

# Serum Immunoreactive Insulin Levels During Glucose Tolerance and Intensive Islet Stimulation Effect of Prednisone

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## SUMMARY

The effects of a potent glucocorticoid (prednisone) on blood sugar and serum immunoreactive insulin (IRI) levels during glucose tolerance and intensive islet stimulation were studied in forty-two subjects whose glucose tolerance ranged from well-within-normal limits to frankly diabetic. The ability to maintain "normal" glucose tolerance under this added stress was not directly related to capacity for increasing serum IRI levels. "Diabetic" subjects were not more susceptible to degeneration of glucose tolerance after prednisone even though serum IRI levels increased little or even decreased in several subjects. The data make it difficult to directly relate the magnitude of serum IRI levels at the times measured to degree of glucose intolerance and suggest that other factors (possibly insulin resistance), as yet unknown, are operative. *DIABETES* 20:410-15, June, 1971.

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In a preceding report<sup>1</sup> we discussed the relationships between plasma immunoreactive insulin (IRI) and blood sugar levels during intensive islet stimulation. The multiple factors that should be considered in their interpretation were discussed and it was noted that among individuals there was a wide range of IRI response until high fasting blood sugar levels were reached, at which levels there was definite diminution of IRI response to the stimuli given.

The purpose of the present study was to examine the

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effect of an additional diabetogenic stress, that of a pharmacologic dose of a potent glucocorticoid, prednisone, which was administered in the preceding twenty-four hours. The response of subjects with a wide range of glucose tolerance was compared.

## MATERIALS AND METHODS

These were exactly as previously described<sup>1</sup> except that 40 mg. of prednisone was given in divided doses (10 mg. per os morning, afternoon and evening the day prior to the test, and 10 mg. two hours prior to testing) during the twenty-four hours preceding the test. The subject population was as described in table 1.

## RESULTS

Figure 1 shows the mean blood sugar and IRI responses of the groups of subjects obtained before and after the administration of prednisone and table 1 gives the responses in detail. For purposes of discussion and since the mean age of these subjects approximated that of the subjects of Fajans and Conn<sup>2</sup> establishing criteria of normality of glucose tolerance, they were divided into groups on the basis of whether or not the one-hour blood sugar exceeded 160 mg./100 ml. and the two-hour blood sugar exceeded 120 mg./100 ml. Group I blood sugars ("normals") did not exceed these values either before or after prednisone administration. Group II blood sugars exceeded these values only after prednisone administration. Group III ("diabetic") exceeded these values before prednisone administration. Group IV included patients with miscellaneous metabolic disease states as listed in table 1. These groupings were selected because the major interest here was to determine the IRI response to a particular pattern of glucose tolerance before and after prednisone. Some interesting observations emerged with these groupings: I had a preponderance of males with few close relatives who were known

TABLE 1  
Detailed data of patients in the four groups tested

Group I: Normal

Pa- tients	Sex	Age	Wt.	Ht.	Per cent deviation ideal body weight	Diabetic family history								
							F	1	2	5	F	1	2	5
B.M.	M	30	165	71	+ 2	None	80 44	72 96	82 64	79 505	90 14	116 195	98 135	104 1,760
M.J.	M	25	165	70	+ 4.5	None	60 19	56 38	56 28	63 335	87 29	100 75	113 80	120 680
M.F.	M	26	120	65	-12.2	MM, FB	78 12	111 127	66 54	92 790	92 30	127 300	90 125	102 1,210
D.W.	M	30	195	71	+20.6	FM	88 10	108 68	89 58	105 710	91 64	115 160	102 205	110 1,400
J.H.	M	23	200	74	+13.9	None	68 51	88 135	44 56	53 370	70 20	153 230	68 72	76 820
D.L.	M	27	205	72	+23.2	None	82 93	106 72	68 72	86 432	82 11	115 104	97 43	112 540
P.R.	M	29	183	72	+10.1	None	70 7	106 72	85 25	80 330	76 12	113 87	94 60	102 476
T.M.	M	26	185	70	+17.6	None	81 29	110 152	78 71	80 610	82 58	143 222	106 117	121 840
D.S.	M	17	140	66	+ 4.5	FFB	75 14	74 60	80 50	109 510	77 28	144 102	109 95	116 840
T.S.	M	48	155	67	+ 7.0	FB	73 18	98 114	69 54	76 540	81 26	115 180	83 76	100 650
E.K.	M	16	214	74	+23.6	F	80 47	110 127	100 141	103 1,140	97 62	136 242	113 160	123 400
W.B.	M	39	220	71	+32.0	FB	82 41	134 129	110 123	108 1,030	79 41	152 165	119 172	119 1,190
A.P.	F	26	169	63	+36.1	FB,MF,FM	73 30	156 232	88 98	98 710	89 61	139 200	118 223	104 1,006
Mean ± S.E.		27.8 2.3	178.1 8.1	69.6 .94	+14.1 3.7		76.1 2.0	102.2 7.2	78.0 4.9	87.0 4.8	84.0 2.1	128.3 4.9	100.7 4.0	108.3 3.5
± S.E.							26.8 4.5	111.0 13.7	68.0 9.4	616.3 70.6	35.0 5.5	174.0 18.7	120.2 15.6	908.6 109.3

Group II: Abnormal After Prednisone

Pa- tients	Sex	Age	Wt.	Ht.	Per cent deviation ideal body weight	Diabetic family history								
							F	1	2	5	F	1	2	5
A.N.	M	39	165	69	+ 7.7	None	68 10	119 120	76 18	87 300	96 16	169 105	100 83	109 930
A.S.	M	30	194	71	+19.9	FB, FM	82 10	107 28	64 11	67 395	98 11	177 64	130 56	140 940
M.R.	M	29	157	68	+ 5.4	None	74 14	106 68	95 54	126 840	103 225	179 220	116 145	120 1,480
L.P.	M	36	185	75	+ 2.4	F, MB	66 36	105 38	120 51	88 313	88 46	172 117	138 155	139 470
T.T.	M	40	180	64	+35.0	M, FM, FF, MM, MF	80 30	146 275	79 144	74 770	88 19	180 97	114 167	118 990
W.M.	M	12	98	60	-16.1	M	64 23	158 152	105 202	100 1,090	82 10	239 410	223 580	219 1,660
L.Y.	F	18	133	66	- 2.7	F	74 10	144 390	78 228	82 1,100	82 19	184 800	113 1,260	116 2,800
S.C.	F	16	155	69	+ 3.9	None	71 18	153 163	96 152	104 590	85 15	258 240	160 84	127 740
N.L.	F	24	140	69	- 3.5	F, MF	95 23	116 180	88 135	77 990	92 24	162 223	143 265	156 870

(Continued on following page)

TABLE 1 (continued)

Group II: Abnormal After Prednisone (continued)														
Pa-tients	Sex	Age	Wt.	Ht.	Per cent deviation ideal body weight	Diabetic family history								
							F	1	2	5	F	1	2	5
S.G.	F	18	120	65	— 8.0	FF, all F sibs	70	101	56	62	79	169	173	165
							26	138	150	1,740	38	460	1,800	4,774
L.D.	F	39	137	64	+ 6.7	F, M, B	66	110	109	97	83	162	139	131
							92	155	168	1,210	72	270	233	1,220
H.P.	F	54	120	68	—17.1	None	70	107	54	76	112	213	138	135
							14	111	72	680	14	140	134	920
F.R.	F	50	133	64	+ 3.6	M	79	124	114	110	106	196	133	119
							21	42	36	210	30	277	235	880
Mean		31.1	147.4	67.0	+ 2.9		73.1	122.7	87.2	88.4	91.8	189.2	140.0	138.0
± S.E.		3.6	7.8	1.0	3.9		2.3	5.6	6.0	5.0	2.8	8.3	8.8	8.0
± S.E.							25.1	143.0	109.3	786.7	26.0	263.3	399.7	1,436.4
							6.0	27.9	20.0	121.9	4.8	55.5	147.0	321.4

Group III: Abnormal Before Prednisone														
Pa-tients	Sex	Age	Wt.	Ht.	Per cent deviation ideal body weight	Diabetic family history								
							F	1	2	5	F	1	2	5
W.R.	M	35	150	67	+ .7	MB	93	161	111	112	78	133	96	88
							10	140	105	860	13	140	66	580
W.K.	M	38	150	67	+ .5	F, FS, FB	70	211	150	129	80	208	110	112
								66	93	518	24	96	107	680
C.S.	M	28	153	66	+ 5.0	M	86	214	170	161	81	171	159	168
							58	356	455	1,840	58	310	342	1,692
L.R.	M	47	145	66	+ 3.1	None	74	171	82	71	104	262	113	201
							27	195	67	162	14	181	168	794
D.K.	M	42	195*	71	+20.6	None	250	314		320	70	162	217	230
							17	22		82	10	11	12	54
M.H.	F	60	140	64	+ 9.1	D	95	184	182	184	108	231	187	191
							10	88	130	750	76	200	255	1,060
F.G.	F	50	144	66	+ 5.3	F, FS, FM	86	245	256	248	96	255	276	306
							12	46	60	250	24	50	32	260
J.C.	F	38	120	62	— .2	F	68	160	161	165	72	219	233	243
							56	114	198	366	10	135	85	456
R.R.	F	37	161	62	+33.9	None	230	372	420	438	247	384	432	456
							14	24	27	228	25	20	19	192
Mean		41.6	150.8	65.6	+ 8.7		116.8	225.7	191.5	203.1	104.0	225.0	202.5	221.6
± S.E.		3.1	6.6	0.9	3.8		23.5	24.4	37.3	38.3	18.4	24.5	35.2	36.6
± S.E.							25.5	116.7	130.6	561.7	28.2	127.0	120.6	640.8
							7.1	35.3	47.7	182.4	7.7	32.0	37.9	168.0

\*Hyperlipoproteinemia, type IV

TABLE 1 (continued)

Group IV: Miscellaneous Disease States														
Pa- tients	Sex	Age	Wt.	Ht.	Per cent deviation ideal body weight	Diabetic family history								
							F	1	2	5	F	1	2	5
H.O.*	M	46	176	72	+ 5.9	None	70	170	172	171	80	174	164	149
							25	164	230	896	31	180	23	810
J.P.*	M	38	180	67	+24.3	None	78	185	113	112	87	169	140	159
							28	207	220	1,440	39	164	188	1,020
E.V.S.†	F	47	130	64	+ 1.3	None	76	157	132	108	87	198	139	135
							28	330	390	1,440	46	275	225	860
J.J.*	M	26	160	68	+ 5.8	None	80	110	114	102	86	122	101	108
							39	115	200	1,160	33	145	180	1,920
A.B.‡	M	42	175	69	+14.3	None	80	127	98	131	80	137	156	158
							42	310	100	1,320	26	195	404	2,100
B.K.§	M	71	168	71	+ 3.9	M	104	121	112	149	104	137	122	153
								110	164	390	58	175	155	640
J.S.	F	37	130	63	+ 4.7	None	83	106	86	105	84	150	108	104
							16	64	54	480	28	133	78	610
Mean		43.8	159.8	67.7	+ 8.6		81.5	139.4	118.1	125.4	86.8	155.2	132.8	138.0
± S.E.		5.2	8.0	1.2	1.3		4.0	11.7	10.4	9.8	3.0	9.9	8.9	8.9
							29.6	185.7	194.0	1,018.0	37.2	181.0	179.0	1,137.1
± S.E.							3.8	38.6	40.7	166.6	4.3	17.0	45.7	232.0

\*Hyperlipoproteinemia, type IV

†Hyperlipoproteinemia, type II

‡Acromegaly

§Previous hyperosmolar coma

||Hypopituitarism, chromophobe adenoma

diabetics; II had a preponderance of subjects who had a close relative diabetic, and the majority were females. The mean ages of groups III and IV were about a decade greater and males and females were about equally divided. Mean body weights of the groups were comparable except that group I was somewhat greater than the others because of a preponderance of males. Per cent deviation from ideal body weight was not a determining factor of IRI response in most subjects studied.

The IRI response patterns were also quite different among the groups (figure 1). Group I had the lowest response before prednisone and increased only moderately after its administration. Group II had the greatest increase in IRI response after prednisone among the groups. This was particularly remarkable at two hours after oral glucose. It was also noticeable in this group that IRI levels continued to rise as the blood sugar was falling. The I/G ratios were consequently much greater at two hours but not significantly different from group I at one hour (see table 1). Group III had low IRI responses relative to the blood sugar levels but these were comparable to those of group I before prednisone. Their I/G ratios were decreased at all times both before and after prednisone (see table 1). There was no significant increase in either the blood sugar or IRI responses in this group after prednisone. The two-hour and the five-minute IRI levels were again correlated ( $p < .001$ ) in all groups as shown in the previous paper and this re-

lationship held true after the administration of prednisone.

Figure 2 shows plots of one-hour blood sugar versus the five-minute IRI and figure 3 the two-hour blood sugar versus the two-hour IRI before and after prednisone of the individuals in each group. These times were selected as representative of the responses in general. As seen in these figures, there was considerable variation in the responses within each group. Some subjects maintained low blood sugar levels after prednisone with minimal increase in circulating IRI, whereas others had a large increase. Some subjects (particularly J.G. and L.Y., two thin, young females) had marked increases in blood sugar after prednisone in spite of very large increases in circulating IRI. Their responses were similar to, but more pronounced than, that of A.B. in group IV, who had active acromegaly with very high growth hormone levels. The lack of unusual response of patient B.K. (group IV) is also of interest in that he had had a previous episode of hyperglycemic hyperosmolar coma. Individual responses could not be attributed to degree of obesity. The variability of responses were not random but characteristic of the individuals, in that low or high IRI values were seen at each of the times sampled after the glucose load.

#### DISCUSSION

Since the initial studies of Fajans and Conn, showing

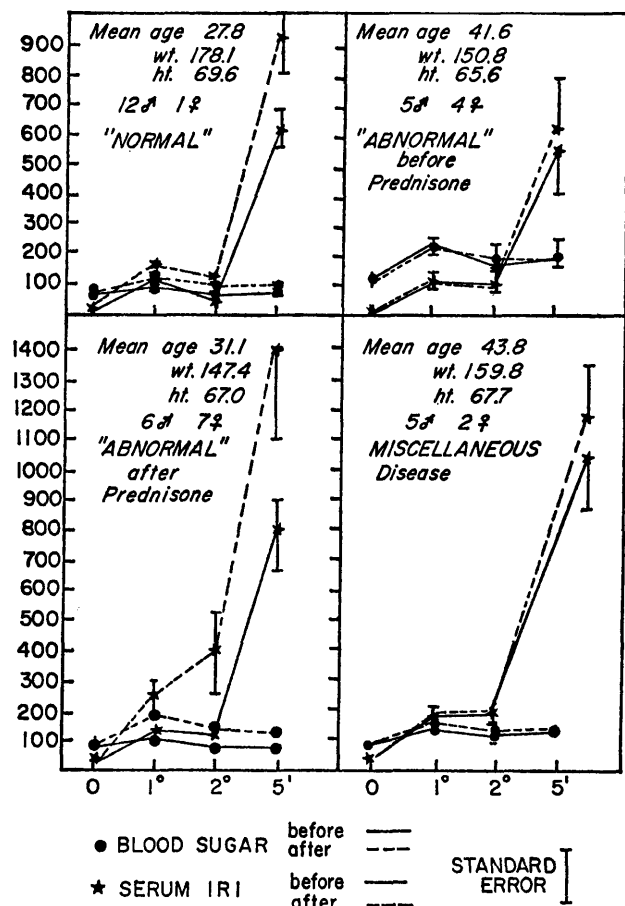


FIG. 1. Mean  $\pm$  S.E. of blood sugar and serum IRI responses before and after prednisone of the four groups tested. See text for details.

a degeneration of glucose tolerance in relatives of diabetics following a pharmacologic dose of cortisone,<sup>2</sup> others have investigated the impact of corticosteroids of several types and dosage schedules. The particular steroid and dosage regimen used in the present study was arbitrarily selected after preliminary studies in a small number of subjects showed that the increase in blood sugar and IRI was greater than after oral cortisone as used by Fajans and Conn. The response did not appear to be significantly enhanced by a larger (80 mg.) or more prolonged (3 days x 20 mg.) dosage schedule.

The findings of Berger et al.<sup>3</sup> who studied the glucose tolerance and IRI responses of subjects who had a diabetic relative are similar to those of the present study, although our subjects were not selected on the basis of family history. They also found that impairment of glucose tolerance after corticosteroid administration was associated with an enhanced plasma IRI response. They did not report any studies of the response of subjects

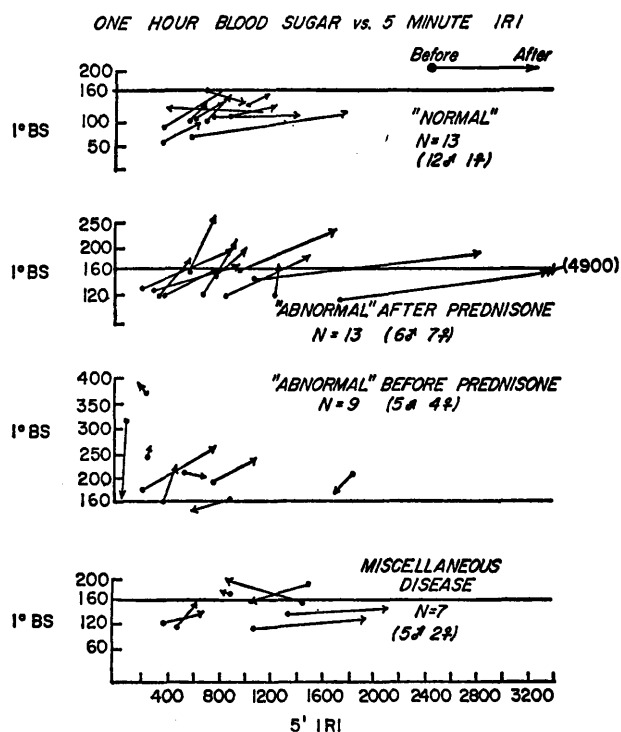


FIG. 2. Individual responses of one-hour blood sugar and five-minute post-stimulation serum IRI before and after prednisone in the four groups tested. Arrows indicate direction of response after prednisone. See text for details.

whose glucose tolerance was already abnormal. Rull et al. however, recently reported that diminished insulin secretory reserve was present in "nondiabetic" relatives of diabetic patients and was demonstrated only during the cortisone glucose tolerance test.<sup>4</sup> Their findings would appear to be at variance with ours but this is possibly due to patient selection and/or type of steroid used.

It is generally agreed that increasing age is associated with an increase in the diabetogenic effect of steroids. Andres has found that the increase in blood sugar two hours after a glucose load approximated 13 mg./100 ml. higher per decade.<sup>5</sup> Corticosteroids have also been found to increase the diabetogenic effect and IRI response to glucose in pregnancy, acromegaly, and obesity.<sup>6</sup>

The marked differences in blood sugar and IRI response seen among subjects in this study were, in most cases, not attributable to the factors noted above and argues strongly against a simple relationship between deficiency of IRI and elevated blood sugar levels. It is possible that subjects with the larger responses may have greater innate insulin resistance. It might also be considered that prednisone induced a greater degree of insulin resistance in some subjects than in others. The

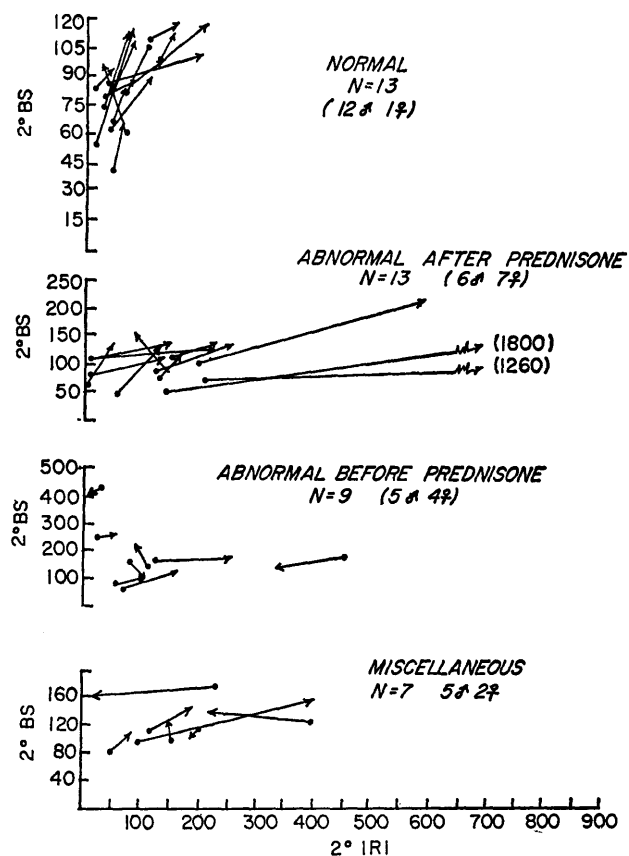


FIG. 3. Individual responses of two-hour blood sugars and two-hour serum IRI before and after prednisone. Arrows indicate direction of response after prednisone. See text for details.

responses are likely the result of interaction of several effects, possibly including the effects of the steroid on gluconeogenesis.

The lack of increase in IRI response in most of the "diabetic" subjects might be expected if we assume that their beta cells were already acting at maximal capacity. A decrease after prednisone might be assumed to be due to some degree of "exhaustion" with the added load of prednisone as an insulin antagonist. If this is true however, it is difficult to explain why there was not an over-all greater increase in blood sugar in this group, whereas in fact, the blood sugars increased the least or even decreased in some subjects.

The present findings might also fit with the presence of variable amounts of proinsulin in plasma as demonstrated by Rubenstein et al.<sup>7</sup> This would explain the seeming lack of effect of IRI on blood sugar in some subjects since proinsulin has cross-immunoreactivity with insulin but little biologic activity. This concept is speculative at the moment, but quantitation of the amount of circulating proinsulin in these patients is currently under investigation in our laboratory. Preliminary results in our laboratory as well as the findings of others<sup>8</sup> suggest, however, that this is not the case.

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