

Complete Remission of Severe Diabetes

Franklin B. Peck, Jr., M.D., W. R. Kirtley, M.D., and Franklin B. Peck, Sr., M.D.

Indianapolis

The life history of diabetes is characterized by its chronicity. Joslin¹ warns against speaking of "cures," and states that the tendency to diabetes is inborn and must remain so for life. Ricketts² has defined diabetes as "a chronic hyperglycemia and, usually, glycosuria which may be either continuous or intermittent and is due to a relative or absolute deficiency of insulin. Its typical form in man is associated with an hereditary tendency." Ineffaceable permanency is thus inherent in our present concept, and with it we agree.

Fluctuations in the severity of the diabetic state, particularly when measured by the quantity of insulin required to maintain carbohydrate equilibrium, are well known, and their causes are usually obvious, as changes in weight, dietary intake, fever, infection, muscular activity and endocrine disturbances. An apparently sudden onset of diabetes has been described, usually in younger persons, but it is more likely to be a sudden discovery of a condition previously existing. The dramatic, abrupt cessation of all manifestations of profound diabetes and coma in one of our patients with disappearance of severe insulin resistance within a period of a few days was, however, singularly striking, and without parallel in our experience. Until proven otherwise it is to be regarded as an unusual if not unique remission.

Since preparing this report, another case somewhat similar has been described by Harwood.³ His search of literature fails to show other cases of recovery *after acidosis* in adults. The remission in his case is attributed to strict controls of glycemc levels within normal bounds by means of diet and insulin. We concur in his opinion that these measures should make remissions a more common occurrence.

CASE REPORT

R.W. (325653), a forty-one-year-old Negro male, was admitted to the Emergency Ward of Indianapolis General Hospital on Oct. 12, 1954, in profound diabetic coma. He had been in good health until one week before admission, when he had an upper respiratory infection, loss of appetite,

and loss of weight. There is no history of diabetes in the family. The day before admission he remained at home because of nausea and vomiting, and was found unconscious.

The physical findings were of a patient in deep coma and a shock-like state, with Kussmaul respiration and an acetone odor to his breath. The eyeballs were soft and funduscopic findings were normal, as were the lungs, heart and abdomen. Generalized hypoactive deep reflexes were noted, and there was no response to painful stimuli. The blood pressure was 0-80/60 mm.Hg., pulse 120, respiration 32.

The urine was strongly (4 plus) positive for sugar and acetone. Blood sugar was 1,280 mg. per cent (Somogyi method); plasma CO₂ was 3 m.Eq. and blood urea nitrogen 60 mg. per cent. Calculation of the Rabinowitch severity index gave a numerical value of twenty-four (any rating of twenty-one or over is exceptionally severe and carries with it a mortality rate of 80 to 90 per cent).

Vigorous treatment over the first twelve hours necessitated venous incisions in the lower extremities in order to combat circulatory collapse by intravenous infusions with norepinephrine added to maintain the blood pressure. The progress of therapy during this period is summarized in figure 1. Note that 1,910 units of insulin were administered, and a total of 6.5 liters of normal saline, 2 liters of 5 per cent dextrose and 65 m.Eq. of potassium. It was on the advice of Dr. D. D. Van Slyke, who was visiting our laboratories that day, that an additional 15 gm. NaHCO₃ was given intravenously as the patient was obviously not responding to treatment. In retrospect, we believe this was probably lifesaving, as the CO₂ values then began to rise, and the patient's general condition began to improve. During the hours when blood pressure was minimal, pressure of the patient's weight on his buttocks resulted in a large area of sacral decubitus which subsequently required surgical debridement before healing occurred. Unconsciousness persisted for two full days. Electrolyte balance was greatly disturbed, the serum sodium being 170 mEq., with serum chlorides 138 m.Eq. despite adequate urinary output. It was thought at the time that this might be the result of too vigorous administration of sodium chloride, although adequate urinary output was present during most of the stormy initial course.

The patient responded poorly during the first few days. Weakness of the left arm and leg was noted, which in conjunction with the altered electrolyte pattern suggested cerebral thrombosis. Spinal fluid was normal. Insulin resistance appeared on October 14, subsequently requiring 200 to 400 units daily in order to maintain normal glycemia (figure 2). Regulation of glycemia between 70 to 90 mg. per 100 ml. of blood sugar was finally established with 90 units NPH insulin per day. A severe insulin shock occurred on the fifth day, with blood sugar of zero, and another insulin shock occurred on the tenth day. There was prompt response to glucose intravenously and

Presented at IV Pan-American Congress on Endocrinology, Buenos Aires, Nov. 7, 1957.

From the Lilly Laboratories for Clinical Research, Indianapolis, Indiana.

COMPLETE REMISSION OF SEVERE DIABETES

FIGURE 1

Cumulative coma record (R.W. 325653)

Date	Time	Blood Pressure	U r i n e			B l o o d			Insulin	K	Na	Cl	Fluids, etc.
			Volume	Sugar	Acetone	Sugar	CO ₂						
10/12	11:30 A.M.	0-80/60	20	4+	4+	1,280	3	m.Eq.	180				1,000 cc. saline and Levophed
	1:30 P.M.	130/70	20	4+	4+	1,288	6.3		510				2,000 cc. saline and Levophed
	4:00 P.M.	112/60	250	4+	4+	766	8.9		1,510	3.6	150	126	5,000 cc. saline and (5 P.M.—15 gm. NaHCO ₃)
	8:00 P.M.	110/70	1,350	4+	2+	322	14.1		1,910				6,600 cc. saline 2,200 cc. 5% dextrose 65 m.Eq. K (dep. S-T)
	10:00 P.M.	100/60	1,500	1+	2+	240	23.4		1,910				
10/13		140/90		0	0	148	24		10 c 30 NPH	3.8	170	138	

FIGURE 2

Blood sugar record (R.W. 325653)

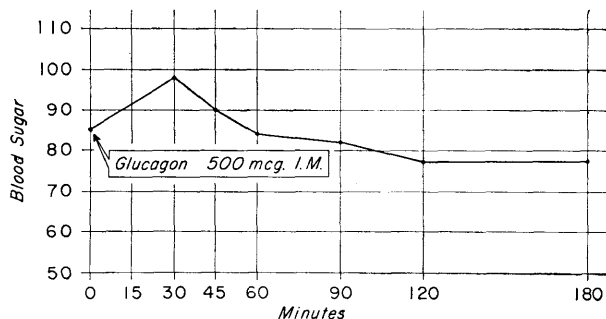
Date	Insulin	Blood Sugar
10/14/54	310	148-294
15	310	215-348
16	440	366-205-0
17	160	254
18	100	188
21	100	152
25	100	96
29	100	100
11/1	90	60
11/5	90	80-90
11/7-23	90	67-96
11/24-27	30	62-90
11/28-1/7	0	67-104
1955	0	79-95
1956	0	85-106
1957	0	84-107

FIGURE 3

GLUCAGON TEST

(R.W. 325653)

11/8/1954



then several days of satisfactory regulation with 30 units of NPH insulin daily. The patient was transferred to the Lilly Research Ward on Nov. 3, 1954, for further study of his metabolic state. Clinical evidence of diabetes completely disappeared.

Insulin was entirely discontinued on November 27. The blood sugar level remained normal in both fasting and postprandial periods. The decubitus healed under treatment with penicillin and Varidase. A glucagon test (figure 3) gave a lower-than-normal blood sugar elevation (usually 30 to 40 mg. per cent by our methods). Oral glucose tolerance tests and a triple glucose tolerance test (figure 4) consisting of two orally administered priming doses followed by an intravenous glucose curve were essentially normal except for delayed return in two hours. In fact, a sharp hypoglycemic reaction occurred one and one-half hours after the intravenous glucose. This "Staub-Traugott" phenomenon⁴ appears in normals, and the less severe the diabetes, the more nearly does the curve approach normal.⁵ An insulin tolerance test displayed some initial slight delay in

responsiveness to insulin (figure 5), but was otherwise within normal limits. The glucose-insulin tolerance test was not abnormal (figure 6), since in normals the hyperglycemia is greater than after the administration of the same amount of glucose without insulin, ranging from 25 to 75 per cent increase from initial blood sugar values.⁶ The Thorn eosinophil test for adrenal function was normal.⁷ Three basal metabolic rates were within normal limits. A four-day ACTH stimulation test⁸ (figure 7) did not show a normal increase in 17-ketosteroids and 11-oxysteroids in the urine. Later a high eosinophil count (50 per cent) was attributed to his long-term penicillin-Varidase therapy, and the count fell rapidly toward normal limits when these agents were discontinued. Skull films of sella turcica were normal, the blood count, liver and kidney function studies were all within normal limits. Evidence of the initial severe diabetes having disappeared, the patient was released to the outpatient Diabetes Clinic for long-term observation, with instructions to maintain his diet within the range of 1,500 to

FIGURE 4
GLUCOSE TOLERANCE TESTS
(R.W. 325653)

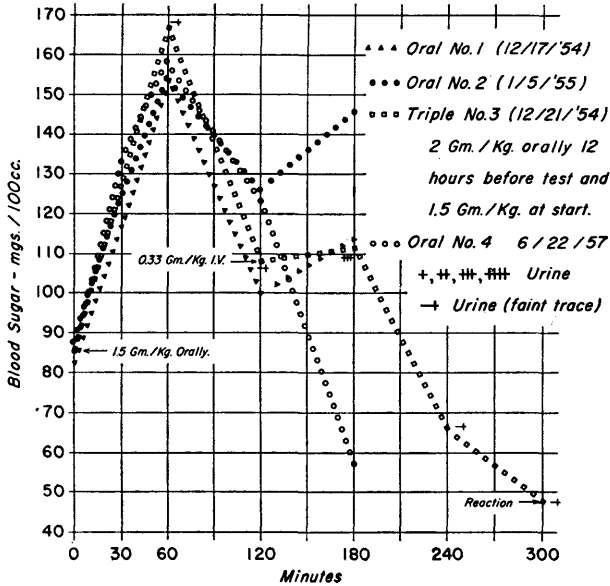
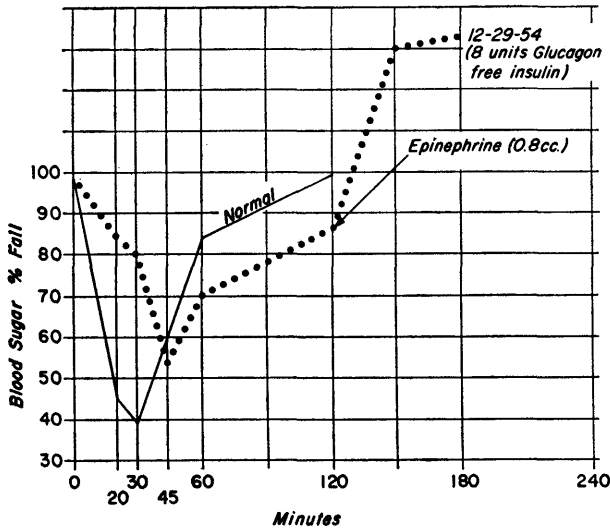


FIGURE 5

INSULIN TOLERANCE TEST
(R.W. 325653)



1,800 calories to avoid gain in weight.

Subsequent visits to the Diabetes Clinic have confirmed the continued absence of any signs or symptoms of diabetes. The blood sugar levels have remained entirely normal since 1954, and there has not been a single positive test for glycosuria, either in the clinic or under home and working conditions.

Periodic rechecks of the patient's glucose tolerance have been continued. The most recent of these is shown in figure 4 (June 22, 1957). Further evidence of the dormant nature of

FIGURE 6
GLUCOSE-INSULIN TOLERANCE
(R.W. 325653)

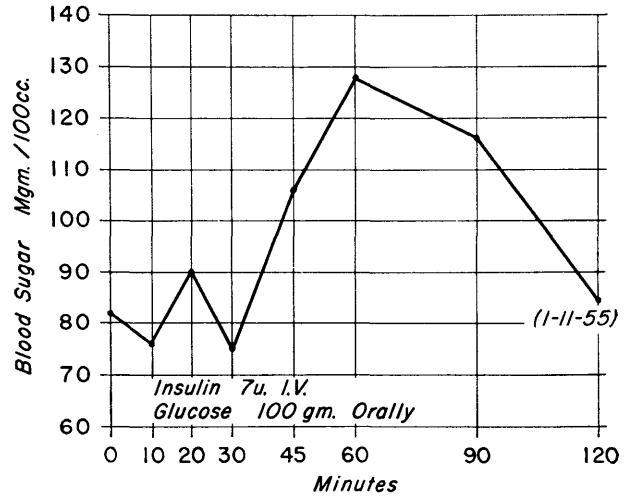


FIGURE 7

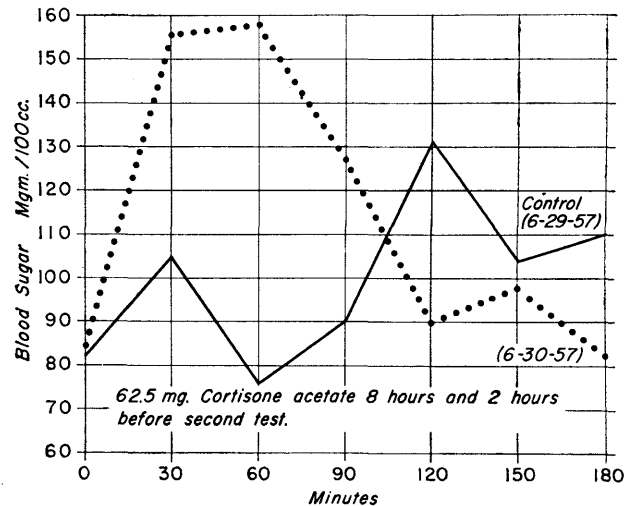
ACTH stimulation test (R.W. 325653)

Date	Vol.	ACTH	17-Keto.	11-Oxy.	Creat.
1/2/55	1,700	No	21.2 mg.	3.4 mg.	1,696 mg.
1/4/55	1,550	20 I.U.	31.8 mg.	0.8 mg.	1,519 mg.
1/5/55	1,320	20 I.U.	11.4 mg.	2.1 mg.	1,526 mg.
1/6/55	2,120	20 I.U.	21.7 mg.	1.7 mg.	1,865 mg.

BMR -1, -1, -9
Liver and kidney function studies were normal.

FIGURE 8

FAJANS-CONN C-G TOLERANCE TEST
(R.W. 325653)



the diabetes in this case is shown by the response to the cortisone-glucose tolerance test of Fajans and Conn,⁹ performed according to their methods on June 29-30, 1957. The findings are outlined in figure 8.

The control curve taken on the day before the cortisone was administered was well within the limits of normal glucose tolerance except for a secondary rise not observed on previous tests. It somewhat resembles the rise in the glucose-insulin tolerance test, and we have no explanation for it. Fajans and Conn⁹ regard the combination of a one-hour value of 160 mg. per 100 cc. or above plus a two-hour value of 120 mg. or above as diagnostic of the existence of the diabetic state. Their third criterion is that the level at ninety minutes be above 140 mg. per 100 cc. to be diagnostic of diabetes. None of the levels in our case exceed these limits, and we must consequently regard the cortisone provocative test as failing to uncover a latent or hidden diabetes in this instance.

DISCUSSION

These data establish beyond question the occurrence in this case of an exceptionally severe and acute diabetes accompanied by profound ketosis, circulatory collapse, and concomitant alterations in fluid and electrolyte balance so characteristic of such a state. In addition there was a striking insulin resistance during the early phases.

The subsequent disappearance of any clinical manifestations has not been accompanied by significant weight loss. Ordinary glucose tolerance tests show only a slight delay in return to the starting value at the second hour. There was a slight delay in hypoglycemic response to an intravenous test dose of insulin. These constitute the only remaining evidence of any abnormality remaining, and a latent defect is not brought out by the Fajans-Conn test after a three-year period.

Joslin¹ has stressed the criteria for recovery from diabetes as follows: "Glycosuria and hyperglycemia should be absent, while the patient is without diabetic medication, both before and an hour after a meal. This meal must contain at least two-fifths of the carbohydrate for the day. The carbohydrate for the twenty-four hours should comprise at least two-thirds of the calories necessary to provide thirty calories per kilogram body weight. Better still, the carbohydrate tolerance should be unimpaired as judged by a normal glycemic curve following the oral administration of 100 gm. of glucose to the patient in the postabsorptive state. A diagnostically proved case of diabetes of one or more months duration, which conforms to the test for recovery at the beginning and end of an interval of five or more years, shall be considered cured." The last of these criteria has not yet been met as the term of remission is only three years. Of special interest, however, is the failure to respond to the cortisone test.

We have no explanation for the bizarre behavior of

the diabetes in this case. In personal discussion Dr. R. D. Lawrence of London mentioned only one rather similar instance—in a patient who was later found to have experienced a pancreatic thrombosis with later resolution disclosed at autopsy. Such manifestations as these must be very rare.

SUMMARY

The findings are reported in a forty-one-year-old male admitted to the hospital on Oct. 12, 1954, in severe diabetic coma. There was no history of diabetes until the onset of illness one day before admission, when he was found unconscious. On admission the blood sugar was 1,280 mg. per cent, CO₂ was 3 m.Eq., the Rabinowitch Severity Index was 24, and the patient was in circulatory collapse. Nineteen hundred and ten units of insulin were administered during the next twelve hours, and subsequently insulin resistance developed requiring 200 to 400 units of insulin daily in order to maintain normal glycemia.

After approximately ten days in the hospital responsiveness to insulin suddenly improved and severe hypoglycemia ensued. Regulation was then established with 90 units of NPH insulin, which was reduced to 30 units daily until Nov. 27, 1954, when insulin was entirely discontinued and the patient's blood sugars remained normal. Intensive study of the patient's endocrine and metabolic status subsequently disclosed no significant abnormalities, and clinical evidence of diabetes is not revealed even to the provocative cortisone-glucose tolerance test of Fajans-Conn. The case represents an unusual instance of temporary severe diabetes accompanied by coma and acidosis with apparently complete recovery as far as can now be determined. Until a five-year period has elapsed, it should be regarded as a remission rather than a cure.

SUMMARIO IN INTERLINGUA

Remission Complete de Diabete Sever

Es reportate le constatationes facite in le caso de un masculo de quaranta-un annos de etate qui esseva admittite al hospital le 12 de octobre 1954 in un stato de sever coma diabetic. Le patiente non habeva un historia de diabete ante le declaration del morbo un die retro quando ille habeva essite trovate in stato de inconscientia. Al tempore del hospitalisation le valor pro sucro del sanguine esseva 1.280 mg pro cento, illo pro CO₂ esseva 3 mEq, le Indice de Severitate de Rabinowitch esseva 24, e le patiente se trovava in stato de collapsio circulatori. In le curso del sequente dece-duo horas, 1910 unitates de insulina esseva administrate. Subsequentemente resistentia a insulina se disveloppava, requirente

200 a 400 unitates de insulina per die pro mantener nivellos normal de glycemia.

Post circa dece dies al hospital, le responsa a insulina se meliorava subitemente con le resultado de un sever hypoglycemia. Regulation esseva establite per medio de 90 unitates de insulina NPH per die. Iste dose esseva reducite a 30 unitates per die usque le 27 de novembre 1954 quando le insulina esseva abandonate complete. Postea le sucros sanguinee del patiente remaneva normal; intense studios del stato endocrin e metabolic del patiente revelava nulle significative anormalitates; e signos clinic de diabete se manifesta non mesmo sub le conditiones del provocatori test de tolerantia a cortisona-glucosa secundo Fajans-Conn. Le caso representa un exemplo inusual de sever diabete temporari accompaniate de coma e acidosis con restablimento apparentemente complete, in tanto que isto pote esser determinate al tempore presente. Usque al fin de un periodo de cinque annos, le resultado debe esser reguardate como remission plus tosto que como curation.

REFERENCES

- ¹ Joslin, E. P., Root, Howard F., White, P., and Marble, A.: *The Treatment of Diabetes Mellitus*. Philadelphia, Lea & Febiger, 1952, p. 272.
- ² Ricketts, Henry T.: Personal communication.
- ³ Harwood, Reed: Severe diabetes with remission. *New England J. Med.* 257:257, Aug. 8, 1957.
- ⁴ Soskin, S., and Levine, R.: *Carbohydrate Metabolism, Correlation of Physiological, Biochemical and Clinical Aspects*. Chicago, The University of Chicago Press, Ed. 2, 1952, p. 287.
- ⁵ Joslin, op. cit., p. 145.
- ⁶ Engel, F. L., and Scott, J. L.: The insulin-glucose tolerance test. *J. Clin. Investigation.* 29:151, 1950.
- ⁷ Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G.: Test for adrenal cortical insufficiency. *J.A.M.A.* 137:1005, 1948.
- ⁸ Renold, A. E., Jenkins, D., Forsham, P. H., and Thorn, G. W.: Use of intravenous ACTH: a study in quantitative adrenocortical stimulators. *J. Clin. Endocrinol. and Metab.* 12:763, 1952.
- ⁹ Fajans, Stefan S., and Conn, J. W.: An approach to the prediction of diabetes mellitus by modification of the glucose tolerance test with cortisone. *Diabetes* 3:296, 1954.

Insulin Hypoglycemia in Angina Pectoris

The clinical dictum that hypoglycemic episodes constitute a serious hazard to the patient with angina pectoris has been supported by relatively few case reports. W. C. Judson and W. Hollander (*Am. Heart J.* 52:198 (1956)) have made a systematic attempt to document this impression by studying the reactions of patients with arteriosclerotic heart disease and the anginal syndrome to hypoglycemia induced by insulin.

The eleven patients had typical anginal pain on effort, associated with electrocardiographic evidence of myocardial ischemia. Insulin was injected intravenously, 0.1 unit per kilogram of body weight, and the blood glucose, sodium and potassium were measured at fifteen-to thirty-minute intervals. An electrocardiogram and ballistocardiogram were simultaneously recorded. Some of the patients received hexamethonium in a dose sufficient to produce postural hypotension before the insulin was given.

When intravenous insulin alone was used, the blood sugar fell from an average level of 81 mg. per cent to 38 mg. per cent. The serum sodium did not change but the serum potassium decreased an average of 0.7 mEq. per liter. Seven of the eleven patients showed electrocardiographic changes which were unlike the myocardial ischemic changes produced by exercise. The most

common change was a flattening and broadening of the T waves. In none of these patients, however, was anginal pain produced, although they displayed the typical signs and symptoms of hypoglycemia during the test.

When the patients were pretreated with hexamethonium in an effort to prevent the effects due to adrenergic stimulation, the electrocardiographic changes and symptoms were not altered.

The effect of this investigation is thus to show that this degree of hypoglycemia does not cause the electrocardiographic changes of myocardial ischemia in patients with arteriosclerotic heart disease. The electrocardiographic changes were consistent with those attributed to hypokalemia (low blood potassium levels) and the decrease in serum potassium supports this idea. No convincing evidence was obtained to suggest that these changes were due to discharge of the sympatho-adrenal system. Although this study allays some of the fears which have previously been emphasized regarding the close control of diabetic subjects with arteriosclerotic heart disease, it should not be assumed that hypoglycemic shock may not, on occasion, cause adverse cardiovascular effects.

From *Nutrition Reviews*, Vol. 15, No. 4, April 1957, pp. 127-28.