secretion) is a matter of paramount importance. In the writer's opinion, the chemical formula of the carbohydrate so attacked is not that of glucose, but of a nearly allied, and, in a free state, much more unstable body, which he has named pro-glucose. This substance he regards as the forerunner of the free glucose found in the blood.
and consequently in the urine.

This attachment between pro-glucose and proteid by means of the pancreatic internal secretion, which, as it were, sensitises the proteid, by providing it with a haptophoric group capable of attaching pro-glucose to itself, takes place immediately the pro-glucose is formed.

This formation of pro-glucose is conceived of as occurring in the intestinal wall during the passage of ingested carbohydrate through it. It (pro-glucose) also is conceived of as being the form assumed, when glycogen is transformed into utilisable carbohydrate in response to a demand by the tissues for that substance, and when carbohydrate is set free, as the result of the breaking down of the tissue elements in severe diabetes.

Since sensitised proteid — as above defined — is constantly present in the circulating blood when the pancreas is
intact and producing effective internal secretion, the lacking-on of proglucose to protoid can occur if necessary, wherever the proglucose is produced.

This attachment of proglucose to protoid means therefore two things:

In the first place it means, that owing to the large molecular gripping, carbohydrate can be carried through the circulation without passing off with the urine.

In the second place it means, that the carbohydrate is carried in a form that can be immediately utilised by the tissues, whether for the purposes of combustion, building up into stable tissue, or storage as glycogen.

If proglucose is set free in the blood, in the absence of sensitised protoid and is not immediately used up for combustion, building up or storage as glycogen — or perchance as fat — it becomes transformed into glucose.
Glucose, as such, is not utilizable. When free glucose occurs in the blood, it is a waste product; it is a carbohydrate substance that has escaped utilisation. According to this view the proportion of glucose normally present in the blood is merely an expression of the prodigality of nature, more glucose being given off than can be utilised. The portion not utilised appearing as glucose. That this proportion should be more or less constant under normal conditions is what we would expect and represents a much smaller loss than occurs— for example— in the working of most machines; in other words, the efficiency of the human machine is high. In the present instance the efficiency may be increased, since any of the circulating glucose again coming within the influence of the intestinal wall would be treated as ingested glucose and transformed again into proglucose and so.
in the presence of sensitised protein, again become utilisable.

Sensitised protein then, is conceived of as existing in the circulating blood, ready at any time, in proportion to its amount, to attach pro-glucose to itself for purposes of transport to the site of utilisation. Pro-glucose produced at the site of utilisation is at once used up. This consideration explains how it is that carbohydrate can be used up - as evidenced by the dextrose-nitrogen ratio - in diabetic animals and human beings.

Briefly put, the above is the working theory of the writer.

He believes it can reasonably explain all the known facts concerning alimentary, composite and chloridized diabetes and any theory that can do that is worth of consideration. He does not mean to assert that free glucose may never be directly utilised by the tissues under any circumstances. If this does occur, however, it must be
an exceptional mode of procedure and in conformity with the rule that the body, under exceptional circumstances and to a limited extent, may be able to proceed in an unusual way, or produce unusual reactions.

The glucose injection experiments can be quite simply explained by the injected glucose entering within the sphere of influence of the intestinal wall and so being transformed into fructose which is utilisable and which becomes transportable in a utilisable form in the presence of sensitised protein.

It is noteworthy in this connection that the slower the injections and the smaller the quantity (per unit of body weight) injected, the greater the quantity of the injected glucose that disappears. Injected glucose in a debauceratized animal does not disappear.

It will be convenient at this stage to take up the consideration of phosphorus diabetes and to endeavour to explain it in terms of the above theory.
The ascertained facts with regard to phloridzin diabetes are briefly as follows: The injection of phloridzin causes glycosuria — the glycosuria continuing as long as the phloridzin is injected. Hyperglycosuria is not present except perhaps to a slight degree, this being due according to Paysy and others (i.e. Coole and Kolisch) to absorption into the bloodstream of some of the glucose produced in the kidney by the action of the drug.

The amount of sugar in the urine is much greater than can be accounted for by the amount of sugar in the blood.

Glycosuria continues after all carbohydrate substances in the body, such as glycogen, have been got rid of.

If the administration of the drug is kept up the animal dies in coma, showing all the signs and symptoms of grave diabetes mellitus.

It is practically universally admitted that these results are due to some
action or effect of the drug and that the locus of the action is the kidney. This was demonstrated first by Luntz, who placed cannulae in the upper portions of the two ureters and injected phloedizin into one renal artery; on that side sugar appeared in the urine in two minutes; on the other side not until three minutes later, the delay being equivalent to the time necessary for the drug to be transported from the injected side to the other side. Two theories have been advanced to account for these phenomena. One is that the drug damages the renal epithelium and so allows an increased quantity of the free glucose of the blood to escape into the urine; the other is that the drug by its own action on the blood circulating through the kidneys, or some interaction between it, the renal epithelium and the blood circulating through the kidneys.
causes a dissociation of glucose, which therefore appears in the urine in abnormal quantities.

The first theory appears to the writer to be untenable even allowing for the peculiarity discovered regarding the avian kidney—its indeed the peculiarity be a kidney peculiarity and not a blood peculiarity—of preventing the transmission of glucose from the blood into the urine, although a certain degree of hyperglycemia is produced—a degree of hyperglycemia that would be at once apparent as increased glycosuria in a mammal. If, however, phloridzin is administered to a bird under these conditions, glycosuria at once ensues, as in mammals. This is taken to prove that the drug damages the renal epithelium of the avian kidney and so permits the escape of glucose in the urine: and the
same explanation is held to apply to the mammalian kidney. That changes in the epithelial cells of the kidneys should be sometimes found after the prolonged administration of phloridzin need occasion no surprise, since the process induced is not only an abnormal process, but also an abnormally active process.

This theory, however, does not and cannot explain how it is, that the quantity of glucose excreted in the urine greatly exceeds the quantity of free glucose in the blood - a constant phenomenon; nor can it explain the absence of hypoglycaemia, which certainly should occur if the theory had a basis in fact.

Further, if the glycosuria was due to damage to the renal epithelium - an epithelium we have reason to believe not easily or readily susceptible of repair.
we should expect the glycosuria to continue after the elimination of the drug had ceased. It is not so; glycosuria continues only as long as the drug is being excreted.

Again, when all the carbohydrate material of the body, such as glycogen, has been got rid of, the dextrose-nitrogen ratio becomes constant, according to Graham-Lusk, indicating a specific action on the part of the drug, and strongly militating against the epitheliun-damage theory. It is a matter of clinical experience also, that when the kidneys in a case of glycosuria become diseased, as by the onset of granular atrophy, the glycosuria diminishes. Experimental induction of nephritis also, in phlorizine or adrenalin poisoning, causes a diminution of glycosuria.

The theory that phlorizine, in
some way, causes a dissociation of glucose from some substance in the blood while circulating through the kidney, appears to the writer to explain satisfactorily all the phenomena regarding this form of glycosuria in all its stages, and what is of infinitely more importance, can be explained in terms applicable to the phenomena of simple and composite diabetes mellitus which phloridzin poisoning in its early and late stages almost exactly imitates. The most remarkable differences between them are the absence of hyperglycaemia and the undiminished power of carbohydrate metabolism in phloridzin poisoning; if these differences can be explained the three conditions fall into line, and the following is an attempt to do so.

Pro-glucose stacked on to protein through the intermediation of effective pancreatic internal secretion.
is set free in the kidneys by the action of the phloridzin. Being set free in excess of any metabolic requirements of the kidneys it immediately becomes glucose and is excreted as such. This excreted glucose is, of course, wasted and the wastage has to be made good. The glycogen stores are therefore called upon to make up the shortage in utilizable carbohydrate.

The substitution of these stores is the next result. Glycogen is converted into bro-glucose and tacked on to protid in the manner previously indicated - no hyperglycaemia will ensue therefore from this transformation. This additional supply of loosely combined carbohydrate, in passing through the kidney, will be set free as described above. The easily available supplies of carbohydrate having been thus got rid of and the demand for carbohydrate continuing, protid disintegration
begins as in composite diabetes. The pancreas being intact, carbohydrate still can be carried through the circulation in a loosely combined and utilisable form. Thus it is that the proglucose split off from the protein and not immediately utilised, is attached to the sensitised protein and so reaches the kidneys where the same process of disintegration takes place. Thus also, hyperglycaemia need not appear even in the stage of protein disintegration. Hyperglycaemia, however, occasionally occurs in advanced chloridric poisoning, and is quite reasonably explained by failure of the pancreas to stand the strain of continued excessive secretion under abnormal and very debilitating conditions. During the whole course of chloridric poisoning therefore, the glucose set free by the agency of the drug is derived from proglucose loosely
tacked on to protein and circulating in the blood in that combined state. The writer therefore is quite at variance with Pavy, Brodie and Siau when they state: "when the animal is starved so that no fresh sugar is available, the renal cells attack the protein molecule itself setting free the sugar that can be derived from it and also the nitrogen containing moiety."

The writer suggests, as clearly set out above, that the protein molecule is disintegrated by the tissues, as in composite diabetes mellitus, in response to the urgent need of the organism for utilizable carbohydrate: the protein disintegration then, is no more the work of the kidney cells than it is in composite diabetes. So long as the pancreas is able to furnish internal secretion, the glucose thus set free is lostly combined to protein and circulating in this combination, no
hypoglycaemia occurs. When the pancreas fails adequately to perform its internal secretory function, hyperglycaemia and glycosuria will occur.

In composite diabetes the pancreas has failed, and therefore hyperglycaemia and glycosuria both are present.

Bouchanet in his Goutetonian lectures, in criticizing the theory of Pavy, Brodie and Sian, that phloridzin acts upon a substance already existing in the blood and converts it into glucose or rather frees the combined glucose, states: "It would seem necessary to suppose that it (phloridzin) produces excess of this intermediate substance in the blood by its own action." This supposition does not seem to the writer to be necessary. The only connection is an indirect one - the drug causes excess of glucose to be lost to the organism and the organism (not the phloridzin) endeavours to make good the loss,
and would do so if the drug was discontinued, but the efforts of the organism are frustrated by the continued administration of the drug. If there is any excess of the intermediate substance in the blood (and there is no proof of this) it is due to the efforts of the organism to compensate for the starvation of carbohydrate. The absence of hyperglycaemia, and the diminished power of carbohydrate metabolism in chloridrin diabetes are thus adequately and reasonably explained by assuming the presence of effective pancreatic internal secretion, acting in the manner indicated.

The phenomena of acidosis and coma, common to the advanced stages of chloridrin and composite diabetes, are therefore due to the same causes, which latter are generally assumed to be the abnormal disintegration of the tissue elements.
in an effort to produce sufficient utilizable carbohydrate.

It will now be apparent how alimentary glycosuria, diabetes mellitus, and phloridzin diabetes can be all explained in terms of the same common denominator.

In alimentary glycosuria and early diabetes, hyperglycosemia and glycosuria are due to absorption of carbohydrate as pro-glucose in excess of the power of the existing pancreatic interval secretion to combine it with protein. The excess of pro-glucose - the unattacked pro-glucose - becomes converted into glucose and circulates in the free state, thus causing hyperglycosemia and glycosuria.

As the disease progresses - in other words, as the amount of effective pancreatic secretion becomes less - the amount of utilizable carbohydrate will become proportionally less until the amount derived from
the usual sources of supply is insufficient to meet the needs of the body. Then it is that protein disintegration begins in an attempt to supply the necessary carbohydrate in a utilisable form. Composite diabetes has set in. Much of the carbohydrate set free from protein is passed, since though set free as free glucose and therefore utilisable where set free if required it cannot, in the absence of effective pancreatic internal secretion, be tricked on to protein and so carried in a utilisable form or stored as glycogen. This increases the hyperglycemia and glycosuria.

Paey believes that excess of glucose in the blood is detrimental to the organism and favours the transformation of alimentary into composite diabetes. This harmful result he attributes to a poisonous influence of the glucose per se; but it has been conclusively proved that glucose is
not a poisonous substance, and therefore the aggravation of the disease accompanying hyperglycemia cannot be due to any poisonous effect of glucose per se. Yet the fact that persistent hyperglycemia is detrimental and tends to aggravate the disease is not disputed. How can we explain this fact in terms of our theory?
In alimentary glycosuria and in mild diabetes, the blood can be freed from excess of glucose by proper regulation of the diet and the patient is admittedly in a better condition in every way, as a result. The idea of the writer is, that this result is due to the amount of carbohydrate absorbed, being such that it all can be effectively dealt with by the available amount of pancreatic internal secretion, such amount of carbohydrate being sufficient for the needs of the body from that source.
Should the amount of carbohydrate that can be so dealt with be insufficient to meet the needs of the body, then composite diabetes sets in, since an effort to obtain the minimum quantity will mean the disintegration of protein.

In our opinion the evil results of hyperglycaemia in mild diabetes — assuming mild diabetes to mean cases in which the urine can be kept sugar-free and the patient in good condition by regulation of the amount of carbohydrate ingested — are actually due to the carbohydrate ingested in excess of what can be normally dealt with by the available quantity of effective pancreatic internal secretion.

Should such an excess be administered the result will be two-fold: first, a demand for pancreatic internal secretion in excess of the powers of the pancreas to provide it, will be created. This will cause speedy exhaustion of the gland.
and a lessened output of internal secretion. It will probably also mean that the secretion produced will be relatively inefficient, since the quality is likely to suffer as well as the quantity and an attempt might be made to sensitise far more protein than the amount of available internal secretion actually allowed, with the result that what was sensitised, was not sufficiently so for its purpose; the resulting combination with glucose not being sufficiently firm to carry it to the site of utilisation.

Second, a vicious circle will be established, since glucose coming again within the influence of the intestine can be re-transformed into proglucose and so be an element in raising the demand for pancreatic internal secretion. When there is excess of glucose in the blood, this vicious circle will be in existence. This consideration also affords a reasonable explanation of why it is
that hyperglycaemia once induced, may persist for a longer or shorter period, 
after the cause has been withdrawn, 
and of the good results obtained in 
many cases by the combination of 
fasting and purgation. 
So long then as only that amount 
of carbohydrate is given which can 
be easily combined by the available 
pancreatic internal secretion, no 
harm is done. Should however, 
that amount be insufficient to 
supply the needs of the body, the onset 
of composite diabetes will not be 
prevented in spite of the most careful 
dieting, although its degree may be 
controlled to some extent by such 
means. It will begin as an 
attempt by nature to supply from 
another source, what she has been 
acclimated to get largely from 
ingested carbohydrate. 
Since composite diabetes invariably 
means hyperglycaemia, the 
disintegration of protein is itself
a source of aggravation of the disease. Yet this process of protein disintegration is not a new process superadded to alimentary diabetes as is argued by Bouadouquet: it is merely a gross exaggeration of a process that has been going on all the time; for protein disintegration is as necessary as protein integration, or as carbohydrate combustion. At first the increase in protein disintegration will be a small increase; its amount will depend on the degree of failure of the pancreas to produce effective internal secretion. Theoretically therefore, when the amount of effective pancreatic internal secretion is sufficient to combine enough carbohydrate for the needs of the body, only that quantity of carbohydrate should be administered. Hyperglycemia can then be avoided and the urine kept sugar-free, if some effective pancreatic internal secretion remains but not enough to
provide the minimum amount of utilisable carbohydrate, from ingested material, necessary for the needs of the body, that quantity of carbohydrate should be given which does not increase the existing hyperglycosuria and consequently the glycosuria.

When no effective pancreatic internal secretion is available, or very little, it matters not whether carbohydrate is administered or not, except that owing to alkaline or other constituents of the carbohydrate, it may stave off coma, but this property has probably nothing to do with carbohydrate metabolism in the sense referred to.

The theoretical conclusions, therefore, would appear to agree very closely with the results of clinical experience in the treatment of the disease.

Bouquenel states his belief that the main fact of diabetes is an
internal formation of sugar probably from fat: in the first instance by defective assimilation and storage of fat: and later by actual breaking down of body fat. He believes such an explanation of the phenomena of diabetes to be capable of embracing both alimentary and composite cases. The causal agent he believes to be a toxin produced in the course of normal metabolism, and under normal conditions, neutralised by the pancreas.

It follows from this theory that there is—in Bouchaquet’s opinion—no such thing as ‘alimentary diabetes’ but only what is designated ‘composite diabetes,’ since the distinguishing feature of the latter condition has always been held to be the internal formation of sugar. Composite diabetes has always been held to be accompanied by wrong katabolism characterised by the
formation, in excessive quantities, of various bodies—the acetone series of bodies. If, therefore, diabetes is composite from the beginning, we would expect to get these bodies in abnormal quantities, from the beginning of the disease—in the so-called mild diabetes. This has never been demonstrated nor asserted. The formation of the acetone series of bodies in excessive amounts is confined to ‘composite diabetes’ as ordinarily understood and this consideration alone is a serious obstacle to Bouchaquet’s theory, the more especially since he insists that the probable source of the sugar is fat, which from its chemical structure is believed to be able to produce acid bodies with facility when undergoing catalytic changes.

This theory also, cannot explain the undoubted benefit to a mild diabetic of restriction of carbohydrate diet, since he believes that excess of glucose in the blood (hyperglycæmia)
cannot aggravate the condition. He writes: “To suppose that the presence of the excess of sugar in the system acts poisonsly and leads in time to a destruction of the body cells, of such a nature that the very poison at work is one of the products of disintegration, is absolutely contrary to all analogy in vital chemistry.” It follows from this that the administration of carbohydrate in excess, should do no harm in mild diabetes. This is absolutely contrary to clinical experience. This theory therefore does not touch the question of alimentary diabetes, as ordinarily understood, nor the question of alimentary glycosuria as distinguished from alimentary or mild diabetes. He cannot “explain alimentary diabetes in terms of composite diabetes,” since for him the former does not exist. His theory that a toxin is formed during normal metabolism, which
toxin is normally neutralised by the pancreas has no reliable evidence to support it. It seems against the laws of nature to imagine that a normal process in the body can produce a toxin, to neutralise which a special secretion is necessary. Nature, so far as we know, does things better than that. Waste products are produced and eliminated. Products which if retained in the body would do harm, but we know if no waste product, which we can point to as being a toxin neutralised by the pancreas, and we ought to be able to demonstrate it if the process is a normal one.

The inference therefore is, if we believe Bouchardet's theory, that the neutralised poison is used up or retained in the body—which is unthinkable.

Any theory of diabetes must explain cases where no morbid changes can be detected in the pancreas, but
Bouguer's theory would seem to postulate a much greater frequency of diabetes than happily exists; for if some specific and imported toxin - specific that is to the disease, and imported in the sense of not being a normal product of the body - is not present, but a toxin of constant presence, produced by normal metabolism, then the large number of cases showing grave disease of the pancreas and no diabetes are inexplicable. If this theory is true, they ought to have diabetes and the disease ought to be much commoner than it is.

It seems to be generally agreed that there is little evidence to support the belief that carbohydrate is not used up in diabetes. This carbohydrate, however, in advanced diabetes, is probably obtained by cleavage from protein, the carbohydrate at the moment of cleavage, being in a utilizable form, and thus a certain quantity of carbohydrate
could be used up by the tissues in the absence of effective pancreatic internal secretion.

Cambridge seems to incline to the view that over-production of sugar is the main cause of the disease, as opposed to diminished consumption. \textit{v. Hoorden} also holds this view.

This whole theory is built up and dependent on the so-called glycogenic function of the liver, which has already been dealt with.

\textit{Magnus Levy}, in his Cartwright Lectures, states that he regards a primary disturbance of the sugar-splitting process, as the essential factor in severe cases. He considers that the complete acceptance of the view that diabetes arises only from an increased formation and mobilisation of sugar must lead to the conclusion that proteins and fats are normally transformed into sugar. There is however no justification for such a conclusion.
Magnus Levy maintained, as does the author, that the conception of diabetes as a concrete unity is justifiable, since the metabolic disturbance and its intensity dominate the pathological process.

The author does not agree, however, that 'a primary disturbance of the sugar-splintering process, is the essential factor in severe cases,' but believes as he has repeatedly stated, that the fault is that the carbohydrate cannot be carried through the circulation in a utilizable form owing to the absence of effective pancreatic internal secretion.

Biedl states '… we are justified in concluding that the pancreas, by means of its internal secretion, inhibits the formation of sugar in the liver. ... Suppression of pancreatic activity abolishes the normal check upon the formation of sugar, in consequence of which the glycogen
Present in the organism is released, that is to say, the glycogen derived from the carbohydrate in the food or in default of these, from other material, is converted into glucose; and as a consequence hyperglycemia and glycosuria follow. . . . The normal pancreatic hormone is a substance which inhibits the diastatic conversion of glycogen into sugar.

It will be observed that the writer would be in complete agreement with the conclusions of Biedl so far as already formed glycogen is concerned; if, instead of assuming that the pancreatic internal secretion inhibits the diastatic conversion of glycogen into sugar, it was assumed that its function was to prevent free glucose appearing in the blood by attaching the free glucose to protein at the moment of the conversion from glycogen. In this sense the pancreatic internal secretion inhibits
the formation of sugar—glucose—by the liver and so prevents hyperglycemia and glycosuria. This process also retains the carbohydrate in a utilisable form and thus prevents the necessity of obtaining utilisable carbohydrate from the destruction of body tissues.

Several other theories, such as that of Wells, and of Chauveauux and Kaufmann have been put forward, but it seems unnecessary to go into these since the writer cannot agree with them and his reasons will be sufficiently apparent from a consideration of what has been written already.

Cohnheim's theory has been disproved. Boruttau has suggested that the adrenals produce a hormone which sets in motion glycochy in the liver, while the pancreas furnishes another hormone in its internal secretion which antagonises the sugar mobilising power of the adrenals.
This raises the whole question of the ductless glands and their interrelations, a most fascinating if, at the moment, endless subject, and the writer must therefore confine himself to a few general statements, indicating his provisional attitude on this subject. The fashionable doctrine at present seems to be that the secretions of the various ductless glands may antagonise each other and to most of them is attributed an inhibitory influence over the pancreas.

This theory of antagonism between secretions seems to the writer to be an unnatural and illogical one. That nature should provide one secretion to antagonise, or render ineffective, another secretion, also produced by herself, and both produced by highly specialised glands - presumably for specific purposes - he is unable to comprehend. Yet it seems to be widely held. The writer believes that each
secretion has its own special function to perform, that secretions do not antagonise each other but on the contrary work together for the good of the whole organism. The action of one secretion may supplement that of another but does not antagonise it. In exceptional circumstances it may be able, even to take up its functions in some degree. It seems more reasonable to suppose that the enlargement of the hypophysis cerebri found in thyroidectomised animals is an endeavour on the part of the hypophysis to take the place of the thyroid, than to suppose it to be due to the removal of an inhibitory influence of the thyroid secretion over the pituitary activity.

The theory that certain glands produce 'toxins' requiring to be neutralised by other glands appears to the writer so unnatural as to be
 untenable. Their production moreover has never been demonstrated. It is stated, for example, that the toxic products of the thyroid are neutralised by the parathyroids, but the available evidence does not support the idea.

The position of the adrenal glands is peculiar and much work has been done concerning them. It cannot be reviewed here but as Cambridge states "All the researches tend to show that the adrenals exert an important influence on carbohydrate metabolism through their internal secretion. Physiologically their task appears to be to mobilise the sugar from the liver, and probably also from the tissues, possibly through the intermediation of the nervous system." The position of the adrenal secretion is peculiar in that it seems, in a greater degree than the other internal secretions, to have an effect on the body generally and on the
whole musculature in particular. It may be that the influence of adrenaline is necessary for the proper combustion of carbohydrate brought to the tissues and that by its means the extent of the call for utilisable carbohydrate is determined. If this call is sudden and far in excess of physiological requirements-as it would be in the ordinary adrenaline injection experiments where the amount injected is enormous compared with what is normally poured into the blood-the amount of glycogen transformed into produce would be large and the pancreas being unprepared for such a call, the amount of sensitised protein in the circulation would be insufficient to attach the whole of the produce produced which would therefore appear in the blood as glucose. It is significant that repeated injections of adrenaline ultimately fail to produce glycosuria and points to the pancreas being
ready to supply sufficient internal secretion to meet the exceptional demand. It is significant also that when a sufficiently dilute solution is used (100,000 to 200,000) it can be allowed to flow into a vein at the rate of 2 c.c. per minute, without sugar appearing in the urine. (Ritzmann).

That the body reacts to adrenalin even when the glycogen reservoirs are empty, in no way invalidates but rather supports this theory, since a demand for carbohydrate that cannot be met in the usual way is met by disintegration of the body tissues such as occurs in composite diabetes. According to this theory then, the secretions of the pancreas and of the adrenals would be complimentary and not antagonistic as is made out by Zuelzer, Dohrav and Marxer. Surely a much more natural and reasonable idea. Additional support is lent to it also by the results of Fronius.
and Mayer's experiments, which showed that extirpation of the adrenals prevents the glycosuria that would otherwise result from depancreatization.

The experiments of Mayer who showed that extirpation of the adrenals prevents glycosuria after diabetic puncture support the same conclusion.

Pituitary Gland.

Overgrowth of this gland is found in acromegaly, which is frequently accompanied by glycosuria: when hypopituitarism is believed to occur - in dystrophy adiposa genitalis - glycosuria is practically unknown. Gortsch, Lushing and Jacobson came to the conclusion that the pars nervosa et intermedia was the part of the gland concerned with carbohydrate metabolism. Manipulative interference caused glycosuria, with diminution of tolerance for carbohydrate for several days: the glucose they assumed came from glycogen. Their results they
supposed to be due to an increased amount of the secretion of the posterior lobe being poured into the blood.
If the amount of this secretion is increased, as it presumably is, by ablation of part of the gland, or other experimental permanent injury to the gland, the assimilation limit for carbohydrate is permanently raised. Under such conditions, if posterior lobe extract is injected subcutaneously or intravenously, the high carbohydrate assimilation limit is lowered:

furthermore, they state, the extract lowers the carbohydrate tolerance of a normal animal and if given in sufficient quantity may cause glycosuria.

If we accept the above results as facts, a simple explanation -- and one not involving antagonism between glands -- would be that the glycosuria was due to an altogether abnormal, and from the point of view of physiological need, totally unnecessary call for easily assimilable carbohydrate.
This is obtained in the way usual with sudden calls—by the mobilisation of glycogen. The pancreas however, is not normally activated to produce internal secretion by a physiologically unnecessary demand for carbohydrate; consequently its production of internal secretion is insufficient to combine all the proglucose produced and free glucose appears in the blood and consequently in the urine. Permanent oversecretion of one part—the pars nervosa et intermedia—of the pituitary gland would thus be liable to cause chronic glycosuria, as often occurs in acromegaly. It is probable, assuming, as seems reasonable, that the two parts of the gland are normally mutual co-workers to one physiological end, that symmetrical and equal enlargement of both parts would not cause glycosuria, since then the physiological need would correspond to the call for carbohydrate and the pancreas be activated accordingly.
The theory of antagonism between the two glands is thus unnecessary. The increased tolerance with diminished functioning of the posterior lobe is thus easily explained, since the call for easily assimilable carbohydrate will be lessened and will certainly never be more than the actual physiological needs of the metabolic processes presided over by the pituitary gland as a whole.

The Thyroid Gland.

That the secretion of the thyroid gland has a function to perform in connection with metabolism is agreed: that it is specially concerned with protid metabolism seems to be generally allowed. It also must be allowed that the activities of the gland must mean, directly or indirectly, a demand for carbohydrate; and, that when the gland is hyperactive, as it is in
exophthalmic goitre, there will be an increased demand for carbohydrate. This demand, as in the analogous case of hyperpituitarism, may be in excess of physiological requirements and so lead to insufficient production of pancreatic internal secretion, this in turn, as has been previously explained, leading to hyperglycosuria and glycosuria.

An associated pancreatic lesion, as supposed by Cecil and by Spie, is therefore not essential. As supporting this position, it has been shown that thyroidectomy, providing the parathyroids are preserved, increases the carbohydrate tolerance and in the human myxedematous subject, the same phenomenon is observed. Here the demand for carbohydrate is diminished, it is probably stored in other forms (fat) and the tolerance is increased.
As Garrod[2] has pointed out, the increase of glucose tolerance in both hypopituitarism and hypothyroidism is accompanied by an increased formation of fat, which may have something to do with the increased carbohydrate tolerance.

The thyroid and pituitary glands are thus brought into line, and the pituitary hypostrophy known to occur after removal of the thyroid gland is quite simply explained as vicarious activity.

Para-thyroid glands.

It is impossible to go into all the ascertained points with regard to the parathyroids, which I may suppose to have an opposite influence to the thyroid on carbohydrate metabolism, mainly because their excision leads to diminished tolerance for carbohydrates. It seems to the writer quite as reasonable and more consistent with the facts to
assume that the actions of the thyroid and the parathyroids are complimentary actions, and that the parathyroid secretion has something to do with the proper disposal of the carbohydrate called for by the thyroid, for its special and peculiar activities.

The point the writer is anxious to emphasise is, that there seems to be no adequate reason to suppose that glands work in antagonism to each other, or that special glands are necessary to counteract poisons normally - as many state - formed in the body.

It is much more natural, reasonable and logical to assume that nature does nothing of the kind.

Mortality Rates from Diabetes.

As shown by Williamson, there can be no doubt that the mortality from diabetes is steadily increasing,
practically the world over, that writer states that, in England it is rapidly increasing, and the same statement——as evidenced by the statistics given below——applies to Scotland.

For England, Williamson states, the mortality in 1857 in males was 75 per million living; in 1907 it was 103 per million living; amongst females it was 57 in 1857, and 90 in 1907.

The corresponding figures for Scotland are:

males 21 and 79; females 20 and 87,

so that while the mortality is less in Scotland than in England, it also is rapidly on the increase.

The statistics for Scotland given below were obtained from the Annual Detailed Reports of the Registrar-General and the figures have been extracted from the year 1875 up to and including the year 1910.
The statistics for 36 years are thus presented. The mortality rates in every case have been calculated to 100,000 of the estimated populations. These rates are given for both sexes taken together and for each sex separately. The figures are given for "All Scotland," for "The Principal Town Districts of Scotland," and for "All Scotland minus The Principal Town Districts." The figures for each County are also given.

"The Principal Town Districts of Scotland" are defined by the Registrar-General as consisting of those towns of more than 30,000 inhabitants at the time of the Census and in intervening years calculated in the usual way from the Census figures. A rough comparison can be instituted therefore between the urban and rural mortality from this disease by comparing the mortality rates of "The
Principa\l Town Districts of Scotland  and  All Scotland minus the Principal Town Districts. The main facts to be investigated are:

1. The changes in the mortality rate.
2. The relation of sex to mortality rate.
3. The relation of urban and rural conditions to mortality rate — as shown by the comparison indicated above.

The tables are given in order and each table is headed by an explanatory statement as to what its contents are. Following each table a short statement is given of what the table appears to show.
Mortality rates for Scotland per 100,000 of estimated populations, for each year from 1875 to 1910. The bracketed figures in red are the total numbers of deaths in each year.

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate</th>
<th>(Num)</th>
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<th>Rate</th>
<th>(Num)</th>
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<tr>
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<td>(83)</td>
<td>1893</td>
<td>2.44</td>
<td>(100)</td>
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<tr>
<td>1876</td>
<td>3.09</td>
<td>(109)</td>
<td>1894</td>
<td>2.32</td>
<td>(96)</td>
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<tr>
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<td>(109)</td>
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<td>1896</td>
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<td>(126)</td>
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<td>1879</td>
<td>3.76</td>
<td>(138)</td>
<td>1897</td>
<td>2.65</td>
<td>(112)</td>
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<tr>
<td>1880</td>
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<tr>
<td>1881</td>
<td>3.33</td>
<td>(125)</td>
<td>1899</td>
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<td>(252)</td>
</tr>
<tr>
<td>1882</td>
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<td>(147)</td>
<td>1900</td>
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<td>(53)</td>
<td>1901</td>
<td>6.71</td>
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<td>2.08</td>
<td>(84)</td>
<td>1906</td>
<td>7.38</td>
<td>(348)</td>
</tr>
<tr>
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<td>(91)</td>
<td>1907</td>
<td>8.37</td>
<td>(400)</td>
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<tr>
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<td>(101)</td>
<td>1908</td>
<td>8.37</td>
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<td>1891</td>
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<td>(96)</td>
<td>1909</td>
<td>10.7</td>
<td>(507)</td>
</tr>
<tr>
<td>1892</td>
<td>2.04</td>
<td>(83)</td>
<td>1910</td>
<td>9.71</td>
<td>(460)</td>
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</table>
Table I shows a steady increase in the mortality rate for Scotland: in 1875 it was 2.37 per 100,000 with 83 deaths; in 1910 it was 9.71 with 460 deaths. The highest mortality for this series of years was in 1909 when the rate reached 10.7 and the number of deaths 507.

A curious feature of the tables and one about which the writer is not prepared, at present, to offer an explanation, is the fall in the rate for 13 years after the year 1882. The lowest rate was in 1883, being 1.38 with 33 deaths; this compared with 3.88 and 159 deaths in 1882 is striking. It is not until 1895 when the rate was 4.37 with 186 deaths, that the rate of 1882 is exceeded. There then is a rapid increase from 4.37 with 186 deaths in 1895 to 7.21 with 320 deaths in 1900. Thereafter, with small fluctuations, the rate goes on increasing and attained a maximum in 1909. The following year (1910) with a rate per 100,000 of 9.71 and 460 deaths represents the second highest rate in the table.

The conclusion is justified then that, in Scotland, the mortality rate from Diabetes Mellitus is steadily and fairly rapidly on the increase.
### Table II

**Diabetes Mellitus.**

Mortality rates for Scotland per 100,000 of estimated male and female populations. The bracketed figures in red are the total numbers of deaths in each year for the male and female populations respectively.

<table>
<thead>
<tr>
<th>Year</th>
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<th>Females</th>
<th>Males</th>
<th>Females</th>
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<td>2.42</td>
<td>4.4</td>
<td>2.22</td>
</tr>
<tr>
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<td>3.69</td>
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</tr>
<tr>
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<td>2.98</td>
<td>3.48</td>
</tr>
<tr>
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<td>3.82</td>
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<td>3.26</td>
</tr>
<tr>
<td>1879</td>
<td>4.48</td>
<td>3.41</td>
<td>2.91</td>
<td>2.74</td>
</tr>
<tr>
<td>1880</td>
<td>5.1</td>
<td>2.91</td>
<td>3.56</td>
<td>3.67</td>
</tr>
<tr>
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<td>2.42</td>
<td>3.36</td>
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</tr>
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<td>4.65</td>
<td>3.16</td>
<td>3.61</td>
<td>6.47</td>
</tr>
<tr>
<td>1883</td>
<td>1.04</td>
<td>1.36</td>
<td>1.54</td>
<td>7.14</td>
</tr>
<tr>
<td>1884</td>
<td>2.62</td>
<td>1.45</td>
<td>2.99</td>
<td>6.76</td>
</tr>
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<td>3.0</td>
<td>1.04</td>
<td>2.01</td>
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<tr>
<td>1886</td>
<td>1.83</td>
<td>1.6</td>
<td>1.91</td>
<td>7.19</td>
</tr>
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<td>1887</td>
<td>2.11</td>
<td>2.09</td>
<td>2.09</td>
<td>7.05</td>
</tr>
<tr>
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<td>1.66</td>
<td>2.47</td>
<td>6.78</td>
</tr>
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<td>1889</td>
<td>2.59</td>
<td>1.99</td>
<td>2.77</td>
<td>7.97</td>
</tr>
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<td>2.32</td>
<td>2.7</td>
<td>3.6</td>
<td>8.01</td>
</tr>
<tr>
<td>1891</td>
<td>2.31</td>
<td>2.44</td>
<td>1.99</td>
<td>8.7</td>
</tr>
<tr>
<td>1892</td>
<td>2.19</td>
<td>1.9</td>
<td>1.99</td>
<td>10.2</td>
</tr>
</tbody>
</table>
It has generally been stated that the number of deaths in males from diabetes mellitus exceeded those in females in the proportion of about three to one. This is not true for Scotland. From 1875 to 1892 the total male deaths was 907; the total female deaths 761; in other words 1.21 males died for every female. The figures for the second eighteen years of the table (1893 to 1910) are: male deaths 3362; female deaths 3391; during these 18 years, therefore, the female deaths exceeded the male deaths in the proportion of 1.037 to 1.

(Table II takes sex constitution of the population into consideration and shows the respective rates for 100,000 living.)

From 1875 to 1892 the female death rate exceeded that for males in only three years, 1875; 1890, 1891; the differences are small. From 1893 to 1910 the female death rate exceeded the male death rate in six years 1893, 1900, 1906-7-8-9 and 10. What is of considerable significance is, that four of these years, 1906-7-8-9, should be practically consecutive; the excess of the female death rate, over that of the male death rate in each of these years, being not trivial, and exceeding the differences noted in other years with a highest female mortality. The conclusion seems justified that the highest mortality has been transferred from males to females.
### Diabetes Mellitus

Mortality rates for "The Principal Town Districts of Scotland," and for "All Scotland minus The Principal Town Districts," for 100,000 of the estimated populations of each of these districts. The bracketed figures in red are the total numbers of deaths in each year in the respective districts.

<table>
<thead>
<tr>
<th>Year</th>
<th>Principal Town Districts (both sexes)</th>
<th>Urban Scotland (both sexes)</th>
<th>Rural Scotland (both sexes)</th>
<th>All Scotland minus The Principal Town Districts (both sexes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1875</td>
<td>(23) 1.9 2.58 (60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1876</td>
<td>(24) 2.1 3.56 (83)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1877</td>
<td>(37) 3.03 3.07 (72)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1878</td>
<td>(41) 3.3 2.63 (62)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1879</td>
<td>(38) 3.2 4.02 (100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1880</td>
<td>(41) 3.4 4.02 (106)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1881</td>
<td>(44) 3.1 3.4 (81)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1882</td>
<td>(48) 3.12 4.35 (102)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1883</td>
<td>(45) 1.02 1.61 (38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1884</td>
<td>(47) 1.81 2.14 (51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1885</td>
<td>(42) 1.45 1.54 (37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1886</td>
<td>(28) 1.82 1.66 (40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1887</td>
<td>(26) 1.66 2.39 (58)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1888</td>
<td>(38) 2.39 1.9 (46)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1889</td>
<td>(33) 2.11 2.4 (58)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1890</td>
<td>(40) 2.53 2.51 (61)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1891</td>
<td>(39) 2.44 2.34 (37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1892</td>
<td>(31) 1.92 2.14 (52)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1893</td>
<td>(40) 2.45 2.45 (60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1894</td>
<td>(39) 2.36 2.36 (57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1895</td>
<td>(47) 2.81 2.81 (82)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1896</td>
<td>(43) 2.53 2.53 (83)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1897</td>
<td>(46) 2.66 2.66 (66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1898</td>
<td>(60) 3.43 3.43 (126)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1899</td>
<td>(77) 4.27 4.27 (175)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1900</td>
<td>(133) 7.27 7.27 (187)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1901</td>
<td>(120) 6.12 6.12 (181)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1902</td>
<td>(119) 5.96 5.96 (191)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1903</td>
<td>(130) 6.41 6.41 (203)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1904</td>
<td>(142) 7.04 7.04 (178)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1905</td>
<td>(127) 6.06 6.06 (192)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1906</td>
<td>(142) 7.06 7.06 (206)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1907</td>
<td>(181) 8.3 8.3 (219)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1908</td>
<td>(160) 7.2 7.2 (241)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1909</td>
<td>(233) 10.3 10.3 (274)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1910</td>
<td>(198) 9.6 9.6 (262)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table III shows that in 26 out of the 36 years shown, rural Scotland showed a higher mortality than urban Scotland. In nine of the last ten years given in the table (1901 to 1910) the rates for rural Scotland were higher than for urban Scotland, the only year showing the reverse being 1909.

Taking this Table in conjunction with Table VIII it is a fair statement that in Scotland, for the years given, the rural mortality from diabetes mellitus is higher than the urban mortality.

It will be noted however in speaking on Table VIII that the percentage increase of mortality in urban areas is higher than in rural areas, so that an equalisation in the rates is to be looked for, probably to be followed by a higher rate in the urban areas.

The conclusions of Dickison that rural districts have the highest mortality from diabetes is therefore, for the period under review for Scotland, while that of Sir (Wm) Robertson, that urban areas give the thickest mortality, may be true for Scotland a variable number of years hence.
Table IV. **Diabetes Mellitus.**

Mortality rates for "The Principal Town Districts of Scotland" per 100,000 of the estimated male and female populations of these districts. The bracketed figures in red are the total numbers of deaths in each year for each sex.

<table>
<thead>
<tr>
<th>Year</th>
<th>Males</th>
<th>Females</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>1875</td>
<td>(10)</td>
<td>1.8</td>
<td>2.1</td>
<td>(13)</td>
</tr>
<tr>
<td>1876</td>
<td>(18)</td>
<td>3.2</td>
<td>1.3</td>
<td>(8)</td>
</tr>
<tr>
<td>1877</td>
<td>(27)</td>
<td>4.6</td>
<td>1.5</td>
<td>(10)</td>
</tr>
<tr>
<td>1878</td>
<td>(26)</td>
<td>4.4</td>
<td>2.3</td>
<td>(13)</td>
</tr>
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<td>1879</td>
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<td>2.7</td>
<td>(17)</td>
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<td>(23)</td>
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<td>(18)</td>
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<tr>
<td>1881</td>
<td>(29)</td>
<td>4.3</td>
<td>2.01</td>
<td>(15)</td>
</tr>
<tr>
<td>1882</td>
<td>(22)</td>
<td>3.21</td>
<td>3.04</td>
<td>(23)</td>
</tr>
<tr>
<td>1883</td>
<td>(9)</td>
<td>1.29</td>
<td>7.7</td>
<td>(6)</td>
</tr>
<tr>
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<td>(20)</td>
<td>2.83</td>
<td>8.9</td>
<td>(7)</td>
</tr>
<tr>
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<td>(15)</td>
<td>2.08</td>
<td>1.88</td>
<td>(7)</td>
</tr>
<tr>
<td>1886</td>
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</tr>
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<td>1887</td>
<td>(13)</td>
<td>1.74</td>
<td>1.39</td>
<td>(13)</td>
</tr>
<tr>
<td>1888</td>
<td>(25)</td>
<td>3.3</td>
<td>1.36</td>
<td>(13)</td>
</tr>
<tr>
<td>1889</td>
<td>(22)</td>
<td>2.97</td>
<td>1.34</td>
<td>(11)</td>
</tr>
<tr>
<td>1890</td>
<td>(17)</td>
<td>2.26</td>
<td>2.7</td>
<td>(23)</td>
</tr>
<tr>
<td>1891</td>
<td>(15)</td>
<td>1.97</td>
<td>2.8</td>
<td>(24)</td>
</tr>
<tr>
<td>1892</td>
<td>(18)</td>
<td>2.34</td>
<td>1.54</td>
<td>(13)</td>
</tr>
</tbody>
</table>

*Note: The data is presented with footnotes for each year.*
**Diabetes Mellitus.**

Mortality rates for "All Scotland minus the Principal Town Districts" per 100,000 of the estimated male and female populations for each year from 1875 to 1900. The bracketed figures in red are the total numbers of deaths in each year for the male and female populations respectively of the selected district.

<table>
<thead>
<tr>
<th>Year</th>
<th>Males</th>
<th>Females</th>
<th>Year</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>1875</td>
<td>2.6</td>
<td>2.57</td>
<td>1893</td>
<td>2.16</td>
<td>2.68</td>
</tr>
<tr>
<td>1876</td>
<td>4.9</td>
<td>2.2</td>
<td>1894</td>
<td>2.65</td>
<td>1.95</td>
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<td>1877</td>
<td>3.2</td>
<td>2.9</td>
<td>1895</td>
<td>3.88</td>
<td>2.74</td>
</tr>
<tr>
<td>1878</td>
<td>3.5</td>
<td>1.8</td>
<td>1896</td>
<td>3.62</td>
<td>3.04</td>
</tr>
<tr>
<td>1879</td>
<td>4.8</td>
<td>3.3</td>
<td>1897</td>
<td>2.55</td>
<td>2.74</td>
</tr>
<tr>
<td>1880</td>
<td>5.5</td>
<td>2.9</td>
<td>1898</td>
<td>6.15</td>
<td>3.97</td>
</tr>
<tr>
<td>1881</td>
<td>4.33</td>
<td>2.67</td>
<td>1899</td>
<td>7.33</td>
<td>6.2</td>
</tr>
<tr>
<td>1882</td>
<td>5.52</td>
<td>3.24</td>
<td>1900</td>
<td>7.03</td>
<td>7.22</td>
</tr>
<tr>
<td>1883</td>
<td>1.47</td>
<td>1.73</td>
<td>1901</td>
<td>6.95</td>
<td>7.37</td>
</tr>
<tr>
<td>1884</td>
<td>2.49</td>
<td>1.8</td>
<td>1902</td>
<td>7.64</td>
<td>7.42</td>
</tr>
<tr>
<td>1885</td>
<td>1.96</td>
<td>1.14</td>
<td>1903</td>
<td>8.31</td>
<td>7.61</td>
</tr>
<tr>
<td>1886</td>
<td>1.77</td>
<td>1.34</td>
<td>1904</td>
<td>6.82</td>
<td>7.04</td>
</tr>
<tr>
<td>1887</td>
<td>2.35</td>
<td>2.42</td>
<td>1905</td>
<td>7.49</td>
<td>7.38</td>
</tr>
<tr>
<td>1888</td>
<td>2.08</td>
<td>1.68</td>
<td>1906</td>
<td>7.87</td>
<td>8.07</td>
</tr>
<tr>
<td>1889</td>
<td>2.38</td>
<td>2.42</td>
<td>1907</td>
<td>7.98</td>
<td>8.86</td>
</tr>
<tr>
<td>1890</td>
<td>2.37</td>
<td>2.65</td>
<td>1908</td>
<td>9.57</td>
<td>9.12</td>
</tr>
<tr>
<td>1891</td>
<td>2.32</td>
<td>2.15</td>
<td>1909</td>
<td>10.9</td>
<td>9.6</td>
</tr>
<tr>
<td>1892</td>
<td>2.11</td>
<td>2.16</td>
<td>1910</td>
<td>9.1</td>
<td>10.4</td>
</tr>
</tbody>
</table>

*Notes:*
- *X* indicates missing data.
These tables show that what is true for "All Scotland" (Table ii) is true, generally, for the two districts taken. It should be noted however that while the female mortality for the Principal Town District exceeds the male mortality in 9 years (marked with a red cross - Table iv) and that these years correspond exactly in the case of one year - with what is found for "All Scotland" (Table ii); in the case of "All Scotland minus the Principal Town District" the female mortality exceeds the male mortality in 13 years (marked with a red cross) and only six of these years correspond with what is found for "All Scotland".

Table iv is interesting in this connection.
Diabetes Mellitus.

The following table shows the average annual death-rate per 100,000 living for ten-yearly periods, except during the 1875 to 1880 period, when the interval is six years. The percentage increase or decrease of the mortality of any of these periods as compared with the immediately preceding period is also shown.

The figures are shown for both sexes taken together and for each sex separately, and the figures are for "All Scotland." The two following tables show the same facts for "The Principal Town Districts" and "All Scotland minus the Principal Town Districts.

The total populations and total numbers of deaths for both sexes together and each sex separately are also shown.

Table vi is therefore complimentary to Tables i - vii, giving the same information, but for periods of years grouped together, instead of for single years; a truer representation of the trend of events is thus afforded.
### Table VI

**Diabetes Mellitus**

**All Scotland**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Population (10th Census)</th>
<th>Total Deaths</th>
<th>Total Male Population</th>
<th>Total Male Deaths</th>
<th>Total Female Population</th>
<th>Total Female Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1875-1880</td>
<td>2,154,910</td>
<td>1,340,817</td>
<td>412</td>
<td>1,120,289</td>
<td>271</td>
<td></td>
</tr>
<tr>
<td>1881-1890</td>
<td>3,908,472</td>
<td>1,894,111</td>
<td>497</td>
<td>2,014,361</td>
<td>393</td>
<td></td>
</tr>
<tr>
<td>1891-1900</td>
<td>4,953,416</td>
<td>2,282,613</td>
<td>770</td>
<td>2,170,803</td>
<td>730</td>
<td></td>
</tr>
<tr>
<td>1901-1910</td>
<td>4,672,567</td>
<td>2,272,379</td>
<td>763</td>
<td>2,394,128</td>
<td>1919</td>
<td></td>
</tr>
</tbody>
</table>

- **A.A.M.** = Average annual mortality per 100,000 living.
- **P.D.** = Percentage difference on ---
The conclusions to be drawn from this table have been foreshadowed in Table 1. It shows that in the ten years 1881-1890 the mortality rate decreased as compared with the eight years from 1875 to 1881, and that the percentage decrease in the mortality rate for females was less than that for males: the figures being 24 for females and 33.3 for males. During the succeeding periods the mortality rates increased; the increase being specially marked during the 1901-1910 period. During this period the average annual mortality per 100,000 living was 79 as compared with 5.6 in the previous decade, representing a percentage increase of 144.4.

During this period the female mortality rate first exceeded the male mortality rate, the figures being 8.01 and 7.78 respectively. The percentage increase in the female mortality rate during 1891 to 1900 was 79 against 42.3 for the male mortality rate; during 1901 to 1910 it was 135.3 for females and 110.8 for males.

[continued overleaf]
Table vi therefore shows:

1. That the mortality rate for diabetes mellitus is increasing for both sexes.
2. That the female mortality rate is increasing at a more rapid pace than the male mortality rate.
3. That the female mortality rate was higher than the male mortality rate during the 1901 to 1910 period.

The two following tables show the same facts as Table vi but for "The Principal Town District of Scotland" and for "All Scotland outside The Principal Town Districts." As Table vi was complimentary to Tables vii and viii, so Tables vii and viii are complimentary to Tables iii, iv, and v.
## Principal Town Districts

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Population (both sexes)</th>
<th>Total Male Deaths</th>
<th>Total Male Population</th>
<th>Total Female Deaths</th>
<th>Total Female Population</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1876</td>
<td>7,199,192</td>
<td>206</td>
<td>3,408,990</td>
<td>128</td>
<td>3,790,202</td>
<td>81</td>
</tr>
<tr>
<td>1877</td>
<td>7,148,898</td>
<td>196</td>
<td>3,404,992</td>
<td>126</td>
<td>3,790,300</td>
<td>81</td>
</tr>
</tbody>
</table>

- **A.A.M.** = Average annual mortality per 100,000 living
- **P.D. on** = Per cent difference on

---

**All Scotland minus The Principal Town Districts**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Population (both sexes)</th>
<th>Total Male Deaths</th>
<th>Total Male Population</th>
<th>Total Female Deaths</th>
<th>Total Female Population</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1876</td>
<td>14,349,914</td>
<td>483</td>
<td>6,931,877</td>
<td>287</td>
<td>7,418,047</td>
<td>196</td>
</tr>
<tr>
<td>1877</td>
<td>13,940,419</td>
<td>474</td>
<td>6,838,774</td>
<td>281</td>
<td>7,091,646</td>
<td>196</td>
</tr>
</tbody>
</table>

- **A.A.M.** = Average annual mortality per 100,000 living
- **P.D. on** = Per cent difference on
These tables have been placed on the same page to facilitate easy comparison.

It will be noted that a levelling up of the populations in the two districts is occurring; in other words, the population of the Principal Town District is increasing at a more rapid rate than that of "All Scotland minus the Principal Town District." This is illustrated by comparing the populations of the 1875-80 and of the 1901-10 periods in the two districts. During the former period the population of "All Scotland minus the Principal Town Districts" was nearly twice that of the "Principal Town Districts"; during the latter period it was only 1.2 times that of the Principal Town Districts.

The main facts are, of course, as those for "All Scotland" shown in Table vi. It will be noted that the percentage decrease during the 1881-1890 period is greater in "All Scotland minus the Principal Town Districts" than in "The Principal Town Districts" and that in both districts the percentage decrease in the female mortality rate, is
much less than in the male mortality rate; the difference also between the percentage decrease in females in the two districts is only 0.2, whereas in males it is 5.2.

The percentage increase in the male mortality during the 1891-1900 period, as compared with the 1881-1890 period was 30.8 in the Town Districts and 49.8 in the Rural Districts, thus showing a difference of 19 against the Rural Areas. When, however, we compare the percentage increase of the female mortality in the two areas for the same periods we find the reverse to be the case: the percentage increase in the Town Districts being 18.4 against 66.6 in the rural areas, a difference of 48.2 against the Town Districts. Comparing in a similar way the figures for the 1901-1910 period with the preceding decade it will be seen that the percentage increase in both sexes has been greater in the Town Districts.

The mortality rate for both sexes taken together for 100,000 living in the rural areas is 8.3 against 7.5 in the Town Districts. It will be noted however
that while the male and female mortality rate is equal in the rural areas (8.3 per 100,000 living), the female mortality (7.6 per 100,000 living) is higher than the male mortality (7.2 per 100,000 living) in the Town Districts.

The conclusion that would seem justified from this table are:

1. The mortality is higher in the rural than in the urban areas.

2. The mortality rate in the urban areas is increasing at a faster pace than in the rural areas.

3. The female mortality rate is increasing at a faster pace than the male mortality rate.

4. The female mortality rate in the urban areas is increasing at a faster pace than in the rural areas.
The Counties of Scotland.

The following table (Table 7x) gives for each of the Counties of Scotland what Table vi gives for “All Scotland” except that the sexes have not been dealt with separately.

There is shown therefore for each County:

α. The average annual mortality per 100,000 living, during the stated periods.

β. The percentage difference in the average annual mortality for any of the stated periods, when compared with the immediately preceding period.

γ. The total number of deaths, in each period, from diabetes.
### Table IX

**Diabetes Mellitus**

**Counties of Scotland.**

<table>
<thead>
<tr>
<th>County</th>
<th>1871 to 1880</th>
<th>1881 to 1890</th>
<th>1891 to 1900</th>
<th>1901 to 1910</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shetland</td>
<td>34</td>
<td>1</td>
<td>1.72</td>
<td>0.73</td>
</tr>
<tr>
<td>Orkney</td>
<td>4.79</td>
<td>2</td>
<td>2.19</td>
<td>0.86</td>
</tr>
<tr>
<td>Caithness</td>
<td>2.07</td>
<td>1</td>
<td>1.37</td>
<td>0.56</td>
</tr>
<tr>
<td>Sutherland</td>
<td>7.52</td>
<td>1</td>
<td>0.94</td>
<td>0.52</td>
</tr>
<tr>
<td>Ross and</td>
<td>4.01</td>
<td>2</td>
<td>1.65</td>
<td>0.82</td>
</tr>
<tr>
<td>Inverness</td>
<td>1.74</td>
<td>1</td>
<td>1.61</td>
<td>0.99</td>
</tr>
<tr>
<td>Nairn</td>
<td>5.21</td>
<td>1</td>
<td>1.11</td>
<td>0.30</td>
</tr>
<tr>
<td>Elgin</td>
<td>4.38</td>
<td>1</td>
<td>2.85</td>
<td>0.77</td>
</tr>
<tr>
<td>Banff</td>
<td>2.55</td>
<td>1</td>
<td>1.97</td>
<td>0.59</td>
</tr>
<tr>
<td>Aberdeen</td>
<td>3.63</td>
<td>5</td>
<td>2.65</td>
<td>0.91</td>
</tr>
<tr>
<td>Kirkcudbright</td>
<td>4.84</td>
<td>9</td>
<td>2.47</td>
<td>0.97</td>
</tr>
<tr>
<td>Forfar</td>
<td>7.09</td>
<td>25</td>
<td>0.54</td>
<td>0.29</td>
</tr>
<tr>
<td>Perth</td>
<td>1.33</td>
<td>4</td>
<td>1.71</td>
<td>0.36</td>
</tr>
<tr>
<td>Fife</td>
<td>2.85</td>
<td>1</td>
<td>1.61</td>
<td>0.65</td>
</tr>
<tr>
<td>Kintyre</td>
<td>3.06</td>
<td>1</td>
<td>1.72</td>
<td>0.54</td>
</tr>
<tr>
<td>Peebleshire</td>
<td>8.96</td>
<td>4</td>
<td>1.42</td>
<td>0.12</td>
</tr>
<tr>
<td>Kirkcudbright</td>
<td>2.53</td>
<td>4</td>
<td>1.59</td>
<td>0.46</td>
</tr>
<tr>
<td>Stirling</td>
<td>2.69</td>
<td>15</td>
<td>1.47</td>
<td>0.59</td>
</tr>
<tr>
<td>Ayrshire</td>
<td>3.16</td>
<td>13</td>
<td>2.29</td>
<td>0.68</td>
</tr>
<tr>
<td>Angus</td>
<td>2.56</td>
<td>12</td>
<td>1.98</td>
<td>0.39</td>
</tr>
<tr>
<td>Northumberland</td>
<td>2.81</td>
<td>4</td>
<td>1.72</td>
<td>0.79</td>
</tr>
<tr>
<td>Strathclyde</td>
<td>2.63</td>
<td>11</td>
<td>1.61</td>
<td>0.58</td>
</tr>
<tr>
<td>Argyll</td>
<td>3.68</td>
<td>57</td>
<td>2.64</td>
<td>0.63</td>
</tr>
<tr>
<td>Banff</td>
<td>6.71</td>
<td>7</td>
<td>2.22</td>
<td>0.37</td>
</tr>
<tr>
<td>Renfrew</td>
<td>2.25</td>
<td>29</td>
<td>1.57</td>
<td>0.37</td>
</tr>
<tr>
<td>Arran</td>
<td>3.8</td>
<td>47</td>
<td>2.54</td>
<td>0.45</td>
</tr>
<tr>
<td>Northumberland</td>
<td>2.59</td>
<td>13</td>
<td>1.98</td>
<td>0.36</td>
</tr>
<tr>
<td>שיורדס</td>
<td>1.98</td>
<td>8</td>
<td>1.09</td>
<td>0.26</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>3.04</td>
<td>97</td>
<td>2.69</td>
<td>0.69</td>
</tr>
<tr>
<td>Haddington</td>
<td>2.63</td>
<td>6</td>
<td>1.61</td>
<td>0.57</td>
</tr>
<tr>
<td>Berwick</td>
<td>6.01</td>
<td>13</td>
<td>1.72</td>
<td>0.55</td>
</tr>
<tr>
<td>Peebleshire</td>
<td>2.85</td>
<td>1</td>
<td>2.69</td>
<td>0.66</td>
</tr>
<tr>
<td>Kirkcudbright</td>
<td>3.97</td>
<td>10</td>
<td>1.72</td>
<td>0.51</td>
</tr>
<tr>
<td>Paisley</td>
<td>4.42</td>
<td>10</td>
<td>1.98</td>
<td>0.72</td>
</tr>
</tbody>
</table>
This table shows that during the 1881-90 period, the only Counties showing an increased mortality rate as compared with the preceding period (1875-80) were five, viz., Shetland, Sutherland, Forfar, Linlithgow and Wigtown. The 28 Counties remaining showed a reduced rate. During the succeeding period (1891-1900) the only Counties showing a decreased mortality rate, when compared with 1881-90, were four, viz., Shetland, Selkirk, Kirkcudbright and Kirkcarr. During the 1901-10 period the only County showing a decreased mortality rate was Shetland, the population of which while it increased during the 1901-10 period, was, before that period, on the decrease.

The position of Orkney and Shetland is peculiar. Here are two areas in close geographical proximity not differing greatly in natural features or in population - Orkney however having the larger population - the one - Orkney - having a consistently high mortality rate from diabetes as compared with the other (Shetland). This is well shown in the table. Orkney is nearer the mainland and its mortality rate corresponds more closely with that of Caithness and of Aberdeen than with that of Shetland. The question might be merely one of accuracy of certification of the cause of death.
This table shows the Counties arranged according to their respective mortality rates per 100,000 living, from the highest to the lowest, for each of the stated periods.

<table>
<thead>
<tr>
<th>Counties</th>
<th>1875 to 1880</th>
<th>1881 to 1890</th>
<th>1891 to 1900</th>
<th>1901 to 1910</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selkirk</td>
<td>8.06</td>
<td>4.83</td>
<td>3.98</td>
<td>4.16</td>
</tr>
<tr>
<td>Berwick</td>
<td>5.41</td>
<td>3.81</td>
<td>2.98</td>
<td>3.03</td>
</tr>
<tr>
<td>Peebles</td>
<td>4.48</td>
<td>3.22</td>
<td>2.75</td>
<td>2.75</td>
</tr>
<tr>
<td>Roxburgh</td>
<td>3.99</td>
<td>2.88</td>
<td>2.81</td>
<td>2.48</td>
</tr>
<tr>
<td>Ardrossan</td>
<td>2.85</td>
<td>1.85</td>
<td>1.75</td>
<td>1.75</td>
</tr>
<tr>
<td>Ayr</td>
<td>1.86</td>
<td>1.65</td>
<td>1.55</td>
<td>1.55</td>
</tr>
<tr>
<td>Elgin</td>
<td>1.26</td>
<td>1.15</td>
<td>1.10</td>
<td>1.10</td>
</tr>
<tr>
<td>Inverness</td>
<td>1.21</td>
<td>1.15</td>
<td>1.10</td>
<td>1.10</td>
</tr>
<tr>
<td>Aberdeen</td>
<td>1.75</td>
<td>1.50</td>
<td>1.45</td>
<td>1.45</td>
</tr>
<tr>
<td>Perth</td>
<td>1.95</td>
<td>1.75</td>
<td>1.70</td>
<td>1.70</td>
</tr>
<tr>
<td>Dumfries</td>
<td>1.85</td>
<td>1.65</td>
<td>1.55</td>
<td>1.55</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>1.80</td>
<td>1.60</td>
<td>1.55</td>
<td>1.55</td>
</tr>
<tr>
<td>Kirkcudbright</td>
<td>1.75</td>
<td>1.55</td>
<td>1.50</td>
<td>1.50</td>
</tr>
<tr>
<td>Berwick</td>
<td>1.65</td>
<td>1.45</td>
<td>1.40</td>
<td>1.40</td>
</tr>
<tr>
<td>Roxburgh</td>
<td>1.60</td>
<td>1.45</td>
<td>1.40</td>
<td>1.40</td>
</tr>
<tr>
<td>Dumfries</td>
<td>1.55</td>
<td>1.35</td>
<td>1.30</td>
<td>1.30</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>1.50</td>
<td>1.30</td>
<td>1.25</td>
<td>1.25</td>
</tr>
<tr>
<td>Kirkcudbright</td>
<td>1.45</td>
<td>1.25</td>
<td>1.20</td>
<td>1.20</td>
</tr>
<tr>
<td>Berwick</td>
<td>1.40</td>
<td>1.20</td>
<td>1.15</td>
<td>1.15</td>
</tr>
<tr>
<td>Roxburgh</td>
<td>1.35</td>
<td>1.15</td>
<td>1.10</td>
<td>1.10</td>
</tr>
<tr>
<td>Dumfries</td>
<td>1.30</td>
<td>1.10</td>
<td>1.05</td>
<td>1.05</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>1.25</td>
<td>1.05</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Kirkcudbright</td>
<td>1.20</td>
<td>1.00</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>Berwick</td>
<td>1.15</td>
<td>0.95</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Roxburgh</td>
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<td>0.90</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>Dumfries</td>
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<td>0.85</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>1.00</td>
<td>0.80</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>Kirkcudbright</td>
<td>0.95</td>
<td>0.75</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>Berwick</td>
<td>0.90</td>
<td>0.70</td>
<td>0.65</td>
<td>0.65</td>
</tr>
<tr>
<td>Roxburgh</td>
<td>0.85</td>
<td>0.65</td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td>Dumfries</td>
<td>0.80</td>
<td>0.60</td>
<td>0.55</td>
<td>0.55</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>0.75</td>
<td>0.55</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Kirkcudbright</td>
<td>0.70</td>
<td>0.50</td>
<td>0.45</td>
<td>0.45</td>
</tr>
<tr>
<td>Berwick</td>
<td>0.65</td>
<td>0.45</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>Roxburgh</td>
<td>0.60</td>
<td>0.40</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>Dumfries</td>
<td>0.55</td>
<td>0.35</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>0.50</td>
<td>0.30</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Kirkcudbright</td>
<td>0.45</td>
<td>0.25</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Berwick</td>
<td>0.40</td>
<td>0.20</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>Roxburgh</td>
<td>0.35</td>
<td>0.15</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>Dumfries</td>
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<td>0.10</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>0.25</td>
<td>0.05</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>
This table is given to show, in a way easy of appreciation, the incidence of the mortality on the various counties for the stated periods. The first thing that strikes the eye on looking over the various columns is the progressive increase in the figures from the 1881-1890 period to the 1901-10 period.

The next thing is that the counties showing the highest mortalities are of a pronouncedly rural character. Of the first six counties, for each of the four periods are examined this becomes very apparent and if the geographical position of these counties is looked at (vide accompanying map) it will be noticed that 18 out of the 24 are situated in the South of Scotland. This would seem then to be a heavier incidence on the counties there.

If the six counties given last on the list are similarly examined it will be found that the rural character is still pronounced, but that out of 24 counties only 3 are situated in the South, whereas 13 are situated in the North.

In the centre of Scotland when the
conditions are, on the whole, more urban than rural, the mortality rates—generally speaking—are intermediate between the two extremes.

It is difficult to account for the difference between the North and South but it may be noted that the fishing population in the North is greater than in the South; that the population of the North is, on the whole, more exposed to severe weather conditions than that of the South; that the North is more mountainous than the South; and that while raising crops is the predominant feature of the Southern Counties, stock-raising and tending game and forests is probably more characteristic of the North.

One word of explanation regarding the position of Bute at the head of the 1901-1910 list is necessary. The rate 15.9 is a high one, much higher, comparatively, than any other on the list, and representing an increase
of 321.3 per cent from the figure for the previous decade.
This high rate is probably to be explained by the fact that Bute is now more than ever it was, a health resort; that delicate people go there to live and that probably some of those are diabetics who die on the island.

The accompanying outline map shows for each County the average annual mortality per 100,000 living during the 1910 to 1910 period.

The conclusions of the writer regarding the mortality from diabetes mellitus for Scotland are given on pages 97 and 101. The only statement that need be added is that the mortality in the South of Scotland would appear, on the whole, to be higher than in the North of Scotland. This feature is fully gone into above.
Causation. The writer may state at once that he is of opinion that the disease known as diabetes mellitus, in the great majority of cases, is caused by a toxin, manufactured probably in the intestinal canal, by a specific microbe. This toxin has the property of preventing the formation of pancreatic internal secretion, or of diverting it, when formed, from its proper function. It might do this by combining with the internal secretion and so neutralizing it, or in other ways render the internal secretion ineffective.

This theory explains cases where there is no apparent lesion of the pancreas, as well as cases where a lesion is present. The writer would therefore look upon diabetes as a specific disease due to a specific microbe. The disease would appear to be contagious but in a very low degree. The seat of the contagion being probably in the small intestine, the risk of spread of the disease, save to uncured people who have Swall.

The writer is quite well aware that in taking up such a position, he is inviting severe and hostile criticism. Sir Patrick Manson, speaking of the large proportion of deaths from this disease included,
said "It might be however that diabetes, which 
has been for so long attributed to food, exposure etc., 
might like other ailments with similar history, 
come to be proved to be due to a specific organism."  
Mr. C.L. Bose 30) (Bengal) said "The possibility of diabetes 
being contagious must not be lost sight of," and  
Mr. Senator 31) "Was of opinion that a communication 
of the disease might happen in certain favourable 
circumstances."

There are several facts in favour of such a view:  
1). Glyceruria is common to man and animals.  
2). Several remarkable instances of the development 
of the disease in people, not related to, but 
coming into close contact with diabetics have been 
recorded. 32)  
3). Conjugal diabetes is strongly believed in by some 
observers 33)  
4). The practically world-wide distribution of the 
disease, and the rapid increase in the mortality, 
favours a specific microbic origin.  
5). Acute cases ushered in by febrile disturbances 
have been observed especially in children, 
in whom the disease is much more rapidly fatal 
than in adults.  
6). Williamson 34) points out that "a family history
of diabetes was obtained more frequently in patients under forty than in those over forty (30.6 and 13.7 per cent. respectively). If the disease were, with difficulty, contagious, we should expect the same age distribution.

Several other considerations point in the direction of the disease being due to a specific micro-organism. The disease until recently has been commonest in males, it is now - in Scotland at any rate - commonest in females. This increase amongst females has coincided with a great increase in the number of working women and while this means increased strain it also means increased chances of infection. Increased strain also means indigestion and this, which is a pronounced forerunner of diabetes in India and elsewhere, means lowered vitality, and increased susceptibility to the development of implanted infection. Purdy 36) states that "The relative mortality of diabetes in rural and urban populations is chiefly determined by temperature, in the colder regions the mortality being decidedly higher in the country, while in the warmer regions, it is higher in the cities." This explanation is as follows: "Cold greatly increases the mortality from diabetes. In cold climates those
who are best sheltered suffer least from the disease. In the warmer climates of the South, the atmospheric conditions affecting the disease are chiefly those of purity. The country people are able to live in the open air the year round without exposure to cold or chill and oxidation attains its greatest activity. In the cities, more or less confinement and impurity of atmosphere is inevitable, which tends to impede oxidation and give greater virulence to the disease.

Purdy here changes the argument from cold (and altitude) to impurity of air. Had the above been written of pulmonary tuberculosis—a microscopic disease—all the conditions facilitating spread of the disease would have been described for cold, especially though not by any means exclusively amongst the poor, though also impure air, since they huddle together for warmth. The conditions described are such as would in high degree favour contagion. In the United States the death rate from diphtheria between 1860 and 1870 increased nearly 100 per centum. From 1870 to 1880 the rate of increase was only about 5 per centum. Purdy attributes the 100 per centum increase to the change in the habits of the people following the civil war, the change being in the direction of extravagant and luxurious living.
It seems to the writer that an entirely different explanation can be given of the increase. The American Civil War began on the 11th April 1861 and ended on the 9th April 1865. That war was accompanied, as are all wars, by much privation and suffering, as the following extract from MacKenzie's History of America shows: "Half the time the army wanted food." "Many of them knew also that their families were starving." "The misery of the country was deep, abject, insufferable." "Many went home stricken with lingering and mortal disease." All the conditions for the development and spread of a contagious disease are here present. The fact that the increase of mortality fell from 100 to 8 per cent in time during the succeeding ten years, does not support the luxurious living theory, since that continued, whereas war conditions and privations had long ceased. The writer ventures to suggest that after the present European war has ceased, the diabetes mortality rate, will, a variable time thereafter, show a very large increase in the countries affected.

Kliic [36] makes the general statement: "Among all people beyond the pale of culture, diabetes is very rare. This I believe to be the correct way
of ensuing the immunity among Africans and the
reason why so little is heard of diabetes among the
Indians of America, or among the numerous
and varied Aborigines of Australia, or in the
English Colonies of mixed but predominantly
coloured population.
As against this however is the fact that if
any of these races begin to come into contact
with civilised people (people having the
disease), they contract it. This is generally
ascribed to their altering their mode of life
and diet to that of the civilised people.
It seems quite as probable that it may be
due to contagion. Tuberculosis introduced
amongst these races by their civilised
conquerors played havoc with them and we
know that ‘civilisation and syphilisation’
go hand in hand.
These are a few considerations that
occurred to the author in thinking over the
possibility of diabetes being a contagious
disease due to a specific microbe, and it
seemed to be worth while to set them out
briefly. The conclusions of the writer
are briefly indicated below:
Conclusions.

1. The pancreas, possibly by means of the Islets of Langerhans, produces an internal secretion.

2. This internal secretion has the property of 'sensitising' protid, so that it attaches carbohydrate in a certain form to itself in a loose combination.

3. The form in which carbohydrate is thus attached is not that of glucose but of some nearly allied but much more unstable body which the writer has named 'pro-glucose'.

4. Pro-glucose is probably formed in the process of absorption of carbohydrate through the intestinal wall and is immediately attached to the 'sensitised' protid.

5. If pro-glucose is not so attached, it becomes converted into glucose, which cannot be directly utilised by the tissues. If this waste glucose comes again within the influence of the original process, as it may, by excretion into the intestine with
subsequent re-absorption and modification into "proglucose", it again becomes utilisable. Coming within the direct influence of the intestinal cells would probably effect the change without the necessity for excretion into and re-absorption from the bowel.

This process explains the harmful effect of hyperglycaemia, which acts by exhausting the pancreas and rendering the pancreatic internal secretion produced relatively ineffective through over-work.

5. The combination of proglucose and protein through the intermediation of the pancreatic internal secretion, thus means that the carbohydrate is carried through the circulation in a utilisable form and being part of a large molecule does not filter off in the urine.

7. This combination is necessary for the formation of glycogen, which cannot be formed from free glucose.

8. Glycogen is a storage form of carbohydrate, and when called upon
to supply carbohydrate, is transformed into proglucose and attached by "sensitised" protein for carriage to the site of utilisation.

9) Proglucose is the form in which carbohydrate is split off from protein and may be utilised at once, or if "sensitised" protein is present (as in phloridzin diabetes) it is attached by it and carried through the circulation as before explained.

If "sensitised" protein is absent (as in depancreatized animals), the proglucose produced and not immediately utilised becomes converted into glucose - a waste product.

10) The continued utilisation of carbohydrate in grave diabetes or in depancreatized animals is thus explained, as also are the facts of phloridzin diabetes.

11) In diabetes, carbohydrate probably begins to be split off from protein, when the quantity of effective pancreatic internal secretion is insufficient to combine carbohydrate enough for the
needs of the tissues.

12. Free glucose is always a waste product and is excreted in the urine in proportion to its amount in the blood.

13. The ultimate cause of diabetes mellitus is diminution or absence of effective pancreatic internal secretion.

14. This diminution or absence may be due to many causes, but in the majority of cases is probably caused by a specific toxin produced in the intestinal canal by a specific micro-organism. The disease is probably contagious, but with difficulty.

15. As the disease is steadily and rapidly on the increase, an effort should be made to check it before it assumes greater prevalence. As a means to this end it should be made notifiable and every case carefully investigated from the pretreatment point of view. The comparatively small number of cases would render this easy of accomplishment and no stigma attaches to the disease.
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