On the Mechanism of Insulin Hypersensitivity in Adrenocortical Insufficiency

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SUMMARY

A study of the sensitivity to a test dose of exogenous insulin was undertaken in eight patients with primary and five with secondary (Sheehan's syndrome) adrenal insufficiency. The great majority showed hypersensitivity to insulin and hypoglycemia-unresponsiveness was present in all.

The hypersensitivity was primarily the result of excessive peripheral insulin action as shown by the increased disappearance rate (k) of an intravenous glucose load, in the well nourished patient.

A possible failure in glycogenesis and consequent reduced glucose release by the liver, which might explain the hypoglycemia-unresponsiveness, was not confirmed by the glucagon test, suggesting that if there is liver impairment it is in its rate of glucose release independent of the amount of glycogen present and related to the glucocorticoid influence on the threshold of blood glucose regulation by the liver.

Increased sensitivity to exogenous insulin has been repeatedly demonstrated in patients with adrenal insufficiency.[1,2] Long et al.[3] have suggested that failure in glycogenesis appears to be responsible and this interpretation has been accepted in more recent reviews on the subject.[4]

The data to be presented in this paper are not entirely consistent with the concept that a decrease in hepatic glycogen stores, as the primary defect in adrenal insufficiency, is responsible for the increased sensitivity to insulin.

MATERIAL, METHODS AND RESULTS

Eight patients with primary adrenal insufficiency (Addison's disease) and five with the form secondary to postpartum hypopituitarism (Sheehan's syndrome) were used in our studies (table 1). The impossibility of performing the test on every patient leads us to present each test separately. Blood glucose was determined by the Nelson modification of the Somogyi method.[5]

1. INSULIN TOLERANCE TEST

The test was performed in eighteen normal controls (ten males and eight females), six patients with Addison's disease and four patients with postpartum hypopituitarism. Every test was performed in the post-absorptive state. In the morning, 0.05 units of glucagon-free insulin per kilogram body weight were given intravenously and venous blood was withdrawn before, and 15, 30, 45, 60, 90 and 120 min. after the hormone administration. Prior to the performance of this and other tests the patients had not received substitution therapy for at least one month or had never been so treated. However, one of the patients (J.A.M.), was maintained in electrolyte balance, by repeated administration of desoxycorticosterone acetate.

The mean values of the blood glucose at each test period in the normal controls, are shown in table 2, as well as the confidence interval for single values. The results shown by the patients with primary and secondary adrenal insufficiency are indicated in table 2.

Insulin hypersensitivity is considered present when each blood sample, until the lowest blood glucose is reached (usually between 15 and 45 min.), demonstrates a glucose value below the normal interval standardized for single values. According to Frazer et al.[2] we also consider hypersensitivity to be present when the lowest glucose value, after insulin injection, is below the confidence limit for control values.

With the same reasoning, decreased responsiveness to the insulin-induced hypoglycemia is considered to be present when, at the time the blood glucose has a tendency to return to or above the fasting value, the values at the sampling times between the lowest blood glucose attained and the last one drawn are below the 95 per cent confidence limit for the single values at the same times. With these criteria, our results in the adrenal insufficient

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TABLE 1

Summary of laboratory findings

(A) Sheehan's syndrome

				Thyroid function				Adrenal function ACTH stimulation test*										Urinary gonadotrophins (mouse units per twenty-four hours)
								Controls		ACTH first day		ACTH second day		ACTH third day		ACTH fourth day		
Patient	Sex	Age in years	Duration in years	Twenty-four-hour I-131 uptake (per cent)	PBI mcg. per 100 ml.	Total serum cholesterol (mg. per 100 ml.)	BMR (per cent)	17-OH-CS†	17-KS‡	17-OH-CS	17-KS	17-OH-CS	17-KS	17-OH-CS	17-KS	17-OH-CS	17-KS	
E.S.G.	F	52	15	20.5	5.7	401	−11 −17	1.2	<1	0.7	0.4	0.4	0.4	—	—	3.1	1.2	<5
F.K.	F	43	6	25	6.1	279	− 5 − 8	1.7	0.2	3.2	<1	5.6	0.3	4.7	1.4	4.3	2.6	<5
A.O.E.	F	30	4	12.5	3.0	185	− 7 − 8	1.4	<1	1.1	<1	1.8	0.2	—	—	—	—	<5
A.C.	F	41	11	4.0	1.4	253	−37 −38	1.9	0.2	2.4	0.05	3.1	1.4	—	—	4.6	6.6	<5
A.B.M.	F	31	6	57	4.5	—	—	1.5	<1	3.76	4.6	6.1	13.87	—	—	—	—	<5

(B) Addison's disease

					Adrenal function ACTH stimulation test*					
					Controls		ACTH first day		ACTH second day	
Patient	Sex	Age in years	Etiology	Duration in years	17-OH-CS†	17 KS‡	17-OH-CS	17 KS	17-OH-CS	17 KS
F.P.	M	48	South American blastomycosis	5	4.1	2.8	3.4	2.4	2.4	2.4
M.S.	M	54	Tuberculosis	7	2.8	3.5	—	—	—	—
E.D.	F	35	Idiopathic	2	2.9	<1	3.7	<1	3.8	<1
P.M.E.	F	34	Idiopathic	5	2.1	<1	1.5	<1	2.9	<1
J.A.M.	M	47	South American blastomycosis	1	4.3	4.8	4.0	3.8	4.5	2.8
A.T.	M	53	South American blastomycosis	2	3.2	2.6	—	—	1.6	—
M.I.S.P.	F	29	Idiopathic	3	4.4	2.9	3.0	3.4	2.8	2.7
G.E.J.	M	45	South American blastomycosis	2	2.74	2.12	3.85	2.23	2.6	0.76

*25 mg. of ACTH, intravenously, for eight hours and twenty-four-hour urinary collections for steroid analysis.
†Normal values for adults: 6-14 mg./24 hr.
‡Normal values for adults: 9-20 mg./24 hr.

patients, shown in the table 2, indicate that only two of our cases present normal sensitivity to insulin. However, every patient has shown hypoglycemia-unresponsiveness.

2. INTRAVENOUS GLUCOSE TOLERANCE TEST

In normal controls (five males and five females) and nine patients with adrenal insufficiency (five Addisonians and four with Sheehan's syndrome), in the postabsorptive state, an intravenous glucose tolerance test was performed, according to the technic described by Amatuzio et al.,[6] i.e., intravenous administration of 25 gm. of glucose, as a 50 per cent glucose solution in distilled water, during four minutes. Capillary samples, by finger puncture, for glucose analysis, were obtained before the test, *four minutes after the end of the glucose infusion and* subsequently every eight minutes for seventy-two minutes. Glucose disappearance rate (k) was obtained from the slope of the straight line obtained when blood glucose expressed in milligrams per 100 ml. was plotted on a logarithmic scale against time. Slope analysis allowed us to establish a common regression for the ten normal controls, after acceptance of the linearity hypothesis for this regression.[7] Therefore, a 95 per cent confidence limit for the regression coefficient, for each sex, was established, resulting in the following limits for normal values for the constant rate for glucose disappearance from the blood (k)[7]:

Males: 0.0130—0.0201

Females: 0.0109—0.0180

The results of the intravenous glucose tolerance tests in the patients are shown in table 3. It can be seen that all but three cases (two with primary and the remaining with secondary adrenal insufficiency) had an increase in the disappearance rate *k*.

It should be mentioned that two of the three patients without increased *k* were extremely malnourished.

3. GLUCAGON TOLERANCE TEST

Ten normal controls and seven patients with adrenocortical insufficiency (six Addisonians and one patient with hypopituitarism) were given 30 μg. of glucagon per kilogram body weight, subcutaneously, as suggested by Van Itallie and Bentley.[8] No significant differences were observed in the results when the subcutaneous or intravenous routes of administration were compared.*

*In five normal controls, the differences in blood glucose at each time were not statistically significant ($p > 0.05$).

TABLE 2

Insulin tolerance test (0.05 U./kg. body weight) in patients with adrenocortical insufficiency and in normal controls

Name	Age (years)	Sex	Diagnosis	Physical condition	Treatment	Blood glucose (mg. per 100 ml.) Minutes after insulin injection 0	15	30	45	60	90	120	Results: Insulin sensitivity	Results: Hypoglycemia responsiveness
F.P.	48	M	Addison's disease	Reasonable	—	73	53	21	30	38	39	43	Hypersensitivity	Decreased
M.S.	54	M	Addison's disease	Good	—	70	24	23	22	22	23	24	Hypersensitivity	Decreased
P.M.E.	34	F	Addison's disease	Bad	—	59	19	19	21	23	30	43	Hypersensitivity	Decreased
E.D.	35	F	Addison's disease	Good	—	67	16	25	31	34	38	39	Hypersensitivity	Decreased
J.A.M.	47	M	Addison's disease	Bad	DOCA	68	47	25	29	35	35	50	Hypersensitivity	Decreased
E.S.G.	52	F	Sheehan's syndrome	Good	—	59	42	23	17	26	34	36	Hypersensitivity	Decreased
A.O.E.	31	F	Sheehan's syndrome	Good	—	56	52	49	35	38	38	56	Normal	Decreased
F.K.	43	F	Sheehan's syndrome	Good	—	107	56	27	36	31	44	50	Hypersensitivity	Decreased
G.E.J.	35	M	Addison's disease	Bad	—	87	58	32	32	32	40	36	Normal	Decreased
A.C.	47	F	Sheehan's syndrome	Good	—	73	41	37	27	37	32	30	Hypersensitivity	Decreased
Normal controls (18 subjects)				$\bar{x}$ (mean)		91.50	57.38	46.89	64.72	74.44	83.83	91.17		
				S (standard deviation)		10.19	17.56	8.82	14.17	13.90	11.99	15.51		
				$x \pm t_{n-1} \cdot s$ *		91.50 ± 21.50	57.38 ± 21.50	46.89 ± 18.61	64.72 ± 29.90	74.44 ± 29.33	83.83 ± 25.30	91.17 ± 32.73		

*Confidence interval for single values.

TABLE 3

Intravenous glucose tolerance test in patients with adrenocortical insufficiency

Name	Sex	Age (years)	Diagnosis	Physical condition	Blood glucose (mg. per 100 ml.) Minutes after glucose injection 0	8	16	24	32	40	48	56	64	72	Disappearance rate (K)	Comparison to the normal (K)
F.P.	M	48	Addison's disease	Reasonable	84	273	226	170	137	123	90	84	78	76	0.0211	Increased
M.S.	M	54	Addison's disease	Good	71	292	224	168	130	119	71	69	67	67	0.0248	Increased
E.D.	F	35	Addison's disease	Good	100	422	312	240	191	129	101	89	55	50	0.0341	Increased
E.S.G.	F	52	Sheehan's syndrome	Good	78	433	278	246	194	160	121	105	103	80	0.0248	Increased
A.O.E.	M	31	Sheehan's syndrome	Good	51	335	272	228	189	157	125	110	93	82	0.0223	Increased
J.A.M.	F	47	Addison's disease	Bad	75	250	300	183	178	176	164	155	151	143	0.0098	Decreased
P.M.E.	F	34	Addison's disease	Bad	78	370	325	291	244	237	221	202	179	167	0.0121	Normal
F.K.	F	43	Sheehan's syndrome	Good	82	422	313	272	234	220	178	156	151	115	0.0181	Normal
A.C.	F	47	Sheehan's syndrome	Good	54	316	236	215	157	131	80	61	46	42	0.0336	Increased

Capillary samples for glucose analysis were obtained before the hormone administration and subsequently every eight minutes for seventy-two minutes.

Table 4 shows the results of the test in normal controls and adrenal insufficient patients, expressed as increments of the blood glucose values, at each sampling, in relation to the fasting glucose (Δ B.G.). The mean and standard deviations of the increments are also indicated in that table.

According to table 4 no significant differences are

TABLE 4

Glucagon tolerance test (30 mcg./kg. body weight) in patients with adrenocortical insufficiency and in normal controls

Name	Age (yrs.)	Sex	Diagnosis	Physical condition	Treatment	Fasting blood glucose* (mg. per 100 ml.)	Difference between each B.G.* and the F.B.G. at different times (Δ B.G.): mg. per 100 ml. Minutes after glucagon injection 8	16	24	32	40	48	56	64	72
F.P.	48	M	Addison's disease	Reasonable	—	75	+19	+40	+50	+65	+70	+60	+42	+25	+13
M.S.	54	M	Addison's disease	Good	—	64	+13	+26	+30	+31	+21	+11	+ 2	— 4	—11
E.D.	35	F	Addison's disease	Good	—	82	+52	+67	+71	+81	+89	+80	+64	+44	+16
E.S.G.	52	F	Sheehan's syndrome	Good	DOCA	63	+27	+56	+69	+80	+62	+52	+49	+31	+19
A.T.	53	F	Addison's disease	Bad	DOCA	78	+17	+34	+45	+64	+64	+65	+65	+45	+35
J.A.M.	42	M	Addison's disease	Bad	DOCA	77	+ 6	+12	+22	+32	+68	+34	+24	0	— 6
P.M.E.	34	F	Addison's disease	Bad	DOCA	83	+22	+42	+62	+77	+85	+79	+67	+53	+42
				Δ B.G. mean			+22.3	+39.5	+50	+61.5	+65.6	+54.4	+44.7	+27.7	+15.4
				Standard deviation			±14.84	±18.42	±18.94	±21.48	±22.18	±24.85	±24.35	±24.69	±19.40
Normal controls (ten subjects)				Δ B.G. mean			+27.2	+51.9	+70.9	+74.7	+71.8	+62.5	+45.6	+31.4	+17
				Standard deviation			±14.64	±23.05	±27.35	±23.44	±33.5	±33.91	±33.16	±37.1	±27.63

*B.G. = Blood Glucose (capillary).

observed between the normal controls and the adrenal insufficient patients as regards the mean increments in corresponding blood samples after glucagon administration. Because of the similarity of responses to the glycogenolytic-hyperglycemic hormone in normal controls and adrenal insufficient patients and considering the increased rate of glucose disappearance (k) of the latter, we performed a series of glucagon tolerance tests with venous blood for glucose analysis where, obviously, the peripheral uptake is included.

The same amount of glucagon was used and the samples were obtained before the test and every fifteen minutes for ninety minutes after hormone administration. The results in ten normal controls and four patients (two Addisonians and two with Sheehan's syndrome) are indicated in table 4. The results are again expressed as increments of blood glucose levels, at each time, in relation to the fasting level.

Even if the sample is too small for statistical analysis, simple observation of table 5 indicates the clear difference between the Δ glucose curves for normal controls and for subjects with adrenal insufficiency cases.

The different behavior of the patients with adrenocortical deficiency when capillary and venous blood are compared (decreased responsiveness to glucagon, compared to normal controls, *only* in venous blood glucose) suggests that increased peripheral glucose utilization, as indicated by the intravenous glucose tolerance test, is the responsible factor.

Accordingly, if peripheral glucose utilization is blocked, the response in patients with adrenal insufficiency should resemble normal controls when venous blood levels are compared. Therefore, a small amount of epinephrine (3 μg per kilogram body weight) was administered subcutaneously, ten minutes prior to glucagon injection, as suggested by Van Itallie and Bentley.[8] With this dosage the epinephrine effect on hepatic glycogenolysis is negligible, but muscular glycogenolysis and the subsequent inhibitory effect on peripheral glucose uptake is clearly seen.[9,10] We found that the administration of 3 μg of epinephrine per kilogram body weight, alone, to four normal controls, one Addisonian and one hypopituitary patient, did not induce a significant hyperglycemic response (table 5).

The epinephrine-glucagon test, as indicated, was performed in ten normal controls and four patients with adrenal insufficiency who had a previous glucagon test with venous blood sampling. The blood glucose increments in relation to the fasting levels and their means and standard deviations are indicated in table 6.[7] There is a complete superposition of the means of the increments, at corresponding times, for the normal controls and the patients with adrenal insufficiency.

DISCUSSION

The insulin tolerance test demonstrated increased sensitivity to exogenous insulin in the majority of the patients with adrenal insufficiency. On the other hand, all of them showed hypoglycemia-unresponsiveness. Similar

TABLE 5

Glucagon tolerance test (30 mcg./kg. body weight) in patients with adrenocortical insufficiency and in normal controls

Name	Sex	Age (years)	Diagnosis	Fasting blood glucose* (mg. per 100 ml.)	Difference between each B.G.* and F.B.G. at the different times (Δ B.G.): mg. per 100 ml. Minutes after glucagon injection 15	30	45	60	75	90
G.E.J.	M	35	Addison's disease	67	+10	+ 7	+ 5	0	— 9	—11
A.C.	F	47	Sheehan's syndrome	78	+ 2	+18	— 3	—18	—24	—23
E.D.	F	37	Addison's disease	111	0	— 5	+ 6	—17	—17	—21
A.B.M.	F	35	Sheehan's syndrome	86	+15	+15	+ 8	—30	—20	—25
			Δ B.G. mean		+ 6.75	+ 8.75	+ 4	—16.25	—17.5	—20
			Standard deviation		±12.74	±11.76	± 4.80	±29.69	± 6.34	± 6.21
Normal controls (ten subjects)			Δ B.G. mean		+32.3	+47.4	+45.4	+35.4	+18.7	+ 3
			Standard deviation		±15.8	±22	±30	±34.2	±27.8	±21.7

*B.G. = Blood Glucose (venous).

TABLE 6

Epinephrine* tolerance test in normal controls and patients with adrenocortical insufficiency

Name	Sex	Age (years)	Diagnosis	Fasting blood glucose (mg. per 100 ml.)	Difference between each B.G. and F.B.G. at the different times (Δ B.G.): mg. per 100 ml. Minutes after epinephrine injection 15	30	45	60	75	90
A.M.	M	32	Normal control	97	+10	+19	+25	+33	+22	+10
M.B.M.	F	29	Normal control	71	+10	0	+13	+30	+13	+15
B.L.F.	F	32	Normal control	71	+ 5	—12	0	—19	0	—10
D.G.T.	F	30	Normal control	71	+15	+15	+ 7	+18	+15	— 2
			Δ B.G. mean		+10	+ 5.5	+ 8.75	+15.5	+12.5	+ 3.25
A.B.M.	F	35	Sheehan's syndrome	86	0	+10	+10	+16	+10	+16
M.I.S.P.	F	29	Addison's disease	61	0	+ 3	+ 7	+10	+ 7	+ 7

*3 mcg./kg. body weight (S.C.)

findings have been previously reported.[1,2] However, Fajans,[4] performing insulin tolerance tests on Addisonians three to twelve days after withdrawal of substitution therapy with glucocorticoids, could not demonstrate hypersensitivity to insulin except in two patients who, according to the author, were debilitated due to the decreased nutritional intake resulting from untreated adrenal insufficiency.

Our findings are not in complete agreement with Fajans' suggestion since patients in excellent nutritional state also manifested increased sensitivity to insulin. Besides, one patient in debilitated physical condition—(G.E.J.—table 2) had normal sensitivity to insulin. It should be mentioned that in Fajans' experiments the period of time elapsed after the last administration of glucocorticoids, before performance of the tests, was too short to eliminate the anti-insulin effect of the medication. It has been demonstrated that the effects of glucocorticoids on carbohydrate metabolism persist for three to four weeks after withdrawal.[11,12]

No distinction was observed between primary and secondary adrenal insufficiency in the insulin tolerance test, despite the possible deficiency in the latter of other insulin antagonists from the pituitary gland. In fact, in two of our patients with Sheehan's syndrome (A.O.E. and A.C.) secondary hypothyroidism was associated with the hypoadrenalism (table 1). The only patient with postpartum hypopituitarism presenting normal insulin sensitivity had secondary hypothyroidism thus mitigating the importance of the thyroid component in the insulin hypersensitivity.

The degree of adrenal insufficiency in our patients with Sheehan's syndrome by the measured parameters (urinary total 17-hydroxycorticosteroids less than 2 mg. per day and no significant response to intravenous ACTH, for eight hours, for two successive days (table 1) was similar to that observed in the Addisonians.

The present studies also suggest that the influence of growth hormone is negligible in the insulin tolerance test since the same degree of hypersensitivity to insulin has been observed in primary and secondary adrenal insufficiency. We used a dose of insulin double that which

is considered to be discriminative, according to Altszuler et al.[13]

Insulin-induced hypoglycemia is primarily due to the acceleration of glucose transport from the extra- to the intracellular compartment, the output of glucose by the liver remaining unaltered or transiently reduced.[14] The return of blood glucose concentration to the pre-insulin level depends on two factors: (a) increase in the rate of glucose release by the liver and (b) progressive decrease in the accelerated glucose uptake by the tissues[15] in response to injected insulin. Thus, hypersensitivity to insulin in adrenal insufficiency could result from: (a) excessive and prolonged peripheral insulin actions, (b) reduced ability of the liver to cope with hypoglycemia, and (c) combination of both factors.

Another factor to be considered is the nutritional state, as in chronic malnutrition increased sensitivity to insulin has been described.[16,17] This hypersensitivity is the result of a greater glucose uptake by the tissues and decreased glucose release by the liver in response to the induced hypoglycemia. Our results indicate that malnutrition did not potentiate the response to the injected insulin, since there was no difference in the degree of hypoglycemia in the patients with adrenocortical insufficiency whatever their nutritional state. In contrast, a normal or decreased rate of glucose disappearance (k) (table 3) in the debilitated patients probably reflects a decrease in the circulating insulin levels.[18] The association of delayed disappearance of a glucose load from the blood and hypersensitivity to insulin has been previously demonstrated by Houssay et al.[19] in hypophysectomized dogs. The correction of the glucose disappearance rate (k) in the patient J.A.M., after improvement of his nutritional state, without the use of glucocorticoids (unpublished data), is in accordance with the mentioned facts.

The important role of the increased disappearance of glucose from the extracellular pool suggested by the glucagon tolerance test with venous blood sampling (table 5) became quite evident with its inhibition by the prior injection of epinephrine (table 7) when the differences in the glucose increments (△ glucose) between the normal controls and the adrenal insufficient patients disappeared.

The nutritional aspects cannot be discussed in the interpretation of these facts because, unfortunately, no glucagon tolerance tests with venous blood samplings were performed in the malnourished adrenal-deficient patients. However, it is felt that despite normal or decreased peripheral glucose utilization, insulin hypersensitivity could be expected, as described by Houssay et al.[19]

In connection with the glucose outflow from the liver, the adequate hyperglycemic response to glucagon (table 4) using pharmacological doses of the hormone, suggests that the decreased responsiveness to hypoglycemia is not due to decreased stores of liver glycogen. Therefore, if there is some liver impairment it should be in relation to the glucose release independent of the amount of glycogen present.

It is conceivable that glucocorticoids could act upon the secretion of glucagon or its action. The hypoglycemia unresponsiveness in adrenal insufficiency could then result from a decreased endogenous glucagon secretion. However, this suggestion is not in accordance with the data of Unger et al.[20] showing that only during the second and third hours of severe hypoglycemia is there a statistical significant rise in endogenous glucagon concentration in plasma when measured in pancreatic venous

TABLE 7

Epinephrine-glucagon† tolerance test in patients with adrenocortical insufficiency and in normal controls*

Name	Sex	Age (years)	Diagnosis	Fasting blood glucose‡ (mg. per 100 ml.)	Differences between each B.G.‡ and F.B.G. at the different times (Δ B.G.): mg. per 100 ml. Minutes after glucagon injection 15	30	45	60	75	90
G.E.J.	M	35	Addison's disease	67	+24	+35	+61	+50	+40	+ 7
A.C.	F	47	Sheehan's syndrome	61	+24	+56	+62	+39	+29	+29
E.D.	F	37	Addison's disease	65	+65	+54	+54	+38	+26	+21
A.B.M.	F	35	Sheehan's syndrome	96	+38	+60	+60	+48	+21	0
			Δ B.G. mean		+38.75	+51.25	+59.75	+43.75	+29	+14.25
			Standard deviation		±19.73	±11.11	± 3.65	± 6.12	± 8.03	±13.12
Normal controls (ten subjects)			Δ B.G. mean		+33.1	+52.9	+61.3	+45.9	+28.4	+ 9.6
			Standard deviation		±14.4	±21.6	±22.7	±26.4	±19.8	±14.3

*3 mcg./kg. body weight (S.C.)
†30 mcg./kg. body weight
‡Venous

blood by a highly sensitive and specific radio-immunoassay method. It is possible that the slight rise in glucagon concentration during the first hour after insulin injection, considered as insignificant by these authors might be of physiological significance. The hypothesis that glucocorticoid deficiency is interfering directly with the glucagon action cannot be discussed as we have performed our tests with pharmacological doses of glucagon which could overcome the possible block to physiological amounts of the hyperglycemic-glycogenolytic hormone.

Another glycogenolytic factor to be considered is epinephrine which we know to be increased during hypoglycemia.[21] This hormone does not seem to be of great importance as patients with hypopituitarism and idiopathic atrophy of the adrenal cortex (subjects P.M.E., J.A.M. and E.D.), with intact adrenal medulla, showed the same insulin hypersensitivity and hypoglycemia-unresponsiveness. Besides, Addisonian subjects are able to correct the increased sensitivity to insulin through the use of glucocorticoids without changes in their already low levels of epinephrine in the urine.[22]

In conclusion, our results suggest that increased peripheral glucose utilization, in well nourished adrenal deficient patients, is a fundamental factor in the insulin hypersensitivity and hypoglycemia-unresponsiveness. However, we have been unable to rule out the possibility of reduced ability of the liver to adjust its rate of glucose release to blood glucose changes, independent of the available glycogen stores. As suggested by Soskin and Levine,[23] anterior pituitary and adrenal cortex activity would influence the threshold of blood sugar regulation by the liver.

SUMMARIO IN INTERLINGUA

In Re le Mechanismo del Hypersensibilitate pro Insulina in Insufficientia Adrenocortical

Un studio del sensibilitate pro un dose experimental de insulina exogene esseva interprendite in octo patientes con insufficientia adrenal primari e in cinque patientes con syndrome de Sheehan, i.e. insufficientia adrenal secundari. Le grande majoritate monstrava hypersensibilitate a insulina. Non-responsivitate hypoglycemic esseva presente in omnes.

Le hypersensibilitate esseva primarimente le resultato de un excessive action peripheric de insulina, evidentiate per le accelerate disparition de un carga intravenose de glucosa in le ben-nutrite patiente.

Le possibilitate de un dysfunction del glycogenese con le consequentia de un reducite liberation de glucosa per le hepate (lo que explicarea le non-responsivitate hypoglycemic) non esseva confirmate per le test a glucagon. Isto suggestiona que si un defectivitate hepatic es presente, illo concerne le intensitate del liberation de glucosa per le hepate in independentia ab le quantitate de glycogeno presente e relationate con le influentia de glucocorticoide super le limine del regulation de sucro sanguinee per le hepate.

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Withering and the Quarterly Journal of Negative Results

The current trend by some of us to stress the scientific side of medicine to the exclusion of everything else has prompted the following editorial, which does not necessarily reflect the opinions of the editors of this journal. It is written by a man who envies both the true scientist and the good clinician, but who would have their personalities and ambitions wedded into one unit. The wondrous physician who emerges from this union would have his research sponsored by the granting agencies, and would be beloved by his patients, a fortunate combination indeed.

On a recent trip to Shropshire, England, I discovered some documents, which are worth discussing. Since they concern Dr. Withering, the discoverer of the therapeutic effects of digitalis, I thought them of sufficient interest to publish them. Although they were written in the 18th century, they appear so modern that they could have been written today. Following are the discovered documents.

Dear Dr. Withering:

We regret that your article on "The Account of the Foxglove and Some of Its Medical Uses," which you submitted to us for publication in the Quarterly Journal of Negative Results, *is unacceptable for publication. The reviewers, whose comments are enclosed, feel that although it is an interesting clinical observation, it lacks the quantitative approach with which clinical studies should be supported. In addition, in the hands of one of the reviewers who had the opportunity to try Foxglove on a patient of his, the drug proved fatal. May we also draw your attention to the fact that the Food and Drug Administration does not sanction the use of any drug without having full information on the toxicity of the drug as obtained in animal experiments.*

Thank you for submitting this manuscript to us.

Sincerely

Editors, Quarterly Journal of Negative Results

Comments of the first reviewer:

Dr. Withering's data are entirely empirical. There are no studies on the chemical composition of the drug; it is particularly difficult to understand why a paper has been submitted to this journal on a drug which purports to influence renal function without the author's including some results on renal clearances, blood potassium, sodium, and blood rhubarb levels. The use of radioisotope scans of the kidney would also have been useful. The absence of statistical evaluation is regrettable. What are the p *and* t *values of these observations? The clinical material is poorly selected. Was the patient population homogeneous; what type of heart disease were the patients suffering from?*

One of the most serious criticisms is directed toward a statement of the author, "I cannot pretend to charge my memory with particular cases, or particular effects, and I had no leisure to make notes." This lack of scientific documentation is regrettable. How does the author expect his paper to be of value without necessary documentations? The whole work demonstrates a degree of unfamiliarity with scientific methods which may well be responsible for the amateurish approach of the author to this complicated subject.

A second reviewers' remarks are as follows:

The author has attempted to convince us of the medicinal value of Foxglove. Although he attempts in his case histories to furnish proof of his contention, his scientific evidence for the value of Foxglove is lacking. In the first place, the author writes, "My opinion was asked concerning a family receipt for the cure of dropsy. I was told that it had long been kept a secret by an old woman in Shropshire who had sometimes made cures after the more regular practitioners had failed." The attitude of the author to commence scientific studies because of an old wive's tale is to be regretted. In addition, this journal does not accept personal communication without written approval by the scientist whose work is quoted. The author writes, "I could not take notes of all cases which occurred." If the author had studied the papers in the Quarterly Journal of Negative Results, *he would have discovered that no paper is complete without detailed tables, charts, and statistics. Why did the author make no attempt to isolate the active principle of Foxglove? Why were such obvious methods as column chromatography, electrophoresis, ultracentrifuge not carried out? It is quite clear that Foxglove can have no therapeutic value unless its active principle is scientifically defined. Despite the recommendation of a Dr. Darwin, which the author includes, the paper appears unacceptable for publication.*

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