Lack of Influence of Insulin-induced Hypoglycemia on Alimentary Hyperglycemia

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SUMMARY

Studies were designed to determine the effect, in diabetic patients, of insulin induced hypoglycemia upon alimentary hyperglycemia. The following results were obtained.

1. In a four-hour study, as a control day, each of four patients was given his usual insulin one hour before the oral administration of 100 gm. of glucose. On another occasion, under identical conditions, hypoglycemia was produced during the hour preceding glucose administration, by intravenous administration of Crystalline Insulin. There was no greater impairment of glucose tolerance during the subsequent three hours than noted in the control study.

2. In ten patients, maintained on constant diets for three consecutive days, blood sugars were determined at frequent intervals from 7 a.m. to 10 p.m. each day. Each patient, if insulin dependent, received his usual dose before breakfast on all three days. On the second day the administration of additional subcutaneous Crystalline Insulin produced hypoglycemia during the forenoon. No carbohydrate supplementation was given and generally the hypoglycemia was corrected only by lunch given at the usual time. The postprandial blood sugar elevations for the balance of that day and throughout the third day were no greater than those of the first or control day.

3. In one patient six identical studies were performed. In each instance 25 gm. of glucose was given by mouth at 7 a.m. on each of three consecutive days. Blood sugars were measured at two-hour intervals from 8 a.m. to 12 noon. On day two hypoglycemia was produced by the administration of 15-25 U. Crystalline Insulin after the 8 a.m. blood specimen was drawn. Although mean blood sugars were statistically significantly higher on day three than on day one at 8 a.m. and 12 noon, the quantitative measurement of urine sugar showed no increase over that of the control day on either the day of hypoglycemia or the following day.

These data do not support the concept, in patients with diabetes mellitus, that hypoglycemia is followed by further impairment of glucose tolerance. DIABETES *15*:307-13, May, 1966.

Hypoglycemic episodes in insulin-treated diabetic patients, even when asymptomatic and unrecognized, have been reported to result in exaggerated hyperglycemia and glycosuria.[1-15] These reports have in common one or more of the following deficiencies: (1) diet and activity were usually not controlled or clearly described. (2) failure to demonstrate a significant degree and duration of hypoglycemia, and (3) absence of suitable data for statistical evaluation of the results.

The concept that hypoglycemia begets hyperglycemia, if validated, has significant application in the clinical management of diabetes, and has even been offered as a mechanism for the production of "brittle" diabetes. Indeed, Somogyi,[11] who is the chief proponent of this concept, has stated that "unstable diabetes, in the case of most adult subjects, is not an idiopathic entity, but a direct consequence of excess insulin action." Somogyi[16] has further postulated that "hypoglycemia, produced by excess insulin action, induces an accelerated release of blood-sugar-raising hormones from the adrenal-pituitary system to an extent that under certain conditions the action of the excited insulin-opposing factors outstrips insulin action." These hypotheses have found support in demonstrations that acute hypoglycemia is associated with increased plasma concentrations of catechol amines,[17] adrenocorticosteroids,[18] and growth hormone.[19] However, irrespective of the hypothetical mechanism, if alteration of carbohydrate metabolism is a consequence of insulin induced hypoglycemia, the phenomenon should be reproducible under carefully controlled conditions.

In the studies described here, documented, single hypoglycemic episodes were induced in diabetic patients under conditions of constant dietary intake, with activity limited to that appropriate to a hospital ward. Each patient served as his own experimental control. Results show that single episodes of hypoglycemia have no significant effect on subsequent blood sugar concentration, when dietary intake is maintained constant.

METHODS

Diabetic patients were volunteers selected from the general medical wards and from the outpatient clinics of the Cleveland Metropolitan General Hospital and

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University Hospitals of Cleveland. Each patient was admitted to a metabolism ward for three to ten days before beginning experiments. Constant weighed diets, estimated to meet the patient's nutritional needs and divided into four feedings daily, were consumed. During the initial observation period, a single daily maintenance dose of insulin was determined and continued throughout the period of the experiments. No oral hypoglycemic agents were given during experimental periods. Ambulation within the bounds of the ward was permitted.

Venous blood samples were obtained at the stated intervals. For blood sugar analyses, blood was added immediately to sodium fluoride treated containers. For 17-hydroxycorticoid measurements, plasma was separated and frozen promptly.

Sugar in blood and urine was measured by the Somogyi-Nelson method[20] or by a modification of the potassium ferricyanide-potassium ferrocyanide method[21] adapted to an AutoAnalyzer. These methods give similar results for blood sugar. Plasma 17-hydroxycorticoids were measured by the Silber-Porter method[22] with minor changes.

EXPERIMENTAL PROTOCOLS AND RESULTS

Four-hour studies

In five experiments in four patients, glucose tolerance was tested by oral administration of 100 gm. of glucose during an episode of insulin-induced hypoglycemia. Blood sugar concentrations were measured for one hour before and over the three-hour period following the administration of glucose. Control studies in which normal saline was substituted for insulin were performed in the same patient. Crystalline Insulin and saline were given in a predetermined random sequence.

Hypoglycemia was induced by intravenous injection of 10 to 15 U. Crystalline Insulin at 8 a.m. after a ten-hour fast. Maintenance isophane (NPH) or Globin Insulin was given at 8 a.m. throughout. At 9 a.m., 100 gm. of glucose was given orally. Blood sugar and plasma 17-hydroxycorticoid concentrations were measured at one-half hour intervals from 8 a.m. to 12 noon, at which time the experiments were terminated. The protocol for the control experiments was identical, except that one milliliter of normal saline was substituted for the insulin injection. Constant diets were maintained for a period of three to seven days preceding experiments and during the three- to eight-day interval between experiments. On the two days when either saline or extra insulin was given, breakfast was omitted, and at 9 a.m. the 100 gm. of glucose was given instead. The three other meals were identical with those of the nontest days.

Results are shown in table 1. On the days when hypoglycemia was produced, blood sugar concentrations of 60 mg. per 100 ml. or less were recorded at 8:30 a.m. or at 9 a.m., preceding the administration of the glucose, in all patients included in this series. At no time following administration of glucose was the mean blood sugar concentration significantly higher following hypoglycemia than at the same time on control (saline injection) days.

Figure 1 shows the plasma 17-hydroxycorticoid concentration in the same blood samples in which glucose was measured. Analysis of these data by the t test for paired variates shows that the concentration of plasma 17-hydroxycorticoids was significantly ($p < 0.05$) elevated over control day values at 9:30 a.m. and at 11:30 a.m. following hypoglycemia.

Seventy-two-hour studies

In these studies the observations were extended over three consecutive days. Day 1 was a control day. On day 2, hypoglycemia was induced with 15 to 40 U. Crystalline Insulin given subcutaneously at 8:00 a.m. On day 3, no extra insulin was given, but the regimen was otherwise identical with that of the preceding two days. All patients ate a constant diet throughout, and all patients requiring isophane or globin insulin were given a predetermined maintenance dose on all three days. Blood sugar concentrations were measured at one-half-hour or one-hour intervals from 8 a.m. to 4 p.m. in three patients and from 8 a.m. to 10 p.m. in eight patients. Clinical characteristics of the patients are shown in table 2.

Postprandial hyperglycemia, statistically significantly in excess of that of the control day, was seen neither during the afternoon and evening of the day of hypoglycemia nor was it observed during the morning, afternoon and evening of the day following the hypoglycemic episode. Blood sugar concentrations for all three days are shown in table 3. Statistical analysis of these is shown in table 4. In additional experiments in two nondiabetic patients (not shown), when day 3 was compared with day 1, no important differences were seen in the postprandial blood sugar concentrations.

Replicate studies in one patient

Six identical experiments were conducted at intervals over a period of eight months in one patient (G.C.), whose diabetes was controlled by diet without insulin. The experimental protocol consisted of giving a test

TABLE 1

Comparison of blood sugar concentrations following saline and following insulin injections at 8 a.m. Breakfast was omitted and 100 gm. of glucose was given orally at 9 a.m.

			Blood sugar concentrations (mg./100 ml.)								
Patient	Date	Injection	8:00 a.m.	8:30 a.m.	9:00 a.m.	9:30 a.m.	10:00 a.m.	10:30 a.m.	11:00 a.m.	11:30 a.m.	12:00 m.
C.	5/4/61	Insulin	75	37	31	93	128	168	199	199	180
	5/1/61	Saline	109	109	115	162	211	230	249	193	149
C.	5/8/62	Insulin	107	69	35	88	176	230	251	223	197
	5/16/62	Saline	129	140	135	206	289	341	355	267	223
W.	2/21/63	Insulin	121	53	43	114	188	254	300	291	272
	2/25/63	Saline	129	124	107	174	267	284	260	212	171
R.	3/7/63	Insulin	135	73	58	137	188	183	245	269	273
	3/1/63	Saline	123	125	128	175	226	256	264	278	304
Ch.	4/3/63	Insulin	83	33	40	60	130	156	213	235	225
	4/9/63	Saline	117	119	102	166	250	287	291	325	281
			Mean blood sugar concentrations								
		Insulin	104.2	53.0	41.4	98.4	162.0	198.2	241.6	243.4	229.4
		±S.E.	11.3	8.1	4.6	13.0	13.7	18.7	17.4	16.4	19.0
		Saline	121.4	123.4	117.4	176.6	248.6	279.6	283.8	255.0	226.0
		±S.E.	2.1	5.1	6.2	7.7	13.9	18.5	19.1	23.7	29.2

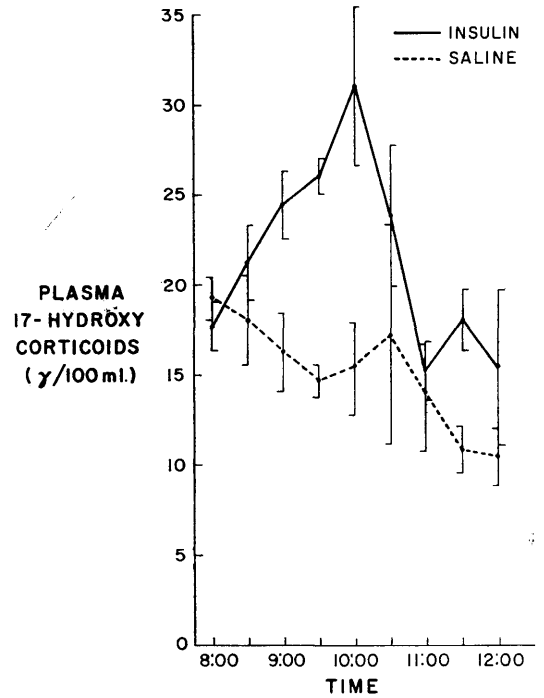

FIG. 1. Plasma 17-hydroxycorticoid concentrations in patients in four-hour study after either insulin induced hypoglycemia or control saline injections. Vertical bars indicate standard errors.

"breakfast" of 25 gm. of glucose by mouth at 7 a.m. on three consecutive days. Blood sugar was measured at 8 a.m., at 10 a.m. and at 12 noon on each day. On the second day, 15 to 25 U. Regular Insulin was given subcutaneously immediately after the 8 a.m. blood specimen was obtained. Dietary intake was maintained constant during each three-day period. Complete 24-hr. urine collections allowed measurement of the glycosuria during each of the three test days.

TABLE 2

Clinical characteristics of patients in seventy-two-hour study

Patient	Sex	Age	Age at diagnosis	Weight (kg.)	Usual insulin dose, or therapy
E.B.	M	50	41	108.1	Isophane 45 U
E.G.	M	64	62	81.8	Isophane 30 U
V.L.	F	53	43	98.2	Diet only
O.H.	F	38	24	65.5	Globin 45 U
L.B.	F	63	58	82.3	Isophane 20-30 U
W.A.	F	44	26	82.7	Isophane 20-90 U
T.R.	M	57	51	61.8	Isophane 35 U
G.C.	M	38	33	62.0	Diet only
A.H.	M	45	34	66.9	Isophane 35 U
D.B.	M	48	38	75.0	Isophane 55 U

Mean blood sugar values at 8 a.m., at 10 a.m. and at 12 noon were higher on day 3 than on day 1, significantly so at 8 a.m. and 12 noon (table 5). The mean differences were small and became progressively smaller. The mean differences on days 1 and 3 are not attributable to a decreased rate of cellular glucose uptake since the rate of blood sugar decline was substantially the same on both days (figure 2). Moreover, quantitative measurement of urine sugar showed no increase over that of the control day on either the day of the hypoglycemic episode or on the day following (table 5).

TABLE 3 (Continued on page 311)

Blood sugar concentrations in eleven studies in ten diabetic patients. Maintenance insulin and food intake were kept constant on all three days except that on day 2 extra Crystalline Insulin was given subcutaneously in order to produce hypoglycemia late in the forenoon.

		Blood sugar concentrations (mg./100 ml.)																		
Pt.	Day	8:00 a.m.	8:30 a.m.	9:00 a.m.	9:30 a.m.	10:00 a.m.	10:30 a.m.	11:00 a.m.	11:30 a.m.	12:00 m.	1:00 p.m.	2:00 p.m.	3:00 p.m.	4:00 p.m.	5:00 p.m.	6:00 p.m.	7:00 p.m.	8:00 p.m.	9:00 p.m.	10:00 p.m.	Urine sugar gm./ 24 hr.
E.B.	1	128	175	185	186	171	160	139	123	117	140	136	106	79	60	131	131	116	123	146	5.6
	2	138	173	194	192	169	150	116	83	44	63	58	41	39	38	143	142	119	121	110	6.6
	3	118	153	193	192	176	151	141	124	102	130	126	97	77	62	100	120	131	140	160	7.4
E.G.	1	94	126	169	176	151	131	115	104	93	167	192	167	140	113	147	173	165	193	189	3.5
	2	98	144	182	171	132	95	61	45	41	102	122	121	111	100	139	173	165	197	204	1.4
	3	106	163	229	229	206	184	155	140	127	184	158	—	108	92	179	211	201	196	198	3.6
V.L.	1	92	119	181	166	157	129	105	95	63	134	108	99	77	70	127	136	135	111	119	2.4
	2	100	205	189	150	109	76	49	50	49	111	87	71	66	62	121	133	130	97	92	2.0
	3	84	137	170	158	139	113	77	59	44	122	94	82	65	59	131	137	115	98	112	1.5
O.H.	1	278	302	360	380	331	318	277	238	197	197	211	202	181	149	245	260	234	201	220	56.7
	2	86	157	148	136	95	65	33	21	23	102	84	68	46	45	120	160	186	198	243	14.1
	3	230	320	338	344	341	285	241	202	143	180	157	135	102	77	110	150	140	121	156	24.4
L.B.	1	141	148	182	215	213	182	168	164	150	175	171	176	157	156	216	206	182	189	203	2.7
	2	102	101	84	110	106	105	83	56	86	130	108	105	98	86	108	143	144	180	196	2.7
	3	148	142	198	225	245	235	236	225	196	164	149	134	118	89	116	123	104	—	—	3.6

TABLE 4 (Continued on page 311)

Statistical Analysis* of seventy-two-hour study (data taken from table 3)

Day	8:00 a.m.	8:30 a.m.	9:00 a.m.	9:30 a.m.	10:00 a.m.	10:30 a.m.	11:00 a.m.	11:30 a.m.	12:00 m.	1:00 p.m.
					Mean blood sugar concentration					
Day 1	176.9	158.1	229.5	222.3	213.7	176.1	182.5	140.6	132.9	181.7
n	11	8	9	8	11	8	9	8	11	9
±S.E.	20.4	50.0	72.5	43.5	14.8	34.4	35.0	27.3	14.4	30.1
Day 2	148.2	150.6	163.5	140.9	103.1	80.6	59.1	50.7	48.5	92.6
n	11	8	9	8	11	8	9	8	11	9
±S.E.	16.5	28.2	25.5	25.2	7.4	55.0	10.2	10.2	3.1	13.1
Day 3	182.2	167.2	235.2	213.6	231.9	190.9	197.0	149.7	144.1	175.4
n	11	8	9	8	11	8	9	8	11	9
±S.E.	25.4	35.2	74.3	41.1	20.0	36.0	34.2	30.4	15.5	27.8
					Mean difference in blood sugar concentration					
Day 2-1	—28.7	—7.5	—66.0	—81.4	—110.6	—95.5	—123.4	—89.9	—84.4	—89.1
n	11	8	9	8	11	8	9	8	11	9
±S.E.	19.7	23.2	24.1	31.2	20.5	28.9	34.4	23.6	20.1	25.1
p	>0.1	>0.5	>0.5	<0.05	<0.001	<0.025	<0.01	<0.01	<0.005	<0.01
Day 3-1	5.3	9.1	5.7	—8.7	18.2	14.8	14.5	9.1	11.2	—6.3
n	11	8	9	8	11	8	9	8	11	9
±S.E.	11.5	14.0	12.0	10.7	9.0	12.2	11.8	11.8	9.7	7.3
p	>0.5	>0.5	>0.5	>0.4	>0.05	>0.2	>0.2	>0.4	>0.2	>0.2

*Mean changes in blood sugar concentrations, day 2 vs. day 1 and day 3 vs. day 1, were statistically evaluated by the *t* test for paired variates. At no time subsequent to the hypoglycemia on day 2 and at no time on day 3 were the mean blood sugar concentrations significantly higher than at the same time on the control day.

TABLE 3 (Continued from page 310)

Blood sugar concentrations in eleven studies in ten diabetic patients. Maintenance insulin and food intake were kept constant on all three days except that on day 2 extra Crystalline Insulin was given subcutaneously in order to produce hypoglycemia late in the forenoon.

		Blood sugar concentrations (mg./100 ml.)																		
Pt.	Day	8:00 a.m.	8:30 a.m.	9:00 a.m.	9:30 a.m.	10:00 a.m.	10:30 a.m.	11:00 a.m.	11:30 a.m.	12:00 m.	1:00 p.m.	2:00 p.m.	3:00 p.m.	4:00 p.m.	5:00 p.m.	6:00 p.m.	7:00 p.m.	8:00 p.m.	9:00 p.m.	10:00 p.m.	Urine sugar gm./ 24hr.
W.A.	1	166	176	192	199	196	158	124	108	84	100	128	102	90	78	143	151	142	130	132	4.0
	2	138	192	150	150	102	38	36	34	29	48	56	52	52	50	94	106	95	83	84	3.2
	3	112	126	172	186	186	168	154	96	72	98	96	88	86	78	156	144	122	114	125	3.6
T.R.	1	99	102	138	156	147	143	139	121	109	130	154	157	152	130	171	194	174	162	151	2.1
	2	70	68	76	76	50	46	50	50	50	83	119	118	113	106	130	171	130	138	112	2.7
	3	84	86	92	110	128	141	151	147	137	167	180	147	117	112	164	—	198	184	182	3.4
G.C.	1	102	117	280	300	250	188	187	172	153	251	225	251	180	158	250	275	225	180	250	
	2	158	165	175	142	110	70	50	67	68	122	128	100	88	67	132	195	190	185	200	
	3	175	205	275	265	260	250	245	205	185	205	253	250	200	170	260	235	205	175	190	
G.C.	1	192				115				85		143		119							3.7
	2	204				54				59		177		138							12.7
	3	201				119				96		168		119							7.5
A.H.	1	334				211				112		266		272							118.3
	2	332				42				60		284		311							133.2
	3	398				286				175		314		246							115.3
D.B.	1	320		379		409		388		299	341	358	281	248							107.5
	2	204		274		166		54		24	73	109	58	28							66.5
	3	354		449		464		373		308	328	311	205	96							98.8

TABLE 4 (Continued from page 310)

Statistical Analysis* of seventy-two-hour study (data taken from table 3)

Day	2:00 p.m.	3:00 p.m.	4:00 p.m.	5:00 p.m.	6:00 p.m.	7:00 p.m.	8:00 p.m.	9:00 p.m.	10:00 p.m.	Urine sugar gm./24 hr.
					Mean blood sugar concentration					
Day 1	190.1	171.2	154.1	114.2	178.7	190.7	171.6	161.1	176.2	30.6
n	11	9	11	8	8	8	8	8	8	10
±S.E.	10.5	27.3	11.1	22.4	32.8	35.0	30.4	28.0	31.8	14.7
Day 2	121.1	81.6	99.1	69.2	123.4	152.9	144.9	149.9	140.4	24.5
n	11	9	11	8	8	8	8	8	8	10
±S.E.	14.2	12.7	20.5	13.8	20.2	25.8	25.3	28.2	30.7	14.8
Day 3	182.3	142.2	121.3	92.4	152.0	160.0	152.0	146.9	160.4	26.9
n	11	8	11	8	8	7	8	7	7	10
±S.E.	13.9	29.7	10.4	18.8	29.5	36.6	27.8	33.2	35.0	12.9
					Mean difference in blood sugar concentration					
Day 2-1	—69.0	—89.6	—55.0	—45.0	—55.3	—37.8	—26.7	—11.2	—17.4	—6.1
n	11	9	11	8	8	8	8	8	8	10
±S.E.	20.9	22.6	20.1	14.3	20.1	14.7	8.5	3.7	9.7	5.9
p	<0.01	<0.005	<0.025	<0.025	<0.05	<0.05	<0.025	<0.025	>0.1	>0.2
Day 3-1	—7.8	—29.0	—32.8	—21.8	—26.7	—30.2	—19.6	—10.3	—12.0	—3.7
n	11	8	11	8	8	7	8	7	7	10
±S.E.	9.9	13.7	13.2	10.9	20.5	19.0	15.7	12.1	13.0	3.2
p	>0.4	>0.05	<0.05	>0.05	>0.2	>0.1	>0.2	>0.4	>0.2	>0.2

*Mean changes in blood sugar concentrations, day 2 vs. day 1 and day 3 vs. day 1, were statistically evaluated by the *t* test for paired variates. At no time subsequent to the hypoglycemia on day 2 and at no time on day 3 were the mean blood sugar concentrations significantly higher than at the same time on the control day.

TABLE 5

Blood sugar concentrations and twenty-four-hour urine sugar in a patient subjected to six episodes of hypoglycemia. Small but statistically significant increases in blood sugar from prehypoglycemic to posthypoglycemic days were observed at 8 a.m. and 12 noon, although glycosuria was not increased.

Date	Blood sugar (mg./100 ml.) at 8:00 a.m.	10:00 a.m.	12:00 m.	Urine sugar (gm./24 hr.)
2/22/60	159	108	88	5.3
2/23/60	169	39	52	6.9
2/24/60	188	120	98	1.9
2/29/60	165	115	100	6.3
3/1/60	170	40	37	7.2
3/2/60	188	126	102	4.6
3/14/60	172	120	106	22.5
3/15/60	180	20	50	18.0
3/16/60	200	146	124	13.9
3/21/60	240	166	120	44.3
3/22/60	206	84	48	24.1
3/23/60	236	160	126	34.5
3/28/60	245	180	154	57.2
3/29/60	278	40	50	41.3
3/30/60	285	218	166	55.7
10/10/60	192	115	85	3.7
10/11/60	204	54	59	12.7
10/12/60	201	119	96	7.5
	Mean blood sugar			
Day 1	195	134	109	23.2
±S.E.	52	36	30	10.4
Day 2	201	46	49	18.4
±S.E.	54	14	13	6.8
Day 3	216	148	119	19.7
±S.E.	58	41	32	9.4
	Mean difference in blood sugar			
Day 3-1	+21	+15	+10	—3.5
±S.E.	6.4	6.4	2.2	2.1
t	3.3	2.3	4.4	1.7
p	<.025	>.05	<.01	>.05

DISCUSSION

In the four-hour studies hypoglycemia induced by insulin was not followed by a greater postprandial elevation of blood sugar compared to a control nonhypoglycemic state. There can be no doubt that physiologically significant hypoglycemia was produced, for at least one physiologic counter regulatory mechanism, activation of the adrenal cortex, reflected by increased plasma 17-hydroxycorticoid concentration, was documented. Despite this, there was no detectable mean increase in the degree of hyperglycemia occurring after the administration of glucose.

Except for V.L., E.B. and L.B. (table 3) all patients with blood sugars of less than 60 mg./100 ml. developed symptoms of hypoglycemia consisting, in different patients, of loss of mental acuity, hunger, diaphoresis, tachycardia and confusion. Diaphoresis and tachycardia are evidences of epinephrine secretion, an important counter regulatory mechanism. Measurements of epinephrine, growth hormone and glucagon were not done.

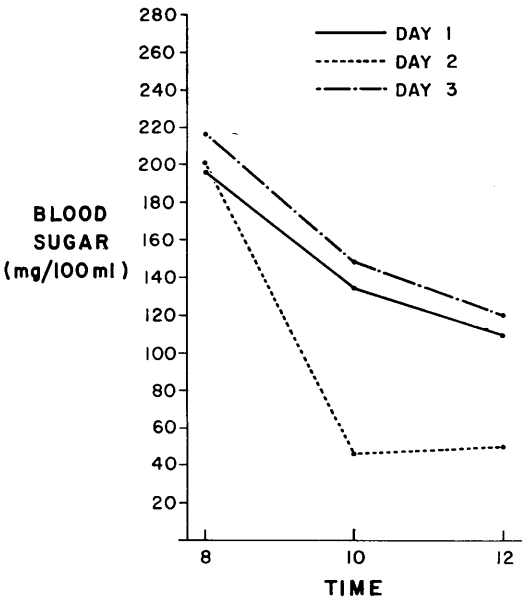

FIG. 2. Mean blood sugar concentrations in a single patient subjected to six replicate experiments in which hypoglycemia was induced on day 2, days 1 and 3 serving as controls.

The seventy-two-hour studies were designed to extend the period of observation and to study carbohydrate tolerance under conditions which simulated the normal day for each patient. Under these conditions, with constant dietary intake, there was no evidence that "hypoglycemia begets hyperglycemia."

Although the levels of blood sugar in the patient subjected to six identical studies were slightly higher on the day following the hypoglycemic episode than they were on the control day, there was no associated increase in glycosuria. Thus, neither the "diabetic control" as measured by urinary sugar excretion, nor the rate of decline of blood sugar during the forenoon of the third day was adversely affected by an episode of hypoglycemia on the preceding day. The absence of increased glycosuria and the minor magnitude of the blood sugar difference, make it difficult to attribute clinical significance to these findings.

These data are neither consistent with the concept that single episodes of hypoglycemia lead to subsequent impairment of control of diabetes nor with the hypothesis that "unstable diabetes . . . is . . . a direct consequence of excess insulin action."[11] It is well known that hyperglycemia and excessive glycosuria may follow the treated insulin reaction. In general, the carbo-

hydrate administered under such circumstances is an unplanned addition to the patient's diet. Thus, clinical examples of apparent rebound hyperglycemia may be the result of excessive caloric intake necessitated by the development of symptomatic hypoglycemia, or the subsequent augmentation of food intake to avoid a recurrence.

The data presented here pertain only to *single* episodes of hypoglycemia. It is possible that frequent, repeated episodes may have a deleterious effect upon control of diabetes, although this has not, to our knowledge, been demonstrated under rigorously controlled conditions.

Somogyi[10] has suggested that hypoglycemia is succeeded by reduced carbohydrate tolerance in normal as well as in diabetic persons. No evidence of this effect was seen in two patients without diabetes whom we also studied.

CONCLUSION

In diabetic patients on constant diets, single episodes of hypoglycemia induced by insulin, untreated by carbohydrate supplementation, produced neither excessive hyperglycemia nor increased glycosuria.

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