

MODERN METHODS IN THE TREATMENT

of

DIABETES MELLITUS

With special reference to Insulin  
Therapy.

-----  
A Thesis presented for the degree of  
Doctor of Medicine

by

James W.G.H. Riddel, Military Cross

Bachelor of Medicine and Surgery  
University of Edinburgh  
Fellow of the Royal College of Surgeons  
Edinburgh

-----  
Major, R.A.M.C. General Reserve of Officers.  
Assistant Surgeon to the South Devon and  
East Cornwall Hospital, Plymouth

-----oOo-----

*February 1924.*



1. Introduction.
  2. Historical.
  3. Classification of the various modes of treatment.
    - a. Dietetic.
    - b. Drug treatment.
    - c. Insulin Therapy.
  4. Summary.
  5. Bibliography.
  6. Appendix.
-

## 1. INTRODUCTION.

Diabetes Mellitus is a baffling and obscure disorder of human metabolism. Treatment has been influenced by the views of different schools of thought in relation to its causation.

With the passage of years methods of investigation have been improved, and research has been carried out on collateral lines, but the whole subject has become more complex as knowledge has been accumulated.

For many years little or no material advance was made in treatment. With the closing decades of the last century, discoveries were made which altered the conception of the nature of the disease.

Attention was directed to hygienic considerations and attempts were made to diminish the amount of sugar in the urine by the administration of various drugs, but the main line of attack lay in control of the dietary. The results were disappointing except in the milder cases.

When Allen propounded the principles of starvation diet a greater measure of relief was expected in severe cases, but again the results were not encouraging, except in comparatively few instances.

In 1922 Banting and Best, two Canadian physiologists, succeeded in isolating an internal secretion of the pancreas, which has been called Insulin.

## 1. INTRODUCTION.

Diabetes Mellitus is a baffling and obscure disorder of human metabolism. Treatment has been influenced by the views of different schools of thought in relation to its causation.

With the passage of years methods of investigation have been improved, and research has been carried out on collateral lines, but the whole subject has become more complex as knowledge has been accumulated.

For many years little or no material advance was made in treatment. With the closing decades of the last century, discoveries were made which altered the conception of the nature of the disease.

Attention was directed to hygienic considerations and attempts were made to diminish the amount of sugar in the urine by the administration of various drugs, but the main line of attack lay in control of the dietary. The results were disappointing except in the milder cases.

When Allen propounded the principles of starvation diet a greater measure of relief was expected in severe cases, but again the results were not encouraging, except in comparatively few instances.

In 1922 Banting and Best, two Canadian physiologists, succeeded in isolating an internal secretion of the pancreas, which has been called Insulin.

This hormone was found to influence favourably the course of Diabetes Mellitus in man and has placed treatment on a more rational basis. Many sufferers from severe types of the disease can now look forward to leading lives of normal activity whilst under its influence.

This discovery is one of notable importance although it is not claimed that insulin will cure Diabetes Mellitus. Yet there is already sufficient evidence to prove that by affording rest to the pancreas of a diabetic, insulin will bring about an increased tolerance of carbohydrate. In the field of biochemistry insulin is regarded as an agent likely to be of value in the elucidation of further problems in metabolism.

It is the author's intention to give an historical outline of the investigations which led up to the present state of knowledge. The hygienic and dietetic principles of treatment will be discussed, and special reference will be made to the indications for the use of insulin, together with the results which have been obtained by its administration in suitable cases.

## 2. HISTORICAL

The Ancients recognised a disease which was probably Diabetes Mellitus, but Willis first described the sweet taste of the urine in his treatise, *Pharmaceutice rationalis* (1674). His name is perhaps better known in connection with the anatomy of the brain, the circle of Willis being named after him, who described this arterial anastomosis. Since that time the practice of medicine has been raised from the realms of complete empiricism and re-established on a scientific basis, but this was not done without the effort of countless workers, whose names have long since been forgotten.

In 1776 Dobson attributed the sweetness of the urine to the presence of sugar. He observed that diabetic urines underwent alcoholic fermentation and rightly concluded from this and other considerations that sugar was present. In 1788 Cawley reported a case of diabetes in which calculi were found in the pancreas at the autopsy. Other writers constantly described atrophic lesions of the pancreas in diabetics and attributed more than a casual connection between the two.

After Claude Bernard's discovery of the glycogenic function of the liver in 1848, attempts were made to correlate Diabetes with derangements of that

organ. So it has been that one organ after another has been concerned in the minds of investigators with the causation of Diabetes.

In 1857 Peters described the presence of acetone in the urine of diabetics, and in 1884 Kutz and Minkowski reported oxybutyric acid. The important relation of both to coma was evidently not agreed upon for in Quain's Dictionary of Medicine (1883) only casual reference was made to the subject.

Glucose is the sugar found in diabetic urine. Though it is derived from the carbohydrate element of the diet, it is also obtained from protein to the extent of one half. The ketone bodies, oxybutyric acid, diacetic acid and acetone, are always present in the urine in severe cases of the disease and by their amount, afford a useful guide to the gravity of the disease. In combination with other tests an estimation of their amount gives an indication of the likelihood of coma supervening. These bodies are derived from the fat of the diet.

In 1889 Mering and Minkowski showed that removal of the pancreas from an animal produced what appeared to be severe diabetes mellitus as known in the human subject. This was an extremely important observation in view of the constant references in the literature to the presence of pancreatic disease in patients dead of Diabetes Mellitus. Lepine in 1909 suggested

that this might be due to the removal of an internal secretion, and his view was supported by analogy with reference to the thyroid, pituitary, and suprarenals. Moreover, it was established by Hedon that pancreatic grafts would prevent the onset of diabetes in depancreatized animals.

There was thus accumulating evidence to support the contention that Diabetes Mellitus is related to pancreatic disorder, in which the internal secretion is defective or absent. Between 1912 and 1919 pancreatic extracts were prepared by several workers, but the results were not such that they could be used for the treatment of diabetes in man. In 1908 Zuelzer reported his results in the treatment of six cases of diabetes mellitus. The extract produced an improvement in the excretion of sugar and ketones and in the general condition of the patients, but the intravenous injection of the extract gave rise to severe chills, fever and vomiting. Minkowski, Sandmeyer, Pfluger and others found that feeding with pancreas had negative or harmful results. Murlin, Klimer and Paulsco used aqueous extracts of pancreas intravenously on depancreatized dogs and produced a transitory reduction in the blood sugar. Clarke showed that the isolated mammalian heart, when perfused with Locke's solution containing glucose, would remove sugar from the perfusion fluid more rapidly when that fluid had first been circulated through the pancreatic vessels, than

from fluid not so circulated. Failure to isolate the internal secretion was deemed to be due to destruction by trypsin and other proteolytic enzymes.

Starting point of the recent advance..

Banting determined first that destruction of the internal secretion of the pancreas could be avoided by making use of ligation of the pancreatic ducts. By this manoeuvre, the islands of Langerhans remain intact, while the acinous tissue, which secretes the enzymes, degenerates in from seven to ten weeks. An extract of the degenerated gland thus prepared by Banting and Best was found to lower the blood sugar in depancreatized dogs and to reduce the excretion of sugar in amount in the 24 hours output of urine. In like manner, the general condition of the animals improved and life was prolonged.

A potent extract was next prepared from the pancreas of foetal calves, which Ibrahim had shown not to contain proteolytic enzymes. After further work a method was evolved by which an active extract was obtained from normal ox pancreas. Alcohol was used as the extracting medium, to avoid the destructive action of trypsin, as had been suggested by E. L. Scott in 1912 when he was working on alcoholic extracts of pancreas. This alcoholic extract was capable of reducing the blood sugar of a diabetic boy aged 14 years. This was insulin (so called as suggested by Schäfer)

isolated and first used for the treatment of diabetes in the human subject.

It remained to discover a method of producing insulin on a large scale and to investigate its physiological and therapeutic properties. Collip was able to procure insulin in a purer form by a method of fractional precipitation with alcohol. Clinical experience showed that insulin reduced the blood sugar of diabetics, lessened the output of sugar in the urine, caused ketone bodies to disappear from the urine, and raised the respiratory quotient. The general condition of the patients treated with insulin improved physically and mentally, and relief from symptoms was obtained. Thus the facts observed in depancreatized dogs to which insulin was administered, were confirmed by its subcutaneous injection in man.

Significant as were the results obtained by the treatment of severe types of diabetes in the first days of the use of insulin they were eclipsed by the effect of insulin on patients suffering from coma. Of ten cases in the first batch treated in Toronto, six recovered from coma, who would otherwise most certainly have succumbed. Insulin is a specific in the treatment of coma.

Before closing this survey of the historical facts in connection with insulin, it is well to recall that opinion is divided with relation to the nature of diabetes. On the one hand, it is regarded as a disease

of the pancreas; glycosuria, when it occurs with disease of the thyroid, pituitary or suprarenals is regarded as symptomatic. In this relation glycosuria bears the same connection with diabetes as albuminuria with nephritis. On the other hand a smaller school regards the disease as a symptom complex and does not attribute it to disease of the pancreas alone. Nevertheless the pancreas is the only organ which, when extirpated in an animal, will produce diabetes mellitus as known in man. Whatever the correct view is, there is no doubt that all glycosurics are not diabetics. All diabetics do not develop the severer types of the disease. Diabetes is normally regarded as a progressive disease, though it is not necessarily so. In interpreting the results of experiments on depancreatized dogs this question of the progressive nature of the disease in man, demands due allowance to be made for the essential difference in the two conditions.

Finally all diabetics do not derive corresponding benefit from insulin therapy, presumably <sup>such</sup> ~~these~~ cases are not uncomplicated cases of pancreatic diabetes.

### 3. CLASSIFICATION OF THE VARIOUS MODES OF TREATMENT.

#### A. Dietetic.

Up to the time of the introduction of insulin, the treatment of Diabetes consisted in control of the dietary. This was the only method of treatment which was of any real value. As a defect in carbohydrate metabolism is the most obvious the older clinicians confined themselves to limitation of carbohydrate intake, and made use of a meat diet, often containing large quantities of fat. It was not realized that Diabetes is a disease affecting the assimilation of proteins and fats as well. Controversies were carried on as to the relative merits of various purely empirical diets. It was observed that patients frequently died in coma a few days after admission to hospital. This was attributed to the excitement and fatigue of the journey, when in reality it was produced by the sudden withdrawal of carbohydrate and the excessive amount of protein and fat supplied: fat being the principal agent in the production of ketosis.

In order to appreciate the modern dietetic treatment of Diabetes it must be emphasised that all the ordinary articles of diet are involved in this general metabolic disease.

During the last ten years the whole conception of dietetic treatment has been altered by the work of

Allen in America. Reference was made before his day to the value of occasional hunger periods, but their significance was not understood and the principle of permanent underfeeding had not been propounded.

Allen performed partial pancreatectomy in dogs and discovered that, fed on a carbohydrate free diet consisting of protein and fat, the animals developed a severe type of diabetes and eventually died in coma. If animals in a similar condition were fed on a low diet in which all the constituents were curtailed, it was found that Diabetes did not supervene. If this low diet was exceeded, the remaining  $\beta$  cells of the islands of Langerhans in the pancreatic fragment were tired out and Diabetes developed with ultimate death.

Allen accordingly concluded that the human diabetic to obtain relief must balance his metabolism on an all round restricted diet, in other words, be permanently underfed on a starvation diet. Here one must recall that in the dog suffering from experimental diabetes, the remaining pancreatic fragment is healthy, whereas in the human diabetic the pancreatic defect is progressive, in the vast majority of cases. In the human diabetic the disease is aggravated by improper diet, but this can be rectified by control; the progressive tendency of the disease cannot be eliminated by diet. If the progressive activity is not rapid, diet is likely to yield favourable results.

The disappointing results are found in cases in which the disease is in an advanced state, quite apart from any errors in diet. At first perhaps the patients improve after dietetic errors are corrected, only to relapse as the remaining islets are overwhelmed by the rapid advance of the pathological process.

Modern dietetic treatment consists first in starving the patient until the urine is sugar free, and, secondly, in gradually building up a diet on which he can balance his metabolism, whilst remaining free from glycosuria and ketonuria. The minimum diet is arrived at by a consideration of the height and weight and the nature of the occupation of the patient. It has been found that to maintain equilibrium, it is necessary for from 25 to 30 calories to be supplied for each kilogram of body weight. One gram of protein is required each day for each kilogram of weight. In this way with the aid of Allen's diet Tables, or a modification of them, a suitable minimum diet can be selected.

#### Allen's treatment in detail.

Most clinicians are now agreed that as a general rule fasting may be begun straightway as soon as a severe case of diabetes comes under observation. There is but little danger of coma supervening. Otherwise, if ketosis is pronounced, one may begin by cutting off first the fats, and secondly the proteins, leaving carbohydrates to the last. The patient need not

necessarily be confined to bed, but it is well for him to keep at rest in one room. Tea, coffee and beef tea are allowed as required to assuage thirst. When the urine is free from sugar it is well to carry out an estimation of the blood sugar, for glycosuria may be absent although there is hyperglycaemia. If the blood sugar curve, plotted after the ingestion of glucose 50 grms., is to be kept for comparison with subsequent curves with a view to detecting increased tolerance of carbohydrate, it is essential to start with the blood sugar at starving level, otherwise fallacious deductions are apt to be made.

An attempt is next made to take the patient up a dietetic ladder. As soon as sugar appears in the urine, the patient goes back to the beginning to starve until he is free from sugar in the urine; he then tries once more to build up the diet. It is remarkable how much higher, after a fast, a patient can be taken up the ladder. If the patient loses weight it is to his advantage in many cases, for it enables him to maintain equilibrium on a diet which previously would have been inadequate in caloric value.

Every case requires repeated trials before a permanent diet can be arrived at. Often the greatest difficulties are encountered, but even these in time

can be overcome provided sufficient attention is paid and experiment made. No deviation can be allowed from a diet once established until sufficient time has elapsed, usually some months, for some degree of tolerance to be recovered by the pancreas, and then only gradually are increases allowed.

When a permanent diet is reached it is usual to give two vegetable and egg days once a fortnight, and a hunger day once a month. These undoubtedly allow of still further rest to the pancreas, and are invaluable.

Under this form of treatment the number of deaths from coma was greatly reduced in institutions, to which usually only the severer types of the disease are admitted; but many of the patients died subsequently in coma, after allowing themselves indiscretions of diet; the natural progress of the disease brought coma to many another.

Before the advent of insulin, coma, when established, meant almost certain death; only a few cases ever recovered from it. Various forms of treatment were advocated, but it is likely that death was actually accelerated in many cases by the enthusiasm with which treatment was carried out - notably with sodium bicarbonate.

Probably the most that can be said for Dietetic treatment of severe cases is that it delays the fatal day. The less severe cases benefit remarkably, many

of them, no doubt, being due to functional disorders of the pancreas brought on by dietetic excesses. Organic types improve when aggravation is removed by the substitution of a well ordered dietary. All these types are essentially those to be subjected to Allen's treatment, or one of its modifications. Dietetic control is still the alpha and the omega of treatment. It remains to show that severe and rapidly advancing cases may have the benefit of insulin therapy in combination with modern dietetic treatment.

## B. Drug Treatment.

Opium, and its derivatives, as well as many other drugs, have enjoyed reputations in the treatment of diabetes, but it can now safely be said that no drug will influence favourably the course of the disease.

Morphine and codeine were largely used, but these drugs have no specific action in diabetes. They act rather by dulling the appetite for food and so indirectly reduce the amount of sugar passed in the urine.

Drug treatment has now definitely fallen into abeyance in the light of recent advances in knowledge.

## C. Insulin Therapy.

### General Considerations.

There is already agreement that most cases of true Diabetes Mellitus will improve by treatment with Insulin. Insulin has, at the same time, complicated the treatment of the disease and controversies are many over details of treatment. There are two main schools of thought in relation to its use, One insists on the necessity of maintaining a normal blood sugar level in order to rest the pancreas entirely, and of supplying artificially all the insulin which is required for metabolism. The other school is content with keeping the urine free from sugar and disregards a slight hyperglycaemia. The best course probably is between these two views. The severe types of the disease will be found to require a normal blood sugar level in order to save the last remaining islets, whilst the milder cases can better stand the strain of a slight hyperglycaemia. It is possible that even a slight hyperglycaemia may be detrimental and produce such degenerative changes, as are found in the cardio-vascular system, when persisting over a long period of time; but this point has yet to be cleared up. In relation to sudden death in a diabetic cardio-vascular changes are of great importance.

The result of insulin treatment is beneficial in the majority of cases, whilst in the remainder it may

well be described as dramatic. The patient's enlightened mental outlook forms one of the most notable improvements, weight is put on, the appetite becomes normal, and thirst is no longer troublesome. Coincident with the abatement of symptoms there is noted a blood sugar level approaching normal, freedom of the urine from sugar and an absence of ketosis.

Insulin is a dangerous drug which demands a special study before one can be said to be sufficiently capable of undertaking its use. It is a good slave, but a bad master. Injudiciously administered it will produce death.. No laxity in dietary or insulin dosage can be permitted. Moreover, it is so subtle an agent that disappointment will come to the most skilled.

#### Cases suitable for insulin treatment.

At the outset it must be stated that the majority of diabetics do not require insulin. The mild and less severe types do perfectly well on Dietetic Treatment, if they will keep to it. If insulin is given to them it is to allow them a more ample diet with a view to satisfying the palate and promoting fidelity to diet tables.

Before deciding whether a case is a suitable one for insulin treatment it is essential to make a diagnosis of Diabetes Mellitus. This may be easy, or it may be difficult, but given that a diagnosis is clear

and established it remains to lay down certain indications for recommending treatment. One must exclude cases with a low renal threshold for sugar, the cases of so-called renal glycosuria; and such a case as one of carcinoma of the stomach, associated with emaciation, weakness, thirst, and diabetes, in which happy results could not be expected from insulin. The more carefully cases are selected, the better will be the results with insulin.

All severe types of Diabetes Mellitus are suitable for treatment with insulin, those in which less than 25 calories per kilogram of body weight can be assimilated; and those which are going downhill in spite of careful dietetic treatment. It would be feasible for a clerk leading a sedentary life to continue on dietetic treatment alone, where a farmer would be unable to carry out his arduous duties on a similar low caloric diet; for him a diet must be supplied suitable for his occupation, which would necessitate the use of insulin.

#### Duration of Treatment.

With the present state of knowledge it is necessary to inform the patient that once begun, insulin must be administered for the remainder of his life. This introduces the economic question, which is the most important consideration to be borne in mind when advocating insulin.

### The Cost of treatment.

It must be remembered that insulin treatment may cost anything from twenty to one hundred and fifty pounds sterling per annum. This is a heavy burden for the majority of members of the middle classes and may be a serious drain on family resources. This point requires thought, for already not a few tragedies have been staged after this fashion. The parents promise to continue insulin treatment for a child, who goes home only to find that they cannot afford to keep up payment for the supply; a few weeks pass and one hears that the child has relapsed, gone into coma, and died. Nothing could be more unreasonable than to allow any patient to experience the benefits of insulin and then to allow him to drift back into so pitiable a condition.

The luxury use of insulin to allow of high diets is indeed harmful. Allen quotes the case of a man who thought himself so much improved that he omitted insulin, and came into hospital in coma, to die  $7\frac{1}{2}$  hours later.

There may be an objection to repeated hypodermic injections. Moreover, if given by the medical attendant or nurse, they greatly add to the cost of treatment. It is dangerous to allow the patient to make his own injections in the early stages of treatment, and on no account should such a practice be permitted.

After treatment has been stabilised, the patient may be trained in the necessary technique of injecting insulin, and should be capable of testing his own urine for sugar and ketones. He should be able to recognize the onset of hypoglycaemic symptoms as such.

#### Insulin in general practice.

It is the duty of the practitioner to give his patient the benefit of insulin treatment, if he has satisfied himself that the case is indeed a suitable one. This can be conducted without blood sugar estimations, but the information which such estimations afford is so valuable that, when available, resort should be made to them in every case. More often than not, it may be impossible to have estimations carried out, much less have a curve plotted. One has a feeling of more definite control over insulin dosage, when the blood sugar level can be gauged accurately. There is not the same danger of hypoglycaemic reaction, and the blood sugar can be kept at a level more approaching the normal. Even a moderate hyperglycaemia must throw extra strain on the remaining healthy islets and tend to aggravate the disease. It is a moot point whether in mild cases a normal blood sugar should be insisted on. In severe cases there is grave danger in allowing hyperglycaemia to continue excessive.

Nevertheless, the practitioner who can devote time to the consideration of a fixed diet, and to the examination of the urine passed after such dietary,

is justified in beginning treatment with small doses of insulin, even without blood sugar estimations. He is handicapped, and is working in the dark, but he can make good. Important as was the control of the diet under Starvation Treatment, it is now a necessity when insulin is in use. Any attempt to allow unrestricted diet with loose insulin dosage, is foredoomed to failure, and may lead to disaster. This cannot be too strongly emphasised.

Having begun insulin treatment, the practitioner will proceed with caution to increase the dosage, until the urine contains but a trace of sugar. Any further increase must be made with the danger of hypoglycaemia ever in mind. But by small increases, the reaction should never be a grave one, and, if premonitory symptoms supervene, they can be quickly countered. The aim should be to provide a maximum diet consistent with a minimum of insulin, on which the patient will remain aglycosuric, or nearly so, and free from ketonuria.

The early phases of treatment are best carried out in a hospital or nursing home. Failing this the patient should be at home, preferably in bed, but at all events he should remain at rest in one room.

There is no suggestion that insulin will effect a cure even in the mildest cases. It must be admitted that insulin increases a tolerance for food, for, after prolonged treatment the dose is often able to be re-

duced; in other words a smaller dose is required to keep the blood sugar within normal limits. This has occurred in patients who showed no increase in tolerance on strict diet. Any improvement must be due to insulin. Insulin strongly supports the contention that true Diabetes is due to disease of the pancreas. It is commonly believed and held that the disease is a progressive one, but as treatment has improved, the disease has appeared to be less progressive. Insulin offers considerable support to the view that the disease is a functional one, following on a lesion, long since passed, such as acute pancreatitis. Insulin has vastly improved the treatment of Diabetes, and has complicated it enormously.

#### Insulin in Coma.

It is in this connection that the value of insulin is indisputably established. It is not known why all cases of coma will not recover with insulin treatment, though the blood sugar is brought to normal and the urine freed from ketones. Some damage must be done from which the body cells are unable to recover, which prevents the process from being a reversible one. Coma is still far from being fully understood.

In coma glycosuria is of secondary importance and the object is to free the body of ketosis. It is impossible to say what doses of insulin will be required for this purpose. It is best to begin with

doses of 30 units, repeated at two hourly intervals, or less, and increased as required. For rapid action the insulin should be given intravenously. Most workers combine the use of glucose, but Maclean holds that although it may do no harm, he saw one case in which it appeared to neutralise the action of insulin.

In cases of coma there is no doubt that blood sugar estimations will render procedure easier, but there is often not time to carry them out, owing to the urgency of the situation, and one has to act with resolution. If the content were high, one would be prepared to leave out the administration of glucose; on the other hand, if close to normal, one would not risk giving insulin, without at the same time allowing sufficient glucose to insure against a sudden hypoglycaemia developing.

Glucose when used, is given intravenously in 5% solution, sterilisation at too high a temperature being avoided. In emergency one could safely use an unsterilised filtered solution. The view held is that glucose, when burnt up with the aid of insulin, permits of the proper metabolism of fats and frees the body of the products of defective fat metabolism. But all the insulin cannot be accounted for in this way and it would appear that it has a direct action on fat metabolism.

All the auxiliary methods of treatment should be applied. Sodium bicarbonate is probably beneficial

in the majority of cases, but massive dosage will do more harm than good.. In many cases of coma the bicarbonate content of the blood is not at fault; but this can only be elicited when laboratory methods are to hand and is beyond the range of practical politics. In the light of present knowledge sodium bicarbonate should safely be given in 5 gram doses up to 50 grams in 24 hours. The bowel should be washed out and saline given per rectum. It should not be forgotten that most cases of impending coma will respond to treatment on these lines, combined with the administration of plenty of carbohydrate, even if insulin is not available. The utilization of carbohydrate will lead to the proper combustion of ketone bodies.

#### Insulin in Surgical Practice.

Even on starvation diet it was possible to operate with a prospect of success on many cases which would most certainly have succumbed, in the days when treatment consisted in the restriction of carbohydrates. Insulin in large doses can be employed, with a generous diet, rapidly to bring the patient into a condition for withstanding operation. For this the large doses are required temporarily to insure that coma will not supervene. After operation insulin can be continued to prevent excessive ketosis and obviate coma.

Septic foci clear up remarkably under insulin, which produces this effect by keeping the tissues free

of excess of sugar. Sepsis in its manifold forms, as frequently meet with in Diabetes, is mainly prevented by insulin.

Thus in its application to Surgery, insulin offers one of its successful fields. Gangrenous limbs can now be removed with comparative safety, the patient's blood sugar having first been brought to normal and ketosis largely dissipated.

#### Effects produced by over dosage with Insulin.

Mention must be made of the now well recognised train of symptoms which follows the onset of hypoglycaemia, produced by over dosage with insulin. This hypoglycaemic reaction is not likely to develop in an alarming manner, if strict control is kept over the dietary, the urinary examination, and insulin dosage. The reaction varies in different individuals as to the level at which it will manifest itself, and in the same individual at different times. If the rules, herein after to be described, are followed, it is unlikely that serious trouble from hypoglycaemia will be encountered. Formerly in the earlier cases alarming incidents occurred, but now that the reaction is better understood, these are seldom seen, and, in effect, are prevented by careful supervision of dosage.

If treatment is not controlled by frequent estimations of blood sugar, the only safe procedure is to allow the patient to remain hyperglycaemic, to the extent of passing traces of sugar in the urine. In-

sulin should be given a few minutes before a meal is to be taken; preferably twice in the day, before lunch and before the evening meal, that is, before the principal meals at which carbohydrate is to be taken. The patient should have sugar available for ingestion at any time, should symptoms of hypoglycaemia manifest themselves.. It is well for a patient to experience mildly the sensations of hypoglycaemia whilst undergoing the preliminary stages of treatment. Once experienced he will recognise them again and be ready with his sugar. A supply of sugar is conveniently carried as barley sugar, or a 50% solution of glucose may be put up in a bottle, with directions for from 1 to 2 oz. to be taken as required.

The effect of insulin lasts from two to four hours, sometimes up to eight hours. It should not be given late at night in order that symptoms of hypoglycaemia may not come on during sleep. This danger has been exaggerated, and should largely be dissipated if dosage and diet are properly controlled. One would not increase dosage at night or begin a new batch of insulin.

If a diabetic under insulin treatment becomes sick and goes off his food,, there may be a doubt in the mind of the clinician as to the cause of the condition. It may be due to hypoglycaemia (over dosage with insulin) or to ketosis with coma impending (under dosage with insulin). Of the two, under proper conditions

of treatment, impending coma is the more likely, if either situation presents itself. When in doubt glucose should be given by the mouth; there is not time to estimate the blood sugar and urinary tests may be misleading. If the condition is due to an overdose of insulin the patient will quickly show signs of recovery. If no such rapid recovery is obtained, the condition demands the administration of insulin to counteract ketosis. It is uncomfortable for the physician to be in the dark as to the exact condition of a sick diabetic, but it is reassuring to know that there is a definite line of action to be pursued in such a case. Glucose is required for hypoglycaemia and for impending coma, for reasons already detailed.

If a hypoglycaemic reaction is well established epinephrin 1 c.c. or pituitarin 1 cc. may be injected as an expedient, rapidly to raise the blood sugar level. Glucose solution must be given intravenously, subcutaneously, or per rectum as quickly as possible.

#### Insulin Dosage.

It is impossible to lay down hard and fast rules for insulin dosage. As with the arrangement of a diet each case is a law unto itself. Dosage can only be gauged by trial, though some indication can be acquired by studying the fasting level of the blood sugar. The writer began by using a fixed diet with a small dose

of insulin, which was gradually increased until by trial the optimum dosage was discovered. He has since found that recently this method has been advocated by Maclean as the most generally applicable. Certainly it seems the simplest method to master, the least fraught with danger, and such as can be carried into effect by the busy practitioner. Short cuts should not be attempted unless the investigation is being carried out in conjunction with a bio-chemist. Increases in dosage should be made gradually in order to avoid any possibility of large over dosage.

The patient should be placed on a diet of about 2,000 calories, and in any case not greatly in advance of his tolerance.

Insulin may be given in doses of 5 to 10 units twice daily according to the severity of the case and increased gradually till the urine is sugar free or there are slight symptoms of hypoglycaemia. When in doubt about making an increase in dosage, the urine should be passed and tested before giving the injection. One may then reduce the dosage for the time or increase the carbohydrate in the next meal.

#### 4. SUMMARY

1. Make sure that the case is indeed one of Diabetes Mellitus by a critical review of the symptoms and signs.

2. When in doubt, and always where possible, study the blood sugar curve after the ingestion of glucose, 50 grms. Or, alternatively, ascertain the fasting blood sugar level.

3. If the case is not a severe one, treat on dietetic lines. (Allen).

4. Insulin benefits most cases of true Diabetes Mellitus, but comparatively few cases require it.

5. All severe types of the disease should have the benefit of insulin treatment, if a suitable diet cannot be built up to allow of normal activities being carried on: and provided that the economic situation permits of insulin treatment being continued indefinitely, as is necessary in the present state of knowledge.

6. Make use of a fixed diet. Begin with small doses of insulin, and increase gradually until the requisite dosage is attained.

7. Blood sugar estimations are not essential; they give invaluable information, and should always be resorted to, if possible.

8. Glucose or barley sugar is always to be carried by the patient; to be taken to obviate a hypoglycaemic reaction.

9. Hypoglycaemic reactions are now infrequent on a fixed diet, with gradual increase in insulin dosage.

10. A diabetic under insulin treatment, who becomes sick and goes off his food usually has coma imminent, if not hypoglycaemia. When in doubt, feed glucose, and if recovery is not immediate, give insulin.

11. Insulin in coma is specific. Combine with it all the accepted auxiliary methods of combating ketosis, including glucose.

12. Treatment with insulin is well within the range of the general practitioner, provided he can give time to the extremely careful supervision of dosage, which is essential.

## 5. BIBLIOGRAPHY.

Allbutt's System of Medicine.

Allen, F.M. and Sherrill, J.W. Journal Metabolic Research. Nov-Dec. 1922 p. 803 Clinical Observations with insulin. The use of insulin in diabetic treatment.

Banting, F.G. and Best, C.H., Canadian Medical Association Journal, March 1922, pp. 141-146. Pancreatic Extracts in the Treatment of Diabetes Mellitus.

Banting and Best, Journal of Laboratory and Clinical Medicine, Vol. VII. 1922, p. 464. Pancreatic Extracts.

Banting, Best, Collip, Macleod, and Noble. American Journal of Physiology, Nov. 1922 p. 559. Effects of Insulin on experimental hyperglycaemia in rabbits.

Banting, Campbell, and Fletcher. British Medical Journal. 1923 Vol 1. p. 8-12. Further clinical experience with Insulin.

Banting, Campbell and Fletcher. Journal Metabolic Research, Nov-Dec. 1922 p. 547. Insulin in the treatment of diabetes mellitus.

C. v. Noorden and S. Isaac, Klinische Wochenschrift. Oct. 22nd - 1923 p. 1968. Experience with Insulin in 50 cases of Diabetes.

Cambridge, Glycosuria and Allied conditions 1913.

Cambridge and Howard. New views on Diabetes Mellitus, 1923.

Campbell, W.R. Ketosis, acidosis and coma treated by Insulin. Journal Metabolic Research, No. 5-6 p. 605

Dictionary of Practical Medicine. Morris, Langmead and Holmes.

Fagge. Principles and Practice of Medicine.

Foster. Diabetes Mellitus 1915.

Fletcher, A.A. and Campbell, W.R. The blood sugar following insulin administration and the symptom complex - hypoglycaemia. Journal Metabolic Research Nos. 5-6, p. 637.

Fitz, R., Murphy, W.P. and Grant, S.B., The Effect of Insulin on the metabolism of diabetes. Ibid.

Graham, G., and Harris, C.F., The treatment of Diabetes Mellitus with Insulin. Lancet, June 9. 1923 page 1150.

Geyelin, H. Rawke Harrop, G., Murray, Marjorie, F. and Corwin Egenia. The use of insulin in juvenile diabetes.

Hill and Eckman. Allen (starvation) treatment of Diabetes 1921.

Joslin, E.P. Insulin in hospital and home. Journal Metabolic Research. No. 5-6. p. 651

Labbe. Diabetes Mellitus, translated Amstutz 1922.

Lyon, D.M. Insulin Therapy. Edinburgh Medical Journal. Nov. 23 p. 565.

Maclean, Hugh. Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes.

Maclean, Hugh. Insulin in General Practice.

Macleod, J.J.R. Insulin and Diabetes, B.M.J. 1923, p. 833.

Osler and Macrae. System of Medicine.

Proceedings of the Section of Medicine, British Medical Association, B.M.J. 1923 p. 445.

Proceedings Royal Academy of Medicine in Ireland. B.M.J. Nov. 24. 1923 p. 983.

Quain's Dictionary of Medicine (1883)

Whitridge Davies, H., Lambie Charles, G., Lyon, D.M., Meakins, J., and Robson, W. The Influence of Insulin upon Acidosis and Lipaemia in Diabetes. B.M.J. May 19th 1923. p. 847.

Wilder, Bothby, Barboroka, Kitchen and Adams . Clinical observations on Insulin. Journal Metabolic Research. Nos. 5 and 6. p. 701.

Williams, J.R., A clinical study of the effects of insulin in severe diabetes. Ibid p. 729.

Woodyatt, R.T., The Clinical use of Insulin. Ibid p. 793.

6. APPENDIX.

The author considers that the special points to which attention must be devoted in using Insulin will be well brought out by relating his first experience with the product.

He made use of insulin on April 26th 1923 with the first supply to reach the South West of England. This was prepared by Messrs Allen & Hanburys. Information for its administration was scanty as only comparatively little experience had been gained in this country with insulin - probably not more than fifty cases in all had been observed under its influence.

The case of which details will be found below was a severe one. When the insulin was injected there was a marked local reaction. So uncomfortable was the urticarial eruption produced at the site of injection, that it precluded lying on the arm at night and prevented sleep. The patient began rather to dread each injection and it was with relief that one found that the next batch supplied by Messrs Allen & Hanburys did not produce a like reaction. It had been made by Lilly of Indianapolis. Both preparations of insulin reduced the sugar and largely abolished the ketones from the urine. They seemed to be equally efficacious in bringing about a sense of well being in the patient. Thereafter insulin prepared by Lilly was used, except

on one occasion when a second batch of insulin prepared by Messrs Allen & Hanburys was injected on May 25th 1923 to ascertain whether it would produce an urticarial reaction or not. In the event the urticaria was more marked than before and the use of this brand of insulin was definitely given up. It evidently contained some protein foreign to the patient, which the insulin prepared by Lilly did not contain. This has been the experience of other workers, who have found that if one brand of insulin produces urticaria, another in all probability will not do so in the same patient.

### Personal and Family History.

Mrs. X. aged 44 years had suffered from Diabetes Mellitus for 15 years. Glucose was found in the urine after the birth of her second child. She had been an athletic woman who, as a school girl, had been an accomplished gymnast. In addition she had played county hockey. She attributed her disease to athletic overstrain during adolescence. There was no family history of Diabetes Mellitus.

At the time that glucose was first discovered, complaint was made of excessive thirst and lassitude, There was a tendency to fall asleep whilst sewing, reading or playing cards. The medical attendant ordered a diet in which carbohydrates were restricted. It had the desired effect and lessened the excretion of sugar. Glucose was not continuously present during the earlier years. The patient noticed that in the summer months the urine became free of sugar, during which time she felt normal in health. But these intervals of freedom became less frequent and the disease progressed from year to year until glucose was always present, with the symptoms associated with Diabetes Mellitus.

### Recent History.

The patient came under the author's care in 1920 when he attended her after a miscarriage, the sixth since the birth of the second child. She refused to

undergo starvation treatment, as two of her friends had submitted to it and had relapsed and died shortly after leaving nursing homes, apparently much relieved. But she submitted to an all round restriction of diet on which she passed less sugar and became free from pruritus. The disease however advanced, vision became impaired though there was no evidence clinically of optic neuritis, carbohydrate tolerance became further impaired, whilst ketones were more often present in the urine than not.

When insulin became available, it was felt that by its aid the disease might be checked in its advance to otherwise inevitable coma.

The blood sugar curve had been plotted after the ingestion of 50 grm. glucose on January 8th 1923.

Three hours after a meal, blood sugar 0.206%, 50 grams of glucose given.

Blood sugar	$\frac{1}{2}$	hour after.....	0.312%
"	"	1 "	" ..... 0.362%
"	"	1 $\frac{1}{2}$ "	" ..... 0.337%
"	"	2 "	" ..... 0.325%

During the whole of this period sugar was passed in the urine.

The curve showed the case to be of a moderately severe to severe type. A resting blood sugar of 0.206% was too high, and an effort had been made to adjust this by further restriction of the diet: but the patient would not keep to a fixed and measured diet until insulin held out to her hope of alleviation.

Blood Sugar Curve of Mrs. X.  
Diabetes Mellitus - 15 years duration.

---



50 gr. glucose given, 3 hours after a meal  
at A. Resting blood sugar .206%  
January 8th 1923.

Grave defect in storage mechanism. High  
resting blood sugar.

### History under Insulin.

When insulin treatment was begun, the patient was kept on a rigidly fixed diet, which she herself weighed out and to which she kept most faithfully. Of a placid disposition, a better patient could not have been wished for. The diet from the standard, was varied as required according to the insulin dose to be given and to the amount of glucose in the urine. The patient tested the urine as soon as it was passed and recorded the presence or absence of glucose and ketones. Fehling's test and the nitro-prusside test were found most servicable. A rough guide to the amount of glucose was afforded by using Cowardine's apparatus. Gerhardt's test was employed as a quantitative guide for diacetic acid.

Unfortunately it was not possible to have the patient in a nursing home during treatment. Neither could she be kept from performing household duties. This no doubt confused the results and made treatment more difficult, but such are the usual conditions under which general practitioners have to treat most of their patients. It is only by simplifying insulin treatment that the preliminary stages can be worked out in general practice.

At first 10 units of insulin were given twice daily with a fixed diet, Maclean's 15th day <sup>diet,</sup> calories 1968. The insulin was given before lunch and tea, and

the patient was instructed to keep a supply of sugar in the pocket in case symptoms of hypoglycaemia should supervene. Once or twice when symptoms of a mild hypoglycaemia presented themselves, recourse was had to this supply of sugar. The symptoms consisted in a feeling of faintness, combined with a sensation of loss of power in the lower limbs, associated with sweating and general lassitude. At no time were the symptoms alarming or pronounced, and a hypoglycaemic reaction proper never developed.

The urine was practically always sugar free in the morning and ketones were present. Ketosis was the chief difficulty. In order to eliminate ketosis, the insulin dosage was increased together with additional carbohydrate in the diet, but the desired effect was not obtained. An unfavourable view was taken of the continued ketosis and as the supply of insulin was strictly limited, two vegetable and egg days were ordered. There after the treatment became easier, the urine became practically free of sugar and ketosis was slight. For many days 10 units of insulin sufficed to balance metabolism on a fixed diet.

Meanwhile the improvement in the mental attitude of the patient was encouraging. There was less irritability and a greater capacity for mental exertion. The patient expressed herself as not having felt in such good health for many years. Constipation had been a troublesome symptom and for many years an

enema each day had been a necessity. Under insulin there was no constipation, a daily evacuation being obtained without artificial aid. The appetite for food became normal; thirst and polyuria disappeared. The skin became less thick and dry, and the hair more glossy. The hectic flush left the cheeks. Whilst under the influence of insulin the patient led a life as near to normal with regard to comfort of mind and body as it was possible to make it.

It is but fair to record that in those early days when but little had been recorded in relation to the clinical application of insulin, one worked with a measure of anxiety. The product is enormously potent and its properties are still but imperfectly understood.

On June 19th Mrs. X. woke up complaining of pain behind the sternum, so severe that prolonged faintness supervened. There was retching and vomiting of mucus. Brandy was administered and the patient took sugar thinking that her symptoms might be due to hypoglycaemia. After this she felt better, but remained in bed. The writer saw her at noon, when she looked pale and heavy-eyed. The question of coma came to the mind at once. There was a trace of sugar and diacetic acid in the urine. One hesitated to give insulin, wishing to wait the development of events. Tea with sugar was ordered and sodium bicarbonate and warm water to wash out the stomach, the patient to remain in bed until the writer's return. Any urine passed was to be

kept.

There was no suspicion that a catastrophe was about to occur. At 5 p.m. Mrs. X. was lying dead on her bed. The urine passed during the afternoon contained sugar and Gerhardt's test was positive - one plus sign - but the patient had taken no solid food for nearly 24 hours.

At 4.30 p.m. Mrs. X. went to the lavatory; shortly afterwards groans were heard. By the time the door had been unlocked the patient was dead, and so the writer saw her on her bed, on which she had been placed by her friends.

After weighing all the evidence one came to the conclusion that death was due to angina pectoris.

During the War the patient consulted her doctor on account of pain behind the sternum, which was taken to be due to indigestion. At various times she had complained of pains in the shoulders and knees, for which a streptococcal vaccine had been supplied. She had also had what was taken to be a fibrositis in connection with the left shoulder and arm.

Early in June 1923, the patient complained of indigestion, a tight feeling behind the sternum, which an alkaline mixture alleviated. The cardio-vascular system was taken to be reasonably efficient and had not given cause for anxiety. It presented no signs of disease on examination. The cardiac response to effort was good.

Owing to the distressing nature of the case a post-mortem examination was not asked for as one had no doubt that death was due to angina pectoris. Having communicated with the coroner, one gave the necessary death certificate.

Death was not due to hypoglycaemic reaction, since sugar was present in the urine all day. There was not sufficient evidence to advance the theory that death was due to sudden coma, and the degree of ketosis was not such as to support it.

Naturally the relatives were inclined to believe that death was due to the new form of treatment. Happily one was able to demonstrate that death was not due to over dosage with insulin, as evidenced by the presence of sugar. Under dosage with insulin could equally effectively be ruled out. The history of an anginal attack in the morning followed by sudden death at stool, left no doubt as to the cause of death.

Similar cases are not unknown in the literature.

Joslin, Grey and Root (Journal of Metabolic Research, Nos. 5-6 pp. 668 and 9) relate the death from angina pectoris of a patient who had suffered for 14 years. He entered hospital on November 16th 1922 and died during the early hours of November 22nd 1922 after having received 28 units of insulin in 6 days. They direct attention to the possibility of under nutrition, lowered blood pressure, and blood

volume, contributing to coronary occlusion. Such a case is of importance and merits attention. Insulin was in no way responsible for death.

SUMMARY OF INSULIN TREATMENT

Mrs. X. aet 44 years.      Weight on May 2nd 1923, 8st. 13 lbs.  
June 16th 1923, 8st. 12 lbs.

<u>Date</u>	<u>Day</u>	<u>Diet</u>	<u>Units of Insulin</u>	<u>Urine etc.</u>
April 24, 1923	1	Vegetable & Egg	Nil	Sugar present.
25	2	Vegetable & Egg	Nil	Sugar present.
26	3	15th day, 1968 calories.	20	Sugar present; slight hypoglycaemia; urticaria
27	4	do	10	Sugar free by 5.30 p.m.
28	5	do	Nil	Practically sugar free all day.
29	6	do, with slight additions	Nil	Trace sugar all day.
30	7	15th day diet only	10	Sugar and trace of ketone
May 1	8	15th day, with additions	20	Sugar free.
2	9	15th day diet only	20	Trace sugar.
3	10	do	10	Fasting, blood sugar 0.207%
4	11	15th day + potato 1 oz. & bread 1 oz.	20	Sugar free, trace ketone.
5	12	do	20	Sugar and ketones.
6	13	15th day diet only	20	Ketones all day

<u>Date</u>	<u>Day</u>	<u>Diet</u>	<u>Units of Insulin</u>	<u>Urine etc.</u>
May 7 1923	14	15th day, with additions	30	Morning blood sugar 0.112 acetone all day till evening, when sugar reappeared and acetone departed. Trace ketone all day; sugar at night. No urticaria.
8	15	15th day	10 (American)	
9	16	do.	30	Trace sugar and ketone
10	17	do.	30	Trace sugar and ketone
11	18	do.	10	Trace sugar and ketone.
12	19	Veg. & Egg.	Nil	Free sugar; ketones present.
13	20	Veg. & Egg.	Nil	Free sugar; ketones present.
14	21	15th day	Nil	Free sugar; some ketones
15	22	15th day c	Nil	Sugar towards evening.
16	23	slight addition do	25	(Approx) Free sugar, some ketones.
17	24	16th day 2228 calories	20	(Approx) Free sugar, some ketones.
18	25	16th day	20	(Approx) Free sugar, some ketones.
19	26	do	15	Free sugar; some ketones
20	27	do	15	do.
21	28	do.	15	do.
22	29	do.	10	do.
23	30	do.	10	do.

<u>Date</u>	<u>Day</u>	<u>Diet</u>	<u>Units of Insulin</u>	<u>Urine etc.</u>
May 24 1923	31	16th day	10	Free sugar; some ketones
25	32	do	10 (Allen & Hanbury's)	do do (Urticaria magna)
26	33	do	10 (American)	Free sugar; some ketones
27	34	do	Nil	Sugar at night.
28	35	do	10	Trace sugar, trace ketones.
29	36	do	10	Sugar free; trace ketones.
30	37	do	10	Sugar free; trace ketones.
31	38	do	10	Sugar free; trace ketones in the morning
June 1 1923	39	do	10	Trace sugar; trace ketones.
2	40	do	10	Free sugar; free ketones.
3	41	do	10	Some sugar, increased ketones after journey in motor omnibus.
4	42	do	10	Trace sugar and ketones
5	43	do	10	Free sugar, trace ketones.
6	44	do	10	Some sugar, trace ketones.
7	45	do	10 (new batch)	Trace sugar, trace ketones.

Date June 8 1923	Day 46	Diet 16th day	Units of Insulin	Urine etc.
9	47	Veg & Egg.	Nil	Increased sugar and ketones after attending public luncheon. Free sugar; acetone all day.
10 11	48 49	Veg. & Egg. 16th day	Nil 10	Free sugar; Gerhardt + Practically sugar free; Gerhardt + in the morning ketones decreased as day advanced.
12	50	16th day	10	Sugar in the evening after dancing a few steps; ketones increased all day.
13 14	51 52	do do	10 10	Sugar free, some ketones Sugar free, trace ketones.
15	53	do	10	Sugar free, trace ketones.
16	54	do	10	Sugar free, trace ketones.
17	55	15th day	Nil	Sugar free, trace ketones.
18	56	16th day	10	Sugar free, trace ketones.
19	57	Sugar, bovril, tea and sodium bicarbonate	Nil.	Sugar and Gerhardt + during afternoon, sudden death at 5 p.m. whilst sitting on lavatory seat.

*Sugar ketones present at 11.00 a.m.*

