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TRADE MARK 'WELLCOME' BRAND

INSULIN

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INSULIN

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INTRODUCTION

As long ago as 1889, it was shown experimentally that diabetic symptoms followed extirpation of the pancreas in the dog. Later work indicated that these symptoms were due to the absence of an internal secretion, necessary for normal carbohydrate metabolism, which is constantly secreted into the blood of the healthy subject, and that this secretion appears to be produced by the collections of specialised tissue contained in the pancreas and known as the Islets of Langerhans. As a result, it is now very generally accepted that *diabetes mellitus* arises from a degenerative condition of these islets, with a consequent deficiency of their secretion, and many attempts have been made to isolate the active principle concerned, with a view to its employment in the treatment of diabetes.

Historical notes

In 1922, it was announced that workers in the University of Toronto had succeeded in producing a preparation containing this active principle—to

which the name Insulin was given—in a form suitable for therapeutic use, and that satisfactory results had followed its injection in cases of *diabetes mellitus*. The aim of the Insulin treatment is to supply the patient with sufficient of the active principle to make up for the deficiency of his natural supply, and so to enable him to metabolise an adequate quantity of carbohydrate.

Control of the manufacture of Insulin in the British Isles is vested in the British Medical Research Council. By them a licence for its preparation has been granted to Burroughs Wellcome & Co., who now supply Insulin of their own manufacture under the 'WELLCOME' Brand.

'Wellcome' Brand Insulin

'WELLCOME' BRAND INSULIN is prepared throughout by Burroughs Wellcome & Co., whose exceptional equipment, together with their pioneer work and extensive experience on the chemical and pharmaceutical side of biological therapy, places them in a particularly advantageous position for work of this nature.

'Wellcome' Brand Insulin consists of a sterile aqueous solution of a material obtained from fresh pancreas by a complicated process of fractionation, designed to concentrate the specific activity of the Insulin, and to eliminate constituents which would lessen its stability or render its injection liable to produce irritating or toxic effects. A method of purification of the final product is adopted which makes it possible to eliminate over 90 per cent. of the

British Insulin

solid matter contained in the crude end-product obtained by the original Canadian process, and to present the active principle in the form of hydrochloride, in high concentration, and free from accidental irritants or other substances.

'Wellcome' Brand Insulin is issued in rubber-capped, amber glass phials containing 100 units in 5 c.c. of solution. **It should be stored in a cool place.** Before issue each batch is biologically tested under the supervision of the British Medical Research Council.

Administration and Dosage

'Wellcome' Brand Insulin is administered by hypodermic injection with due precautions as to asepticity and sterility. The injection should be made with a fine needle, preferably under the skin of the upper arm. A slight tingling or discomfort may be caused for a few minutes, but no prolonged effects of local irritation or reaction have occurred, and the same place may be used again and again for injections.

The dose is indicated in units, the unit being determined by an animal test, and being defined as the quantity needed to produce a prescribed change in the blood-sugar of the normal rabbit. For a mild or moderately severe case of *diabetes mellitus*, the effective dose is about 20 units daily, preferably divided into two or three injections, each given 15 to 30 minutes before one of the principal meals. For severe cases, twice this dosage, or more, may be necessary.

Clinical Evidence

The use of Insulin in diabetes was investigated at various hospitals during a period of four months, and the results obtained were published in a report to the British Medical Research Council. A general summary is given of the experience of workers at the various clinics in those centres where the Council had organised local laboratories for the production of Insulin. Samples of Insulin prepared at these laboratories were at first used, but latterly samples prepared on a commercial scale were employed with identical results. At each clinic special cases were selected and the results of the administration of Insulin carefully observed in detail. The information thus obtained may prove of service to physicians who are desirous of commencing treatment on their own account.

Medical Research Council Report

Effect on Diabetes Mellitus

Treatment with Insulin was carried out at eight different hospitals for a period of about three months, and during that time fifty cases, including seven of coma, were dealt with. The results obtained were very satisfactory, all the patients, except the cases of coma, showing admirable improvement. As a result of each injection, the blood-sugar was found to fall rapidly, and it was discovered that sugar may be prevented from appearing in the urine even on a diet three or four times as great as could formerly be tolerated. There is a steady

Fifty cases treated

increase of weight, together with a sense of greater warmth and energy. Acetone vanishes from the breath and aceto-acetic acid from the urine; lipæmia disappears, while acidosis and dyspnœa are immediately brought under control. It must be emphasised, however, that such results were obtained only with Insulin. Other commercial extracts of the pancreas tested were found to be totally incapable of producing the slightest fall of blood-sugar.

No alternative method to hypodermic administration has yet been evolved. Injections must be repeated at least once each day, and though these are able to control all the ordinary symptoms of diabetes, the effect is only temporary. So far, there is no real evidence that Insulin can effect a complete cure of the more serious forms of diabetes, but to such cases it holds out the hope of at least a prolongation of life, with greater strength and ampler dietary, though to gain even that result the treatment must be continuous.

Dosage and Effect

The average single dose of Insulin for an adult patient is 10 units, and the physician is recommended to think in units rather than in so-called doses. In a healthy subject, starved previously for 15 hours and remaining without food, the injection of 30 units will cause a fall of blood-sugar, commencing in less than half an hour and progressing for about three hours. This fall may vary from the normal level of 0·12 per cent.

Fall of blood-sugar

to 0·06 per cent., near which level definite and serious features of sugar deficiency are likely to appear. A larger dose of Insulin is required to produce this critical fall in the healthy human being whose liver is stored with glycogen, than in the emaciated diabetic, in whom a rapid fall of blood-sugar and the development of hypoglycæmic features more readily occur. The incidence of this hypoglycæmia can be immediately checked by the administration of glucose, but it should be avoided altogether by a careful attention to the time of giving Insulin in relation to the taking of food.

Administration in Relation to Food

Insulin should never be administered during periods of abstinence from food. The effect of Insulin lasts for a period up to eight hours, while glucose reaches the blood soon after a meal and continues to do so for from two to four hours, varying as the meal is carbohydrate or protein. Each injection should, therefore, be followed by a meal in about a quarter of an hour, and more food should be given at periods of three to four hours until the effect of Insulin has passed beyond the stage where it might reduce the blood-sugar to a dangerously low level. Two small doses at fully-spaced intervals are obviously safer than one large dose daily, and a large dose should never be given in the evening, since serious changes might occur during sleep with its consequent abstinence from food.

Time for administration

It has been found that one unit of Insulin provided for the consumption of 2 grammes of carbohydrate taken as such in the food of a completely diabetic patient. Since protein food contains nearly half its weight of potential carbohydrates, the same dose of Insulin should provide for at least 4 grammes of protein. It must be borne in mind, however, that the carbohydrate from protein enters the blood much more slowly than does that of carbohydrate food taken directly as such, and that diabetic patients in general vary greatly in the amount of Insulin required to cover the food taken, while individual patients may vary from time to time. The dosage of Insulin necessary to suit any special scale of diet cannot, therefore, be definitely stated at present. Each case must be tried and settled on its own requirements, while a careful lookout must be kept for any changes in amount that may be indicated by the patient's symptoms.

Dosage and diet

Hypoglycæmic Reaction

The danger of hypoglycæmic collapse occurring from the use of Insulin would appear, from reports of cases treated, to be remote. This, however, may only be due to the careful treatment accorded to the patients and the watchful eye kept on their blood-sugar curves. Where a reaction does occur, it usually commences with a sense of weakness, sometimes associated with profuse perspiration, and further accompanied by faintness, dizziness and mistiness of vision. The patient may

Symptoms and treatment

experience a sense of drowsiness or exhibit anxiety from the sense of rapidly advancing weakness. The nervous reflexes are depressed. In this state the blood-sugar is generally as low as 0·06 or 0·05 per cent. Prompt recovery takes place in about a quarter of an hour on the oral administration of glucose from 10 to 20 grammes, or about ½ oz. in 3 or 4 oz. of water. Where a case has been allowed to pass into unconsciousness, subcutaneous or intravenous injection must be resorted to, 5 per cent. glucose solution in normal saline being used. Mild cases may be treated with cane sugar; the use of glucose is only essential for intravenous injection. The importance of a careful watch over the case cannot be over-emphasised as a reaction may result from some unsuspected chance, such as the patient failing to eat the meal that should follow an injection of Insulin. Glucose or cane-sugar should always be kept in readiness in case of any symptoms of hypoglycæmia becoming evident.*

Selection of Cases

Insulin is suitable for use in *diabetes mellitus* only, and must not be used in cases of renal glycosuria where, owing to excessive permeability of the kidneys, sugar is present in the urine after food though the percentage of blood-sugar remains normal. Renal glycosuria must, therefore, be carefully distinguished and excluded, since the use of Insulin

* In the *Lancet*, of April 7, 1923, *page* 716, the use of orange juice, 50 c.c. to 100 c.c., or glucose, 5 gm. to 25 gm., with orange juice, by the mouth, or glucose, injected intravenously or subcutaneously, is advised. Adrenalin, 1 c.c. of 1 in 1000 solution, injected intramuscularly, is also stated to be useful.

would be likely to bring about early signs of hypoglycæmic collapse. As a preliminary measure, ordinary diabetics should be put upon some recognised form of diet. In cases of fairly short duration, diet treatment may be sufficient or may, perhaps, require only a slight assistance from Insulin. Where, however, the disease is of long standing, with pronounced excess of blood-sugar and the patient, after starvation, is unable to tolerate any diet of less value than 1000 calories in 24 hours, so that strength and weight continue to fail, the systematic use of Insulin is clearly indicated.

Contra-indicated in renal glycosuria

Dosage in Severe Cases

In severe cases of diabetes the dosage indicated may be as high as 20 or 30 units twice a day, or a smaller amount divided between three doses. Where the disease is so severe as to warrant such doses, the patient should be treated at first in a special institution where the diet can be carefully controlled and the blood-sugar determined.

Special precautions

Under such conditions the ideal aim may be attained, namely, to keep the urine entirely sugar-free.

The following cases are quoted, briefly, to illustrate the doses of Insulin needed in severe cases :—

Case A.—Woman, 56 years old, with steadily progressive and very severe diabetes. During the last eighteen months she had repeatedly undergone dietetic treatment in hospital, at

first with immediate success, but ultimately tolerance could not be established on any diet sufficient to maintain life.

After five days' continued starvation, the urine became sugar-free. The subsequent tolerance was of a diet of only 190 calories in 24 hours.

By the administration of 60 units of Insulin each day she was enabled to tolerate 1350 calories daily, with 80 grammes carbohydrate, and her weight was raised in ten weeks from 5st. 10lb. to 7st. During the day the urine was sugar-free and contained no acetone bodies on this diet; but each morning the blood-sugar was over 0·4 per cent., and the urine contained sugar and a trace of ketone from the failure of her own unaided metabolic processes during the night.

Case B.—Man, aged 18, with severe diabetes for three years. On a diet of 600 calories, containing 20 grammes carbohydrate, he excreted 30 grammes of sugar daily. With Insulin, about 12 units daily, he could tolerate a diet of 1400 calories daily, containing 48 grammes carbohydrate, the urine being sugar-free and the blood-sugar below 0·2 per cent. His weight and strength have steadily increased.

Case C.—A very severe case, who had been kept just alive for the two months preceding Insulin treatment on a diet of 600 to 800 calories daily. On this he was excreting large amounts of sugar and ketone bodies, and seemed unlikely to survive many weeks. Insulin twice daily enabled such increase of diet to be made that there was a gain of weight of 15 lb. in the first fortnight. He was eventually raised to 2500 calories with 70 grammes carbohydrate, upon which, with slight glycosuria, he was able to return to work while continuing Insulin injections twice daily.

In the treatment of diabetes it is generally recognised that the essential principle is to avoid hyperglycæmia and glycosuria, in order that the

intrinsic powers of carbohydrate metabolism may be allowed to recover in the period of comparative rest from overstrain. The use of Insulin should assist this period of rest. Where Insulin is administered in such doses as to prevent sugar in the urine, the only remaining means of estimating the effect of the dosage is the blood-sugar test. If this cannot be carried out frequently, it may be safer to avoid the danger of hypoglycæmic collapse from too much Insulin by reducing the dosage so that the patient may show a very slight glycosuria which will act as an indicator. Though, perhaps, a slower means of approaching a cure, this method undoubtedly exhibits distinct advantages.

Blood-sugar test

In one case reported, which showed real improvement, all carbohydrate as such was excluded from the diet under Insulin. The report runs :—

Case D.—A man with severe diabetes, which had not yielded to rigid dietetic treatment some weeks previously in hospital. On 1360 calories, with 16 grammes carbohydrate, he passed from 25 to 33 grammes of sugar daily. The blood-sugar at 9 a.m. was 0·24 per cent. He was given Insulin, 12 units, each day at 9 a.m. with a meal, the first meal being at 6 a.m. The 9 a.m. blood-sugar gradually fell to 0·15 per cent. It was then found that three hours after 12 units of Insulin, the blood-sugar had fallen to 0·055 per cent. The daily dose of Insulin was consequently reduced to a lower level at 8 units daily. There was no glycosuria for three weeks, and only a small amount of ketone bodies persisted. Subsequently, the Insulin was reduced to 4 units daily, upon which a diet of 2000 calories,

consisting chiefly of protein and fat with carbohydrate as vegetables, is tolerated without glycosuria and with a blood-sugar of 0·11 to 0·13 per cent.

If this dietetic method should prove generally applicable, an economy in the use of Insulin and a better hope of cure will result.

Treatment of Coma

Only seven cases of coma treated at British clinics are reported, but these fall into two distinct classes. Three are described as coma developing as a result of surgical operations on diabetics. In these cases the blood-sugar during coma was very high—from 0·7 to 0·8 per cent. Air-hunger and dyspnœa were not conspicuous features, acetone in the breath was slight, nor was there much aceto-acetic acid in the urine. Hyperglycæmia was, therefore, great, though ketosis was not severe. Insulin effected no improvement, though in one case only was sufficient given to reduce the blood-sugar, so failure need only be written in that case. In one of the other cases, Insulin was administered too late, when the circulation had practically failed, and in the third the blood-sugar of 0·78 per cent. was practically unaffected by Insulin.

Coma following operations

Case E.—A woman of 70, with gall-stones but no obvious liver disease, with arterio-sclerosis and slight diabetes. She passed into coma directly after an operation in which the gall-stones were removed. After five hours of coma the blood-sugar was 0·79 per cent. Dyspnœa moderate, with faint odour of acetone in the breath and only a slight ferric chloride reaction in the urine. No extensor response or other neurological physical signs. Insulin was given subcutaneously in repeated doses of 30 or more units. Five

hours later, after a total of 105 units had been given, the blood-sugar was 0·4 per cent. Saline solution had also been given freely. There was absolutely no clinical improvement, and the patient died ten hours later. Post-mortem examination was refused. Clinically the condition appeared to be that of simple coma, though other possibilities cannot be rigidly excluded.

The other group of cases, four in number, were ordinary diabetic coma not associated with operations, and showing a low blood-sugar content, 0·2 to 0·4 per cent., but having greater air-hunger with depression of the alveolar CO_2 and with abundant ketosis. It is noteworthy that this second class, which showed ketosis rather than hyperglycæmia, was also the one in which the administration of Insulin caused a striking improvement.

Ordinary diabetic coma

Case F.—A man was admitted to hospital on the verge of diabetic coma, being just conscious, and with extreme air-hunger as shown by the big respiratory movements of his abdomen and chest. The blood-sugar was 0·33 per cent., a figure often seen in ordinary diabetics while in fair health; but the alveolar CO_2 was 1·1 per cent., a reading so low that in the experience of the physician in charge of the case it always meant death within about 12 hours, for he had never seen recovery in any patient with alveolar CO_2 lower than 1·8 per cent. Insulin, 18 units, was given; and abundance of water (15 oz. hourly), together with sodium bicarbonate 2 drachms by the mouth every two hours for three doses. In two hours the patient began to feel better, and his air-hunger was lessening at the third hour. At six hours the blood-sugar was 0·11 per cent. and the alveolar CO_2 had risen to 2·7 per cent. The patient recovered and now has a morning blood-sugar of 0·15 per cent. on 12 units daily of Insulin, and a diet of 53 grammes protein, 105 grammes fat, and 16 grammes carbohydrate in vegetables. There has been no glycosuria for three weeks.

CASE G.—A boy admitted in diabetic coma, with air-hunger and low bicarbonate reserve in the blood. Insulin given, but no sugar. Death.

CASE H.—A young woman of 25, in coma, with air-hunger, acidosis, and blood-sugar of 0·4 per cent. She was given Insulin subcutaneously, 10 units, every three hours; at the same time, fluid was given freely and glucose solution both intravenously and subcutaneously. The blood-sugar was thereby raised to the very high figure of 1 per cent. The patient recovered.

In the last case described there seems to be a paradox. Sugar is sometimes given in conjunction with Insulin in diabetic coma to prevent the comatose state being further aggravated by hypoglycæmic collapse. From the cases quoted above it would seem that coma might arise when the blood-sugar is not exceptionally high, and that the patient may be brought out of the comatose state even though the blood-sugar has been raised by the addition of 1 per cent. glucose. Another case reported above (*Case E*) of coma occurring after a surgical operation with high blood-sugar percentage, was not benefited by reducing the blood-sugar to 0·4 per cent. by Insulin. From these results it would appear that the percentage of blood-sugar has no direct relation to the occurrence of diabetic coma.

Since hypoglycæmic collapse is a result of lowering the blood-sugar to half its normal level in health, and since it is at once relieved by the administration of sugar, it would seem that the brain is as sensitive to the withdrawal of sugar as it is to sudden diminution of oxygen. An explanation of the condi-

tion of diabetic coma may be that the brain cells are no longer able to consume sugar even though it abounds in the blood stream. Insulin may restore their metabolic power, and their recovery may possibly be assisted by increasing the amount of sugar on which they can begin to feed. Whether or not this is correct, experience has suggested that, in the treatment of diabetic coma with Insulin, glucose should be simultaneously administered orally, by the stomach-tube, or even intravenously. The Insulin should be administered hypodermically, but in cases of extreme circulatory collapse it can be given without danger intravenously. Fluid should be given at the same time in all cases, but in amounts not exceeding half a pint per hour, lest the patient, on recovery from coma, be exposed to the danger of death from pulmonary œdema.

Simultaneous administration of glucose

From the scanty experience as yet gained in the treatment of coma following surgical operations, it would appear that treatment of that condition is a matter of difficulty. This should emphasise the desirability of its avoidance, to ensure which careful preparation of the patient before operation should be carried out, dietetic control together with Insulin being employed to free the urine from sugar and ketones.

Other Indications for the Use of Insulin

Such complications of diabetes as sepsis tuberculosis, or peripheral neuritis, as are influenced by ordinary dietetic methods may presumably also be

assisted by Insulin. This, however, is merely speculation, as, so far, the effects of Insulin on ordinary diabetes only have been investigated.

Conclusions

After many years of research on *diabetes mellitus* and on the physiology and pathology of the pancreas, it appears that at last there has been evolved a pancreatic extract which has a specific action on carbohydrate metabolism. It is, perhaps, as yet, too early to draw definite conclusions, but already some of the limitations of Insulin have been defined. Its indiscriminate or improper use is likely to produce results which will give a wrong and harmful impression of its merits. To avoid such, a proper knowledge of dietetics on the part of the physician, and a careful attention to the controlling factors already described, are essential. The practising physician who desires to make use of this remedy should carefully study all these points, and, if the precautions indicated are observed, there seems to be no reason why he should not obtain valuable results.

Advantages and limitations of Insulin

Preparation

TRADE MARK 'WELLCOME' BRAND INSULIN [B. W. & Co.]

Issued in rubber-capped, amber glass phials, containing 100 units in 5 c.c.

SPECIAL NOTE.—An extract from a statement, prepared under the direction of the British Medical Research Council, and giving authoritative details as to administration, type of cases suitable, and conditions necessary for Insulin treatment, dosage, etc., appears on pages 17-20.

The Insulin Treatment of Diabetes Mellitus

(Extract from a statement prepared under the direction of the British Medical Research Council)

Insulin is the name which has been given to that active principle of the pancreas which is constantly secreted into the blood of the healthy subject and plays an essential part in the normal metabolism of carbohydrates. This principle appears to be formed by the collections of specialised tissue known as the Islets of Langerhans, and it is a degenerative condition of these, and the consequently deficient production of Insulin, which produces the condition known as *diabetes mellitus*. The aim of the treatment of the diabetic patient with Insulin is to supply enough of the principle to enable him to metabolise a sufficient quantity of carbohydrate. Insulin has not yet been isolated in a state of chemical purity. It is supplied as the sterile, watery solution of a material obtained from fresh pancreas by a complicated fractionation, designed to concentrate the specific activity, and to eliminate constituents which impair the stability of the Insulin, or which have an irritating or toxic action when injected.

Aim of treatment

Mode of administration

The Insulin solution is administered by subcutaneous injection, with precautions as to sterility. Intravenous injection of Insulin is neither so safe nor so effective. When given by the alimentary canal, Insulin has no demonstrable action. Preparations of the pancreas recommended for administration by the mouth, whatever their effects may be, have not the action of Insulin.

Type of case suitable, and conditions necessary, for the treatment

There is no clear evidence, as yet, of a *curative* action of Insulin. It can replace the defective natural supply, but there is no ground for assuming that it can bring about a resumption of the normal function. While, therefore, a

With these qualifications, it may be stated that the effective dosage of Insulin, for the mild or moderately severe case of *diabetes mellitus*, will be about 20 units *per diem*, which should preferably be given in two or three injections, each injection preceding, by about 15 to 30 minutes, one of the principal meals. In severe cases, twice this number of units, or even more, may be needed. Each unit injected should enable the patient to take, with the ensuing meal, from 1 to 4 grammes of additional carbohydrate, or its equivalent, according to the severity of the case, without excreting sugar. The aim of the treatment should be to keep the blood-sugar of the patient, throughout the day, at or just above the normal level, so that no sugar escapes into the urine although the diet is augmented.

Effective dosage

NOTICE.—If any abnormal local or general reaction is produced by an injection of Insulin, the name of the manufacturer and the batch number on the label of the phial should be carefully noted. These should be sent immediately, accompanied, if possible, by the phial of solution responsible for the complaint, and a full description of the symptoms produced, to:—

THE DIRECTOR OF THE DEPARTMENT OF BIOLOGICAL STANDARDS, MEDICAL RESEARCH COUNCIL, THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH, HAMPSTEAD, LONDON, N.W. 3

NOTE.—The word 'WELLCOME' is a brand which designates fine products issued by Burroughs Wellcome & Co.

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