

A Clinical Assessment of Fetal Calf Insulin

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Early in their original work with insulin, Drs. Banting and Best were confronted with the problem of discovering a source of the hormone to meet the inevitable demands of the diabetic population throughout the world. At that time, the extraction of insulin seemed to depend upon the prior elimination of the external secretory portion of the pancreas. With this in mind Banting and Best, while working alone, explored the possibilities that fetal pancreas, before the development of its exocrine function, might provide a useful source of the hormone. Although fetal calf insulin was prepared in 1921 and used with dramatic success in diabetic dogs, it was never tested clinically, presumably because of an abundance of insulin soon made available from adult cattle by alternative technics.¹ Now, almost forty years later, a series of clinical trials of this substance have been initiated in order to fill this gap in the history of insulin.

METHODS

Banting's and Best's original notes were consulted and the insulin was prepared according to the procedure they used in 1921. Banting and Best used the pancreas immediately after they had removed it from the fetuses. Since we wished to prepare relatively large amounts of fetal insulin at regular intervals, it was necessary to collect and freeze the glands whenever they became available.

Two hundred grams of frozen fetal pancreas were cut into thin shavings and extracted for four hours in 200 ml. of acid alcohol (95 per cent ethanol, 0.6 concentrated HCl). The extraction was performed with continuous agitation at a temperature of 5 degrees C. The mixture was then filtered (later lots were centrifuged) and the filtrate was saved. The tissue debris was re-extracted for four hours with another 200 ml. of acid alcohol. The filtrates from the extractions were combined and evaporated nearly to dryness in a small vacuum still. The residue was dissolved in 50 ml. of

saline. The insulin content was assayed by the mouse convulsion technic and was found to be 24 units per ml. Berkefeld filtration provided sterility.* The insulin solution administered to the children (patients R.K. and I.D.) was diluted to 12 units per ml. while that administered to the adults was diluted to 20 units per ml.

Prior to its clinical use, two volunteers received small subcutaneous or intracutaneous injections of the fetal insulin extract on four separate occasions. It produced no detectable irritation or side effects.

RESULTS

At the Hospital for Sick Children,† Toronto, three children with diabetes of recent onset, while in the hospital for stabilization, volunteered for this experiment. They were treated with diet and were receiving 12 to 25 units of Lente and Crystalline Zinc Insulin. The material to be tested was injected in the morning, twenty to twenty-four hours after the last dose of insulin. The patients were fasted overnight and their breakfast consisted only of eight ounces of unsweetened orange juice, given approximately two hours before the experiment.

Fetal calf insulin, Lot CHB-2, was injected subcutaneously in a boy, R.K., and in a girl, I.D. Both were seven years old. Figure 1 shows the effect of this material upon blood sugar concentration and the precipitous fall is quite evident when compared to the blood sugar curve obtained on a thirteen-year-old diabetic boy who received 0.5 cc. of saline under the same experimental conditions. The material was well tolerated and there were no side reactions of any kind.

It was possible to compare fetal calf insulin with the

*Recent experiments carried out in this laboratory indicated that the original procedure also extracts a substance (possibly an enzyme) that destroys insulin over a three- to four-month period. This slow inactivation was not evident during the early work because preparations were used promptly. Heating the insulin preparation rapidly to 70° C. for three minutes and then cooling, prevents subsequent deterioration and allowed more prolonged storage of the fetal insulin. This heating procedure was used in the preparation of the later lots of material.

†The facilities of the Hospital for Sick Children were provided by Professor A. L. Chute.

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EFFECT OF FETAL CALF INSULIN IN CHILDREN WITH DIABETES OF RECENT ONSET

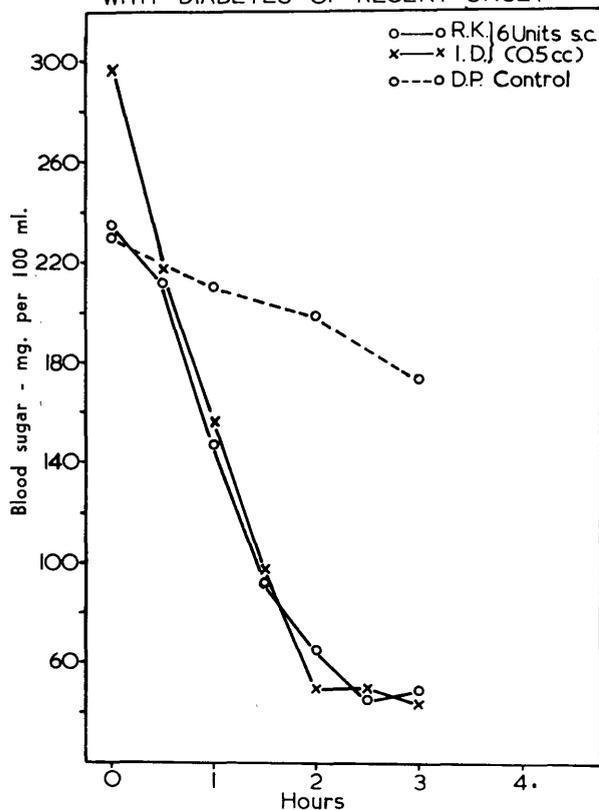


FIGURE 1

action of Crystalline Zinc Insulin at the Baycrest Hospital* for the chronically ill in Toronto. At this institution, the patients are in permanent residence and physical activity, emotional environment and dietary intake are constant within practical limits. The subjects selected for study were changed from their usual depot insulin to divided doses of Crystalline Zinc Insulin. A baseline was established by determining their blood sugar profiles which were repeated at three widely spaced intervals. These were followed in each case by a similar survey after the patient had been receiving the same doses of fetal insulin for a period of two weeks. The results of these investigations are displayed on the succeeding graphs. During the course of the latter therapy no local irritation at the sites of injection was seen, nor were there any remote toxic effects from the fetal calf insulin.

Mrs. E.W., aged seventy-seven years, was discovered

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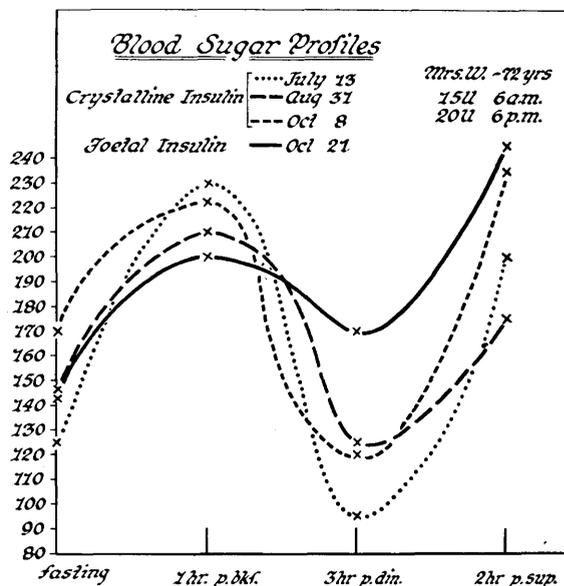


FIGURE 2

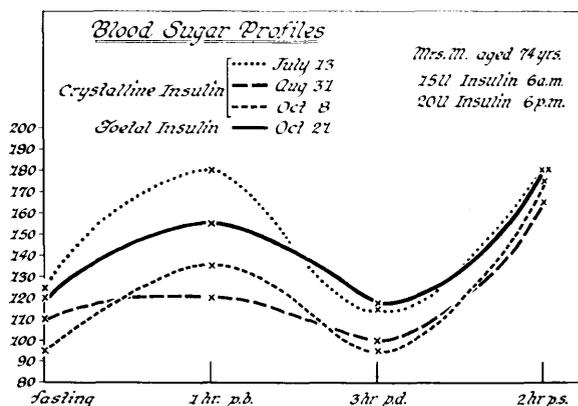


FIGURE 3

to be suffering from diabetes seven years ago. Twenty years ago she had a myocardial infarction and developed congestive cardiac failure which has been controlled satisfactorily. Three years ago she fractured her left hip which was pinned successfully. The control of her diabetes mellitus has been uneventful.

Mrs. J.M., aged seventy-five years, developed diabetes six years ago. At first she was controlled by diet alone, but subsequently also required insulin. In 1957 she was changed to tolbutamide therapy. Following a good response initially, she relapsed in six months and was then placed on insulin therapy. Nine years ago she had a posterior myocardial infarction and in recent months has been under therapy for essential hypertension and cerebrovascular disease.

CONCLUSIONS

Fetal calf insulin, prepared by the original technic of extraction and purification used by Banting and Best in 1921, exerts the same effect in diabetic patients as does modern Crystalline Zinc Insulin. The fetal calf insulin produced no local reactions and presumably would have provided a useful source of hypoglycemic material for the initial treatment of cases of diabetes mellitus in Toronto in 1922 if a more readily available source (adult beef pancreas) had not proved satisfactory.

SUMMARIO IN INTERLINGUA

Evalutation Clinic de Insulina ab Vitellos Fetal

Insulina de vitello fetal, preparate secundo le technica original de extraction e purification que esseva usate

per Banting e Best in 1921, exerce le mesme effecto in diabeticos como le moderne insulina a zinc crystallin. Le insulina de vitello fetal produceva nulle reactiones local e, sin dubita, haberea representate un satisfacente materia hypoglycemic in le tractamento initial de casos de diabete mellite in Toronto in 1922, si le plus preste-mente accessibile fonte de pancreas bovin adulte non se habeva provate adequate.

ACKNOWLEDGMENT

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REFERENCE

¹ Best, C. H.: Reminiscences of the discovery of insulin. The first clinical use of insulin. *Diabetes* 5:65-67, 1956.

Because a considerable proportion of overweights who reduce fail to maintain their lower weight, those who succeed in keeping their weight down for a time constitute a select group. However, this can be only a partial explanation of the favorable findings for those who reduced their weight. Evidence of specific benefits from weight reduction is available from other sources. One striking illustration was the decrease in mortality—particularly from cardiovascular disease and diabetes—in many parts of Europe during World War II, when food supplies were drastically restricted, and the general reversal of this trend when food became more abundant. The great improvement in the mortality of American women reflects, in part, the benefits of weight control, as shown by the decrease in average weight of women. Men, whose average weight increased in the past generation, experienced a much smaller reduction in mortality.

On the clinical side, weight reduction is virtually routine in the treatment of heart disease and hypertension. Reduction of excess weight decreases the strain on the heart, and thus tends to lower blood pressure. The Build and Blood Pressure Study provides abundant evidence of the rise in blood pressure with increase in degree of overweight. A recent study of elderly obese

patients in a nursing home—most of them hypertensives—showed that almost all those who reduced their weight experienced a marked decrease in blood pressure. Studies of middle-aged overweight diabetics indicated that weight reduction improved their glucose tolerance, and in those who reduced to average weight, normal tolerance was restored in most cases.

Overweight is a more significant factor in longevity now than ever before because of its association with the cardiovascular diseases, which now account for the majority of all deaths. The situation is particularly serious among males. Accordingly, whatever measures are effective in reducing the death toll from these diseases are likely to make the greatest contributions to further improvement in health and longevity.

The reduction of weight and its maintenance at optimum levels depend upon the relation of caloric intake to caloric utilization. Overweights can reduce only if they consume less than their body needs. A reasonable and persistent program of diet and exercise, under the continuous guidance of a physician, and the avoidance of fad diets will accomplish the desired result.

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