

# Effects of Insulin with and without Tolbutamide in a Depancreatized Woman

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In 1942 Loubatières hypothesized that the pancreas was necessary for the hypoglycemic action of oral sulfonamides.<sup>1</sup> Since then extensive experimentation has produced some, but not complete, information regarding the mechanism of the action of these drugs. The opinion was voiced recently in an editorial<sup>2</sup> in *DIABETES* that the hypothesis that the hypoglycemic action of these drugs depends upon the stimulation of the pancreatic beta cells is gaining credence.

A few studies with depancreatized human beings have substantiated Loubatières' theory. All of the patients studied were chronically or acutely ill. Those with pancreatectomies or chronic pancreatitis failed to show hypoglycemic responses to sulfonamides administered orally or intravenously.<sup>3-6</sup>

Following a total pancreatectomy five years ago our patient is a healthy, active woman, on whom we measured the effects of exogenous insulin on blood sugar values with and without the accompanying intravenous administration of tolbutamide.

## CASE REPORT

The patient first was examined at the age of thirty-three years because of moderately severe, painless jaundice; the jaundice apparently had been present throughout a pregnancy, which had ended prematurely five months before. She weighed 104 lb.

At operation a carcinoid that involved the head of the pancreas was found. Two adjacent lymph nodes were involved. A radical pancreaticoduodenostomy and a partial gastrectomy were done, followed by a cholecystojejunostomy and a gastroenterostomy. The involved lymph glands were removed. The operation was performed in January 1954.

Before surgery the laboratory findings were as follows: fasting blood sugar 94 mg. per 100 ml., blood urea 27 mg. per 100 ml., total plasma protein 6.9 gm. per 100 ml., serum albumin 3.8 gm. per 100 ml., serum amylase 930 units, and serum bilirubin (direct) 0.39 mg. per 100 ml. One day postoperatively the fasting blood sugar content was 666 mg. per 100 ml. Regular insulin was prescribed: 4 units three times after meals the first day, and 6 units four times the second

day. Two weeks postoperatively she was taking 16 units of NPH insulin before breakfast; the blood sugar content was 97 mg. per 100 ml. before the evening meal, and 131 mg. per 100 ml. after fasting.

The diabetes was labile. Diarrhea was difficult to control. Seven months postoperatively a pelvic abscess required drainage. Anxiety and moderately severe depression were other complications. Fourteen months postoperatively the patient's weight had declined to 94 lb.

At present, five years postoperatively, she is in excellent health. She weighs 121 lb. She has moderate arterial hypertension, with blood pressure at 170/110 mm. Hg. Retinopathy is not present. The diarrhea has stopped. Her diet consists of carbohydrate 215 gm., protein 72 gm., and fat 67 gm., in six feedings per day. The NPH insulin dose had been increased to 24 units per day. Blood sugar levels two days before the test to be described were 213 mg., 176 mg., and 141 mg. per 100 ml. before the morning, noon and evening meals, respectively. Urine tests done on single specimens before meals showed three-plus glycosuria before breakfast, four-plus before lunch, and were negative before the evening meal and at bedtime. The serum calcium content was 9.4 mg. per 100 ml., and the serum phosphorus content was 4.3 mg. per 100 ml. No 5-hydroxyindoleacetic acid was found in the urine.

## PROCEDURE

Two tests were done on separate days. In the first test, tolbutamide was not given, and in the second test the drug was administered.

On the first day, 1,000 ml. of a 5 per cent solution of dextrose in water was given intravenously over a four-hour period in the morning to the fasting patient. This amount of dextrose was approximately equivalent to the available glucose in her usual breakfast. Six units of regular insulin was added to the solution because this amount was approximately that required to control the blood sugar content after the ingestion of an equivalent amount of glucose. Blood was drawn for blood glucose determinations before beginning the intravenous administration of dextrose and insulin, hourly for four hours during its administration, and one hour after absorption; the graphed curve is shown in figure 1. The patient ate her regular diet at the noon meal and for the remainder of the day. Twenty units of NPH insulin was given after the intravenous solution was absorbed.

On the second day the patient's usual diet and insulin dosage were resumed. On the third day, one and one-half hours before beginning the administration of intravenous fluid, blood was drawn for a determination of the blood sugar content, and 2 gm. of tolbutamide was given intravenously. The second dose of 2 gm. of tolbutamide was given when the

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TABLE 1

Blood glucose values (in a woman who had undergone pancreatectomy) in tests with and without tolbutamide

Intravenous infusion of 1,000 ml. 5 per cent dextrose in water and six units regular insulin	Blood glucose determinations, mg./100 ml.						
	Before intravenous infusion 1½ hr. before	Immediately before	During 4-hr. infusion (hourly)				After infusion 1 hr.
Without tolbutamide		179	250	250	214	208	171
With intravenous injection of tolbutamide	142 (2 gm. tolbutamide)	155 (2 gm. tolbutamide)	241	285	227	208	161

intravenous administration of 1,000 ml. of water containing 5 per cent dextrose and 6 units of regular insulin was begun. The intravenous infusion was given over a period of four hours. Two hours after it was begun, blood was drawn for a determination of the tolbutamide content of the blood;<sup>7</sup> the findings were checked against a blank and later against the patient's blood. The blood glucose concentrations throughout the test are shown in figure 1. The values represented in figure 1 are listed in table 1. The determinations of blood sugar were done by the Somogyi-Nelson method, in duplicate, with great care by an expert technician.

It is seen from figure 1 and from table 1 that the blood glucose concentrations in the first two tests on the day of the administration of tolbutamide were somewhat lower than the concentration before the test in which no tolbutamide was given. It seems unlikely that tolbutamide was responsible in view of the subsequent figures. The blood glucose levels were not, however, within the normal range. The remaining portions of the curves are remarkably similar, especially in view of the fact that the diabetes was so unstable. The blood sugar content rose slightly higher following the administration of tolbutamide than it did during the test on the preceding day. It was slightly—but not significantly—lower after five hours.

### CONCLUSIONS

We were unable to demonstrate in a healthy young woman who had undergone total pancreatectomy that the hypoglycemic effect of insulin after the administration of tolbutamide was greater than the hypoglycemic effect of insulin in the absence of tolbutamide.

### SUMMARIO IN INTERLINGUA

#### *Le Effectos De Insulina, Con E Sin Tolbutamido, In Un Dispancreatisate Patiente Feminin*

Nos non poteva demonstrar, in un juvene femina de bon stato de sanitate qui habeva essite subjicite a pancreatectomia total, que le effecto hypoglycemic de insulina post le administration de tolbutamido esseva plus grande que le effecto hypoglycemic de insulina sin le administration de tolbutamido.

### ACKNOWLEDGMENT

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THE ABSENCE OF INSULIN-ENHANCING EFFECT OF TOLBUTAMIDE AFTER TOTAL PANCREATECTOMY

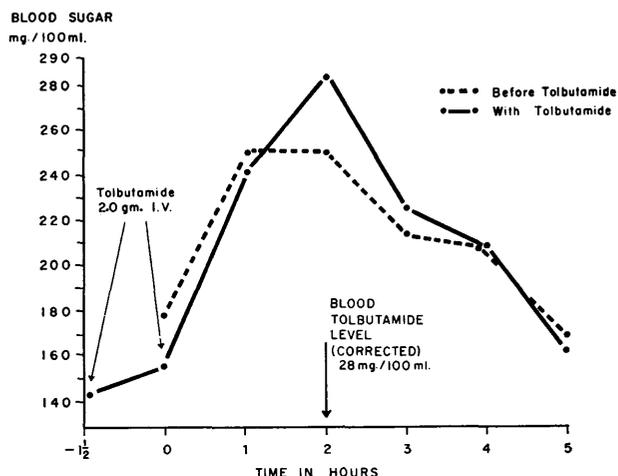


FIGURE 1

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