GLUCOCORTICOIDS, GLUCOSE METABOLISM AND HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

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GLUCOCORTICOIDS AND GLUCOSE METABOLISM

It is well-established that excess of endogenous or exogenous glucocorticoids (GCs) impair glucose metabolism. When a subject with normal glucose tolerance is treated with GCs, there is usually a deterioration in glucose tolerance. The worse the patient's pre-treatment glucose tolerance the greater will be the effect of the GCS.[1] At the same time that mild to moderate increases in glucose levels are observed, there is a considerable increase in plasma insulin levels.[2] The abnormal glucose tolerance in the presence of hyperinsulinemia (in the absence of hypoglycemia) in response to a glucose load is characteristic of an insulin-resistant state. In this mild to moderate form of insulin resistance, as most frequently observed in obesity and maturity-onset insulin dependent diabetes,[3] insulin levels are often elevated only a few-fold, and the response to a dose test of exogenous insulin is modestly impaired.

There are several features of the clinical effects of GCs which should be noticed:[4] a) the chronic effects of corticoids on glucose tolerance are less severe than the acute effects; b) the degree of impairment will be proportional to the pre-existing status of glucose tolerance; c) development of frank diabetes mellitus in a previously normal patient is unusual; and d) in general terms, the abnormalities of carbohydrate metabolism fit the criteria for an insulin resistant state. In effect, when GCs are administered to

nondiabetic human subjects, some deterioration of glucose tolerance may be noted in most patients within 12 hours.[1] On continuation of GC administration, the changes in glucose tolerance tend to pre-treatment levels.[5] When the effects of prolonged corticoid administration on glucose tolerance are examined, only very minor changes in a small percentage of patients can be discerned.

In a comparative study of two synthetic GCs, prednisone (Pd) and deflazacort (Dfl), in normal female healthy volunteers, using equipotent anti-inflammatory doses (20 mg/day of Pd or 24 mg/day of Dfl, for 2 weeks), we were able to demonstrate that Dfl induced in 4 subjects, (half of them with slight obesity) a very small insignificant

	N° SUBJECTS	AGE * yr	HEIGHT * cm	WEIGHT * Kg
DEFLAZACORT	4	28.8 ± 2.9	160 ± 0.7	59.0 ± 5.0
PREDNISONE	4	30.0 ± 4.2	161 ± 3.6	63.0 ± 5.9

* MEAN ± SEM

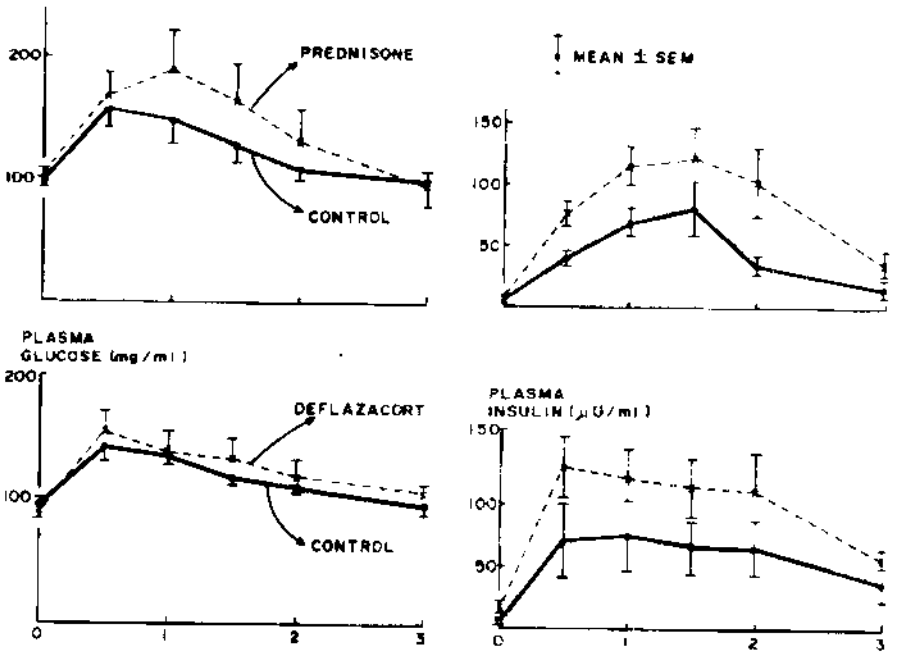

Figure 1: Comparison of the effects of a 2-week treatment with equipotent anti-inflammatory pharmacological doses of deflazacort (24 mg/day) and prednisone (20 mg/day) on oral glucose tolerance test in 2 groups of female healthy volunteers.

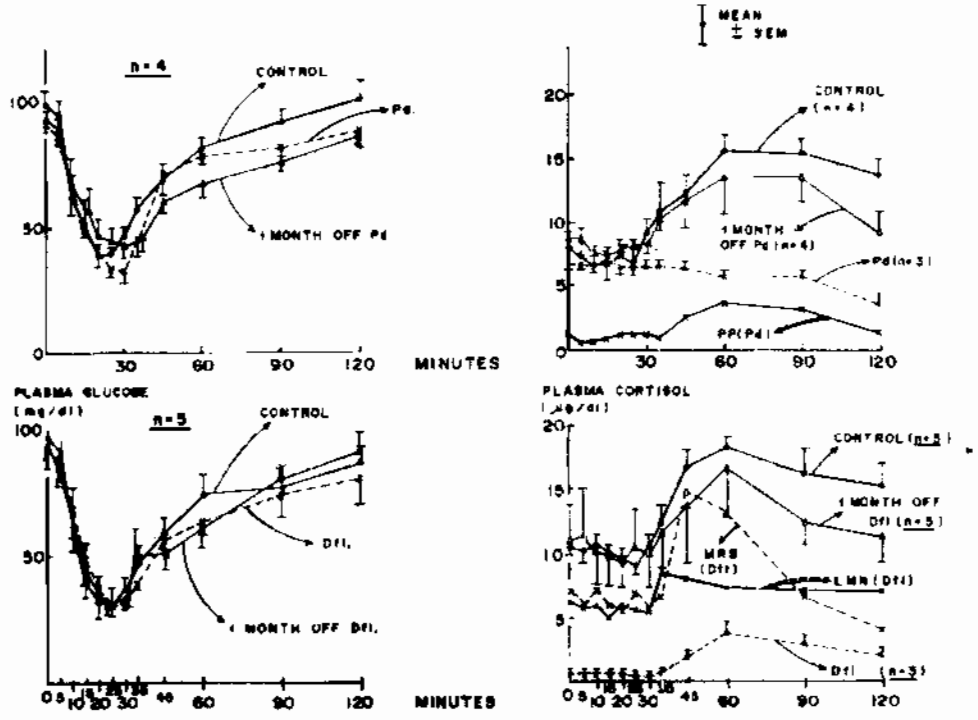

Figure 2: Comparison of the effects of a 2-week treatment with equipotent doses of deflazacort - Dfl (24 mg/day) and prednisone - Pd (20 mg/day) on insulin tolerance test (0.1U/kg/I.V.) in 2 groups of female healthy volunteers.

change in the plasma glucose levels observed during oral glucose tolerance testing; a much greater increase in fasting and glucose-stimulated plasma insulin concentrations was observed (Figure 1). After Pd administration to four normal females, (two of them obese) the impairment of glucose tolerance was greater than that observed after Dfl; two of the non-obese subjects developed an impaired glucose curve.[6] Insulin secretion was also greater after this synthetic steroid, but in only half of the subjects was there an increase in basal insulin levels. These results are consistent with previous known experimental and human data,[7] demonstrating that equipotent anti-inflammatory doses of synthetic GCs with similar structures can have different effects on carbohydrate metabolism. Despite the development of an insulin-resistant state, there were no significant changes in the exogenous insulin-treated hypoglycemia with either Dfl or Pd when compared to the control test (Figure 2).

Animal experiments clearly indicate that GC excess for a few days can increase hepatic glucose production. The latter results

from an inherent increased capacity to produce glucose associated with an increased availabillity of gluconeogenic substrates interacting with augmented plasma glucagon levels, as well as from a decrease in glucose utilization [4] Hepatic glucose production (HGP) and glucose utilization (glucose clearance rate) were evaluated respectively after an overnight fasting and during an insulin+glucose+propranolol+ somatostatin infusion in normal volunteers and patients with Addison's disease who were off replacement therapy for 72 hours. The patients were on physiological (Pd, 5 to 7.5 mg; or cortisone, 24 to 37.5 mg/day for at least 1 month) and pharmacological (Pd, 30 mg; cortisone, 150 mg /day for 10-15 days) GC replacement therapy. The mean HGP in the post-absorptive state was not significantly different in the normal controls and GC-treated Addisonian patients even when they were on high steroid

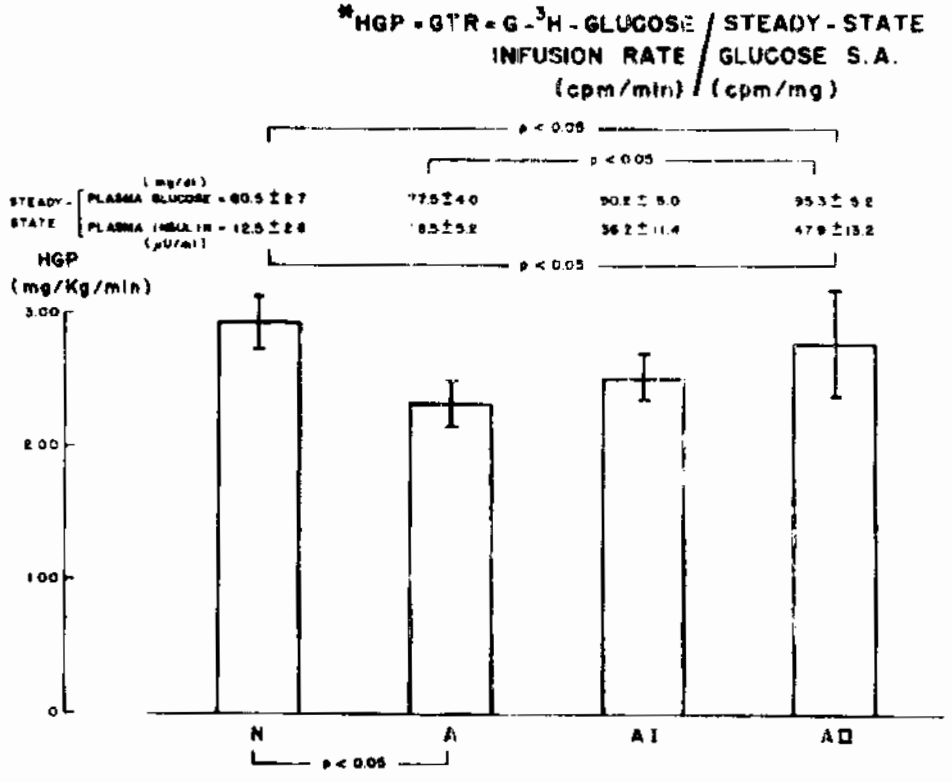

Figure 3: Hepatic glucose production (mean ± SEM) in 6 normal individuals (N) and in 6 addisonian patients off therapy (A), with physiological (A_I) and pharmacological (A_{II}) doses of glucocorticoids obtained through the continuous infusion of tritiated glucose in the post-absorptive state (basal).

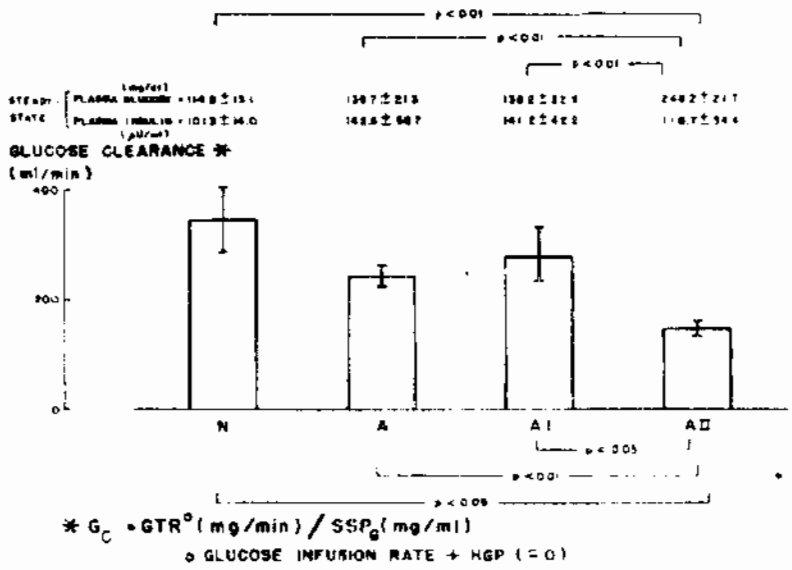

Figure 4: Steady-state glucose clearance (mean ± SEM) of 5 normal individuals (N) and 6 Addisonian patients off therapy (A) with physiological (A_I) and pharmacological (A_{II}) doses of glucocorticoids during the continuous fusion of glucose (6 mg/Kg/min) + insulin (0.8 mU/Kg/min) + somatostatin (6 ug/min) + propranolol (0.8ug/Kg/min) - "Insulin clamp".

doses, at the time when basal plasma glucose and insulin were significantly greater than in the normal subjects (Figure 3). The glucose clearance was measured during the steady-state period of a constant infusion of glucose, propranolol and somatostatin, when similar plasma insulin levels were maintained in all subjects (SSPI).[8] Glucose clearance was significantly depressed only when the hypoadrenal patients were treated with the larger doses of GC (Figure 4). Using the "insulin clamp" technique we could demonstrate a defect in peripheral glucose utilization, but not an increase in HGP after GC excess. In effect, the results of <u>in vitro</u> studies which demonstrate that the unopposed actions of GCs result in selected protein catabolism, inhibited protein synthesis, increased amino acid mobilization, and increased hepatic gluconeogenesis could not be confirmed by data obtained from intact animals and humans. It is possible that the potential catabolic action of GC excess is offset by insulin and a new state of homeostasis is established resulting in the lack of an increase in basal HGP.[9]

PARAMETERS MEASURED	DEFLAZACORT		PREDNISONE	
	BEFORE	AFTER	BEFORE	AFTER
PLASMA GLUCOSE (mg/dl)	96 ±2.7	90 ±6.5	90 ±2.2	96 ±4.8
PLASMA INSULIN (μU/ml)	8.0±1.2	16.5±2.8*	8.5±2.1	10.2±2.8
SPECIFIC INSULIN BINDING (%)	7.1±0.9	8.4±0.5	7.9±0.9	8.4±1.2
RECEPTOR NUMBER (per cell)	38 ±4	55 ±7*	60 ±4	61 ±4
AVERAGE AFFINITY (10^8 M^{-1})				
AT LOW OCCUPANCY ($\bar{K}_e$)	2.64±0.27	2.36±0.10	1.91±0.25	2.00±0.25
AT HIGH OCCUPANCY ($\bar{K}_f$)	0.42±0.10	0.37±0.08	0.28±0.03	0.28±0.02
$\bar{K}_e/\bar{K}_f$	0.19±0.07	0.15±0.03	0.15±0.03	0.15±0.02

(* : $p < 0.05$)

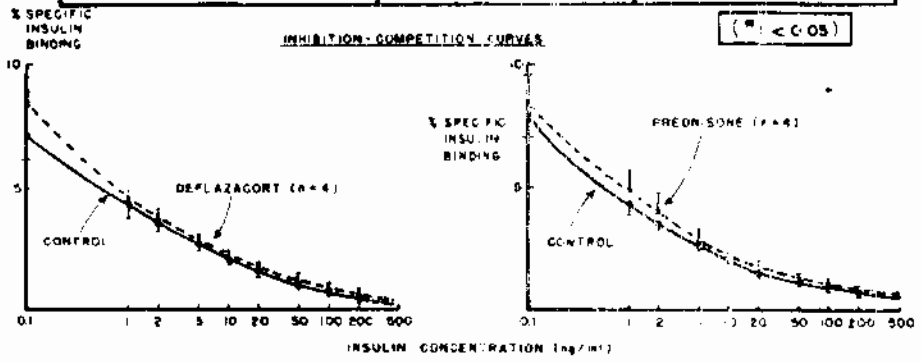

Figure 5: Plasma glucose, insulin and parameters of insulin binding to erythrocytes in 2 groups of healthy subjects before and after deflazacort (24 mg/day - 2 weeks) or prednisone (20 mg/day - 2 weeks) - Mean ± SEM are indicated.

To evaluate if the effects of GCs on peripheral glucose uptake are mediated by alterations in insulin receptor binding, we measured specific insulin binding (IB) in erythrocytes. The latter have binding characteristics comparable to insulin receptors in target tissues.[10] Two weeks of Dfl administration, in pharmacological doses as indicated above, did not significantly change the IB at insulin tracer concentrations (from 7.1 ± 0.9% to 8.4 ± 0.5% - mean ± S.E.M.) (Figure 5). Since the total number of insulin receptors, determined by Scatchard analysis, increased slightly but significantly after Dfl (38 ± 4 to 55 ± 7, $p < 0.05$), it can be concluded that changes should have occurred in the apparent receptor affinity to explain the lack of significant alteration in IB. Analysis of the binding data, according to the negative cooperativity model, indicated that there were proportional decreases in the affinity of the receptor in half of the 4 subjects studied. In the remaining two, there were primary changes in receptor affinity as indicated by change in the ration K_f/K_e (Affinity constant at high occupancy

of the receptor/Affinity constant at low occupancy of the receptor). On the other hand, equipotent doses of Pd, given during the same period of time to another group of 4 health subjects, did not change the parameters of IB (Figure 5). This observation is consistent with the conflicting data regarding the effect of short-term GC administration on insulin receptor binding to circulating cells.[11-13] The reasons for this discrepancy may be due in part to the heterogenous distribution of tissue insensitivity to insulin in exogenous and endogenous GC excess.[14,15] It is possible that binding studies using target cells (adipocytes, muscle cells) other than erythrocytes may uncover insulin-resistant tissues with possible receptor defects. Furthermore, in studies designed to evaluate the in vivo effects of GCs on IB to rat adipocytes and hepatocytes, others have demonstrated that one week of dexamethasone administration led to marked decreases in the ability of these target cells to bind insulin.[16] When treatment was continued for 3 weeks, IB to adipocytes returned to near normal levels whereas in hepatocytes, the return of IB to normal levels was much less pronounced. The tendency toward amelioration of this defect in IB (especially with adipocytes) during more prolonged dexamethasone treatment was related to the known clinical "adaptation response" to the steroid-induced glucose intolerance and insulin resistance discussed earlier. Caro and Amatruda[17] have recently demonstrated that hepatocytes from rats treated with dexamethasone for 4 weeks were resistant to insulin as evaluated by α-aminoisobutiric acid uptake. However, IB was comparable to the levels observed in hepatocytes fom control animals. Thus, the relationship between insulin binding and insulin resistance postulated by Olefsky et al.,[16] was not supported by these data. Another factor to be considered, is the effect of an increase in IB to RBC due to the direct action of GCs, and a decrease in IB due to the CG-induced hyperinsulinemia.[15] The finding that Dfl administration induced an increase in insulin RBC receptor concentration (Figure 5), similar to the observation by Beck-Nielsen et al.,[11] with Pd on monocytes, is in accord with the suggestion that GCs act on insulin receptors directly or through a factor(s) other than insulin since they seem to eliminate the down-regulatory effect of insulin. Assuming that IB to erythrocytes reflects IB to insulin target tissues, our results could suggest that insulin resistance produced by corticoids depends upon a post-receptor alteration, leading to a decreased peripheral glucose utilization. In addition, increased HGP (gluconeogenesis) with diminished suppression[18] could also be involved.

In endogenous hypercortisolism, the significant elevations of blood glucose at all times observed during oral GTT, was associated with increased mean-plasma insulin values (Figure 6). These data are consistent with an insulin resistant state. Evidence that the hyperinsulinemic state in our Cushing's subjects was not exclusively due to the patients' obesity was provided by the study of the

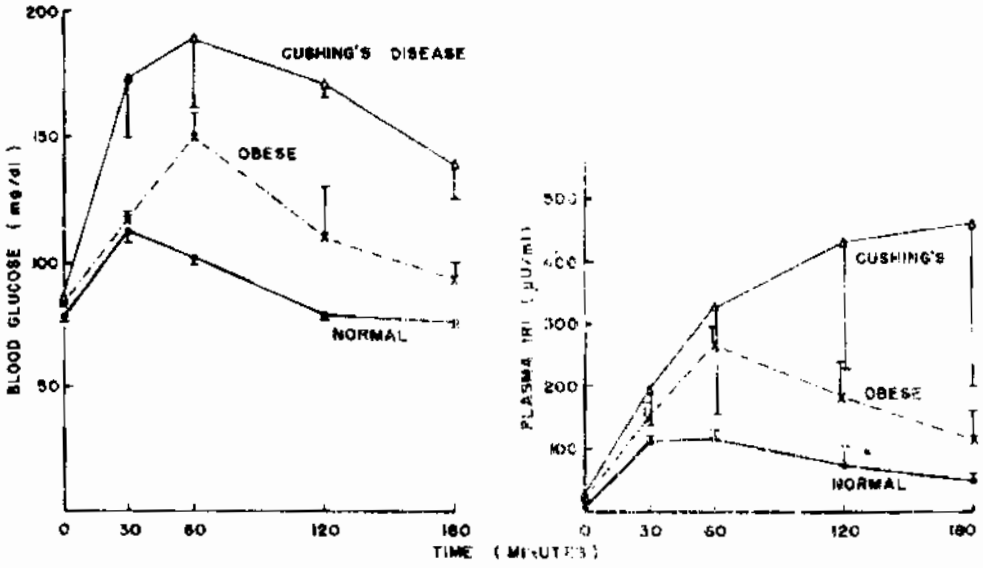

Figure 6: Mean ± SEM blood glucose and plasma insulin responses to oral glucose (100 g) in normal controls (n = 5), obese non-diabetics (n = 5) and patients with Cushing's disease (n = 5), all females.

relationship between the ratio body weight (Kg)/Height (cm) - BW/HG - and basal plasma insulin (IRI) (Figure 7): The Cushingoid patients had proportionally higher levels of plasma IRI relative to the ratio BW/H, as compared with the data obtained from normal plus obese subjects. These observations suggest that GCs alone can lead to insulin resistance independent from alterations in body weight.

The mildness of the insulin resistance in Cushing's disease is indicated by the normal or slightly decreased glucose response to the usually employed dose of intravenous insulin (0.1 U/Kg). Evaluating the response to intra-arterial (brachial artery) insulin in 3 patients with Cushing's syndrome, we have shown no selective fall in the glucose level of venous blood from the injected arm, this finding is consistent with an impairment in the direct peripheral action of insulin. The effect of the circulated insulin, evaluated from the difference between the arterial and contralateral venous levels of glucose, is greater than normal in two of the patients.[14] Thus, tissue insensitivity to insulin appears to be heterogenous in endogenous hypercortisolism.

On the other hand, HGP, evaluated in the post-absorptive state by tritiated glucose equilibrium technique in two patients with severe Cushing's syndrome, was below the normal range in one subject

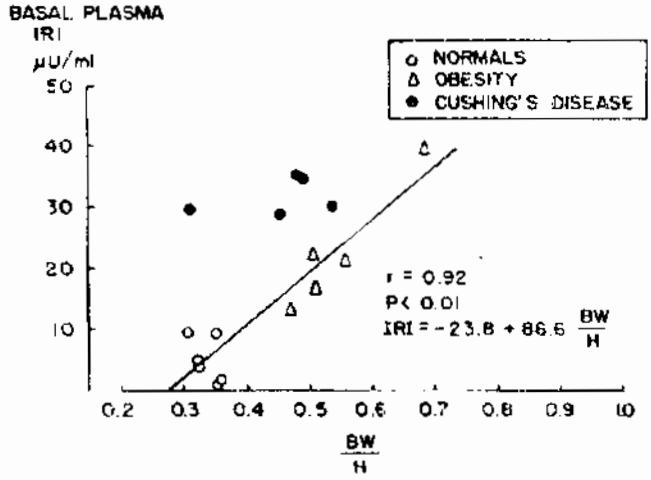

Figure 7: Correlation between the ratio body weight (Kg) over height - BW/H - and basal plasma insulin (IRI) obtained with data from normal and obese non-diabetic subjects. Cushing's patients have disproportionally higher IRI levels than normals and obese subjects, in relation to the BW/H ratio.

and in the upper limit of normal in the other patient with fasting hyperglycemia (Table 1). The hyperinsulinemia present in patient 1 (39 uU/ml) could offset the potential catabolic action of hypercortisolism and hypergluconeogenesis with suppression of HGP. However, in case 2 the insulin levels (52uU/ml) were probably not adequate to overcome the hyperglycemic effects of GCs both on the liver and the periphery.

The extent to which chronic cortisol excess causes insulin resistance in man by impairing the ability of insulin to suppress glucose production and stimulate glucose utilization is unknown. Whether such potential effects are mediated by alterations in insulin receptor binding is also unknown. We have demonstrated that, in Cushing's disease, IB to red blood cells (RBC) at tracer insulin concentrations was not statistically different from normal subjects (6.88 $\pm$ 0.93% in Cushing's vs. 5.90 $\pm$ 0.42 in normals; mean $\pm$ SEM; $p>0.05$). The obese non-diabetic controls had lower binding curves, and were statistically significant when compared to data obtained from patients with Cushing's disease (Figure 8). The total number of insulin receptors per RBC, determined by Scatchard analysis, was similar in the normals (41 $\pm$ 7) and Cushing's patients (42 $\pm$ 5), but lower in the obese subjects (31 $\pm$ 6). The affinity profile was similar in the three groups (Figure 9). Thus, while in the obese subjects the insulin resistance could be attributed to a decreased number or receptors per cell and at least partially to a defect at

Table 1

Patient	SSPG (steady-state plasma glucose) -mg/dl-	SSPI (steady-state plasma insulin) -uU/ml-	HGP (hepatic glucose production) -mg/Kg/min-
1	89	39	2.01
2	186	52	3.64
normals (n = 6) Mean ± SEM	80.5 ± 2.6	12.5 ± 2.6	2.93 ± 0.19

the receptor levels, patients with Cushing's disease with comparable degree of obesity had normal binding and no alterations in the parameters of hormone-receptor interaction. Therefore, neither the presence of obesity nor the elevated plasma insulin levels had any apparent effect on the insulin-receptor interaction in Cushing's disease. This suggests that the insulin resistance associated with the long-term hypercortisolism of Cushing's syndrome could be independent from alterations at the receptor level, contrasting with data obtained in short-term experiments of others.[11-13] Our cumulative results suggest that chronic endogenous hypercortisolism results in a post-receptor impairment in insulin action, leading to decreased peripheral glucose utilization in a variety of tissues. This conclusion, however, is at variance with the enhanced overall glucose disposal observed in patients with Cushing's syndrome (Table 2). Indeed, Issekutz and co-authors, studying the metabolic clearance rate of glucose *in vivo* by radiolabeled glucose infusion techniques in dogs, demonstrated that 3-day treatment with methylprednisolone leads to a 70% increase in glucose turnover.[19,20] These observations could be interpreted to indicate that cortisol excess had blunted the suppression of hepatic glucose production by insulin but not extrahepatic stimulation of glucose utilization by insulin. This conclusion is not in accordance with the well established effect of GCs to inhibit glucose utilization *in vitro* in a variety of tissues.[4] Since glucose utilization *in vivo* is a function of both plasma insulin and plasma glucose concentration,[18] the increased rates of glucose utilization were probably not appropriate for the prevailing hyperglycemia and hyperinsulinemia.

GLUCOCORTICOIDS AND THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS (HPA)

When the levels of circulating cortisol increase, binding sites in the hypothalamus (and probably also in the pituitary) are occupied and corticotropin-releasing factor (CRF) is no longer elaborated until concentrations of cortisol in the extracellular fluid decline. Levels of GCs equipotent to or greater than

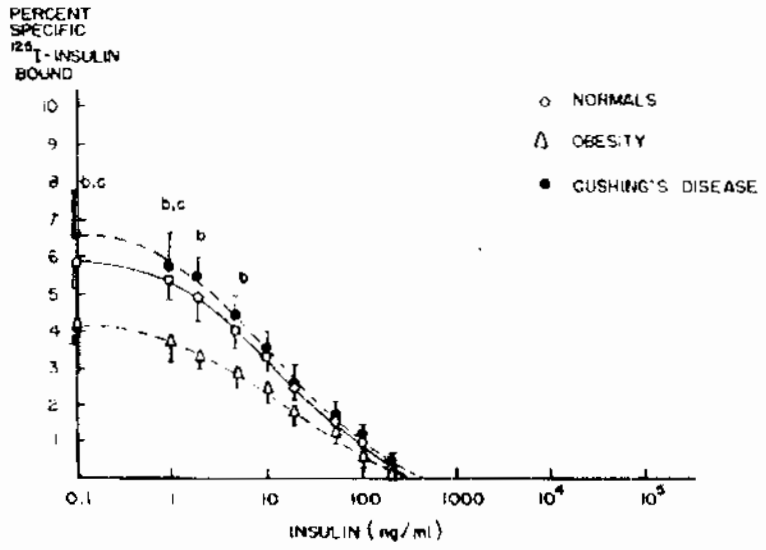

Figure 8: Inhibition – competition curves with data from Cushing's patients, normal and obese non-diabetic subjects
b – Cushing's patients, statistically different from obese subjects at a 5% level.
c – Normal subjects, statistically different from obese subjects at a 5% level.
Results are corrected to a final erythrocyte concentration of 4.5×10^9 RBC/ml.

physiological concentrations of cortisol (correspondent to more than 7.5 mg/day of Pd [21]) when maintained, activate the inhibitory feedback pathways. The adrenal atrophy is apparent after 10 days of high-dose GC therapy. Adrenal hypofunction is completely reversible when caused by deprivation of ACTH and reduced ACTH-secretory activities, resulting from deprivation of CRF.[22] CRF production is variably suppressed during the first 1 and 2 weeks of steroid therapy, but if therapy is extended, responsiveness of the HPA is progressively diminished and continues after steroids are withdrawn. Inhibition of the feedback may persist for 6 to 12 months if corticosteroid levels are maintained in the supraphysiologic range for only 2 weeks.[23] The responsiveness to stress however may recover much earlier.

During our comparative study in normal healthy volunteers of a 2-week treatment with equipotent anti-inflammatory pharmacological doses of Pd (20 mg/day) and Dfl (24 mg/day) we were able to evaluate the abnormalities in HPA and to characterize HPA function 1 month after steroid cessation. The insulin tolerance test (ITT) was used to measure the HPA function.[24] Because the ITT is dependent upon

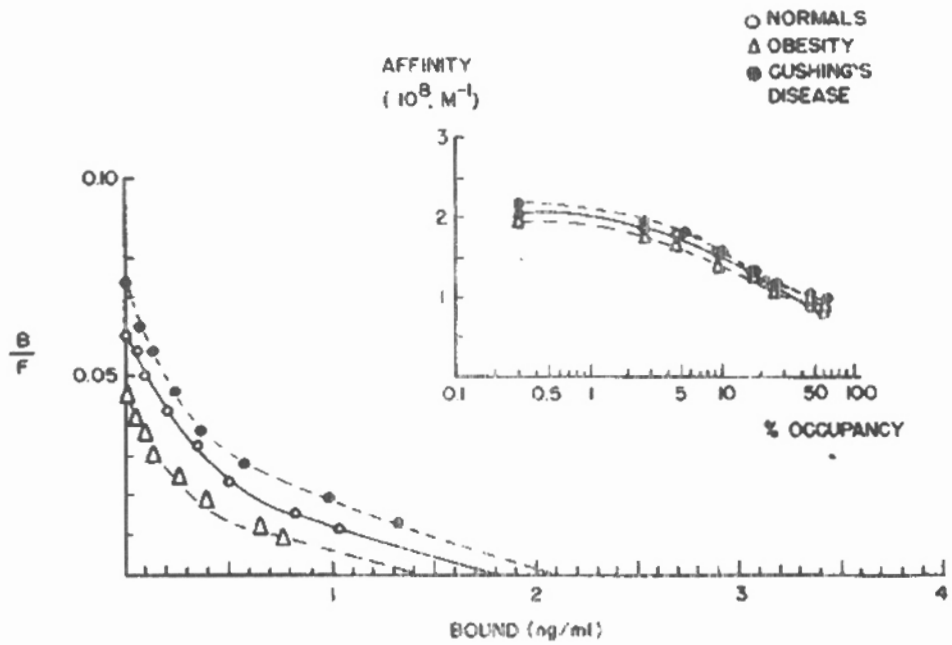

Figure 9: Scatchard analysis obtained from mean data from patients with Cushing's disease, normals and obese non-diabetic subjects. The inset shows the affinity profiles also obtained with the mean data.

adrenal cortisol output as an in vivo assessment of physiologic ACTH release, this test was paired, at least in some patients, with a standardized synthetic ACTH stimulation test using pharmacologic doses of ACTH (81-24 ACTH; 250 ug I.V.). This allowed correlation of cortisol increments induced by hypoglycemia with the maximum ability of the adrenal gland to respond. The Lysine-vasopressin (LVP) test (10 PU I.M.) was used to evaluate pituitary ACTH reserve. By combining the 3 tests, we could better identify the character of the HPA hyporesponsiveness that occurs after a suppressive course of GC therapy.

Diurnal rhythm of plasma cortisol levels were also measured in order to estimate hypothalamic control of the early morning rise of plasma cortisol. As noted in Figures 2 and 10, there was a decrease in fasting plasma cortisol (F). This effect was more intense in the majority of subjects on Df1 but less in the Pd-treated ones. While glucose responses to ITT were similar prior, after 2 weeks GC treatment and 1 month after GC cessation, the assessment of hypothalamic-pituitary release of ACTH by F response to insulin-induced hypoglycemia showed a significant reduction in basal F in 3 of the 5 subjects on Df1. However, the relative maximum response

Table 2: Intravenous glucose tolerance test in 7 women with Cushing's syndrome (Pupo, Wajchenberg and Schnaider, 1966).

PATIENTS	AGE (yr)	DISAPP. RATE k	COMPARISON TO NORMAL %
1	20	0.0216	↑
2	18	0.0237	↑
3	35	0.0113	N
4	26	0.0152	N
5	28	0.0159	N
6	19	0.0285	↑
7	26	0.0209	↑
NORMAL WOMEN*: 0.0145 ± 0.0035			

* MEAN ± 95% CONFIDENCE LIMITS

(Δ/Basal x 100 = Δ%), which permitted evaluation of the F resonse to hypoglycemia independent of factors influencing the basal level, was significantly greater on Dfl than in the control test (mean control: 73% vs. mean Dfl: 698%, $p<0.01$). Furthermore, despite low 8 a.m. F levels, there was an evident decrease to much lower values at midnight followed by the expected rise in the early morning sample (Figure 10). The same group of patients responded well to LVP (mean Δ for control: 3.00 vs. mean Δ for Dfl: 3.64 ug/dl, $p>0.05$) or mean %Δ for control: 34% vs. mean %Δ for Dfl: 319%, $p<0.01$). The "blunted" response by the adrenal to insulin-induced hypoglycemia has been previously shown after short-courses of high-dose GC therapy,[25] chronic steroid therapy[23] and long-term intermittent steroid treatment.[26] Similarly, the response to LVP was found to be abolished or markedly impaired, using the same criteria, in all patients receiving GC's.[27] However, accordingly to the well known fact that a variation of response of the HPA is observed from patient to patient, in the 2 remaining subjects on Dfl with lesser reduction of basal F (MRS and LMN - Figure 2) there was a normal F responsiveness to ITT in one, and greatly blunted increase in F in absolute and relative values in the other subject. In the tests indicated in Figure 10 they behaved normally. When Δ% was taken into consideration, during ITT and LVP, we could suggest that, on a two-week Dfl treatment, the responses were appropriate relative to the basal cortisol concentrations, the HPA being reset at a lower level. Similar conclusions can be drawn from the data obtained during studies of the diurnal rhythm of F using a highly sensitive radioimmunoassay.

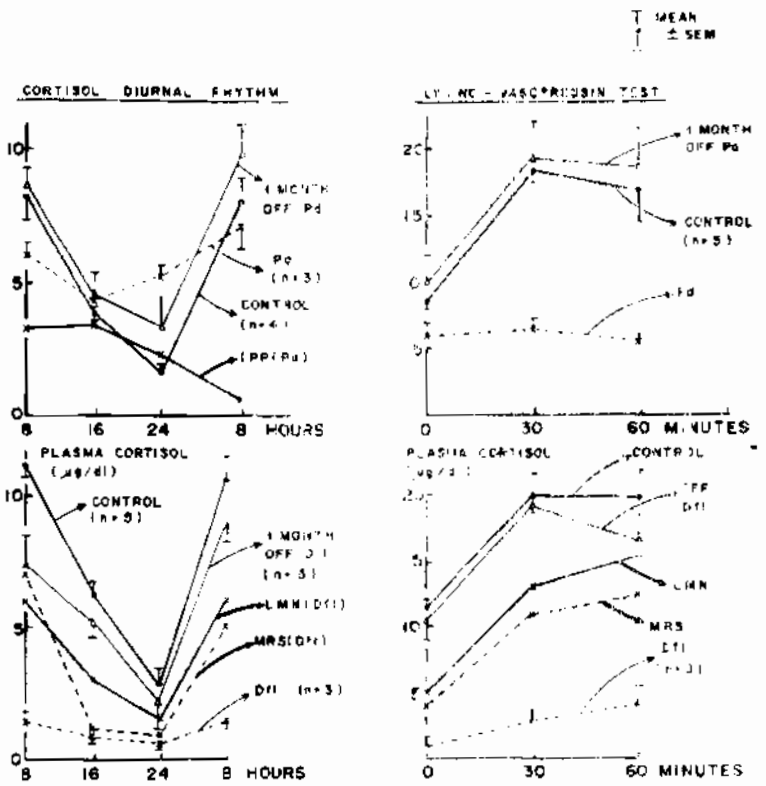

Figure 10: Comparison of the effects of a 2-week treatment with equipotent doses of deflazacort - Dfl (24 mg/day) on cortisol diurnal rhythm and lysine/vasopressin test (10 P.U. I.M.) in 2 groups of healthy female volunteers.

In patients treated with Pd a different pattern emerged (Figure 2). A similar reduction in the 8 a.m. basal plasma F levels was observed with no rise during ITT in 3 of the 4 patients studied. The same subjects had a small decrease in F concentrations at 4 p.m. but at midnight the values were actually higher (5.17 ± 0.40 ug/dl, mean ± SEM) but much more when compared to the very low F values observed at this time in the control study (1.60 ± 0.17 ug/dl). Furthermore, they did not respond to LVP (Figure 10). When these tests were paired with the standardized ACTH stimulation, results obtained in two of the subjects (lack of F response) suggested that the limiting factor in the overall HPA response was the reduced ability of the adrenal gland to produce F. This had led others to suggest that a normal response to the administration of an intravenous bolus of synthetic ACTH predicts intact HPA function after long and short-term GC excess.[29,30] As expected, when ACTH levels

were measured during the LVP testing, a decrease in basal ACTH levels was not observed when compared to the control test. There was also no elevation after LVP injection. These data revealed that the adrenal failure was consistent with the reduction in pituitary ACTH reserve.

It has been indicated that the maximum response to exogenous ACTH corresponds to the maximal cortisol level observed during the induction of general anesthesia and surgery in patients who have received GC therapy.[23] While it has been shown that a normal response of the plasma F level to anesthesia and to surgery is associated with a normal response to insulin-induced hypoglycemia,[28] it has not been shown that an impaired response to anesthesia and surgery is regularly associated with an abnormal response to insulin-induced hypoglycemia in patients who have received GCs. Furthermore, some patients who have been on GCs have normal response to ACTH and abnormal response to insulin-induced hypoglycemia and LVP.[23] These last two tests are perhaps more sensitive indicators of the HPA reserve than ACTH testing. Since pharmacokinetic and metabolic studies did not show substantial differences in the metabolic fates of deflazacort in rat and man, the longer duration of action of deflazacort as compared to prednisone in rats, if confirmed in man,[31] could be a factor in the interpretation of the different results obtained with the tests when Dfl and Pd were compared. Thus, Dfl could block the hypothalamus decreasing CRF, the HPA being reset at a lower level. Pd being a shorter-lasting GC,[31] would have less suppressive action on the hypothalamus, with less reduction in basal F levels when compared to Dfl treatment. However, the lack of ITT and LVP response is not compatible with our suggestion unless we postulate a significant pituitary action of the steroid with either loss to stress responsiveness, or a lesser effect on feedback responsiveness and impairment of the ability to respond to stress as it has been demonstrated in patients on intermittent steroid therapy.[25] However, it is difficult to explain the significantly greater midnight level after Pd in comparison to the control study. Suppression of HPA is less when GC's are given as a single dose in the morning, than when a single evening dose is given or the dose is divided throughout the day. Furthermore, if the morning dose is given on alternate days or even less frequently, less inhibition results than observed from daily dosing patients even when the total amount of drug given is identical.[22,23] An alternate-day regimen may not, however, maintain therapeutic control, particularly with diseases such as asthma. Giving ACTH concurrently with steroids[32] or transferring from oral steroids to ACTH does not speed recovery from HPA inhibition.[33] In general, therefore, the minimum possible dose of steroid should be given for the minimum period of time - a requirement that may conflict with the sort of regimen needed to control a chronic disease. GCs should not be given more often than once daily-in the morning. Patients taking high enough doses of steroids, equivalent

to 20 or 30 mg per day of Pd, for more than a week have a suppressed HPA axis; the occurrence of any form of stress is an indication for an increase in dose. When patients are treated with GCs within the previous 2 to 3 months, the response to insulin-induced hypoglycemia indicates whether the response to stress has recovered.[34] If not the case these patients should be treated if surgery is essential or for any febuli illness. When the interval since steroid treatment is 3 to 12 months resumption of treatment should depend on clinical assessment of signs of adrenal insufficiency during severe illness or during an ACTH test. The maximal responses of the plasma F level to such a test correlates, in general, with the maximal response to general anesthesia and surgery.[30] Otherwise, one may treat the patient as though adrenocortical insufficiency was present. In patients who have received long-term ACTH therapy, there is no convincing evidence of the development of HPA suppression.[23] Since there are physiological reasons to anticipate that such therapy may cause hypothalamic-pituitary suppression one cannot dismiss this possibility if such a patient becomes hypotensive or develops other symptoms or signs which suggest GC insufficiency. In such patients, ACTH testing is of no value, but the LVP or insulin-induced hypoglycemia may be helpful. In case of suspected hypothalamic-pituitary suppression following ACTH therapy, one should attempt to demonstrate this condition by either a plasma F level or an appropriate function test (as the clinical situation permits) and then manage the patients as though insufficiency were present, at least until the results of the test become available.

It has been shown that following the abrupt termination of high-dose short-term GC therapy (25 mg Pd twice daily during 5 days) hypothalamic-pituitary perception of stress is intact but the cortisol out-put is suppressed due to adrenal gland hyporesponsiveness. This accounts for the reduced peak F response to physiologic ACTH release following hypoglycemia. Some decrease in response (18%) to ACTH stimulation may still be present 5 days after the treatment.[25] In our comparative study of equipotent pharmacological doses of Pd and Dfl, for 2 weeks, the patients were tested 1 month after steroid therapy was discontinued. The presence of normal or slightly lower basal, 8 a.m., plasma F level with return of its normal circadian rhythm and LVP responsiveness indicated that upon cessation of steroid treatment there was complete recovery of HPA. However, Jasani *et al.*,[35] and Livanou *et al.*,[21] after long-term GC treatment, observed that feedback responsiveness was regained before stress responsiveness. The difference between feed-back regulation and stress responsiveness may be quantitative rather than qualitative, the different degrees of hypothalamic suppression presenting a spectrum of impairment of variable severity. Following prolonged suppression of HPA with GCs, pituitary-adrenal recovery was found by Graber *et al.*,[29] to follow a definite pattern requiring several months for completion, as indicated in Table 3. As noted in Table 3, recovery of ACTH secretion occurs initially followed some time

Table 3: Recovery of the HPA following long-term glucocorticoid treatment (Graber et al., 1965).

TIME AFTER STEROID INTERRUPTION (MONTHS)	PLASMA F	PLASMA ACTH	ADRENAL RESPONSIV. TO EXOG. ACTH
1	LOW	LOW	DECREASED
2–5	LOW	NORMAL TO HIGH	DECREASED
6–9	NORMAL	NORMAL	DECREASED
⩾ 9	NORMAL	NORMAL	NORMAL

later by normal adrenocortical steroid production, when the adrenal had been sufficiently stimulated by endogenous ACTH. Pituitary recovery appears to be the limiting factor. This pattern explains why the recovery of pituitary-adrenal responsiveness cannot be accelerated by exogenous ACTH therapy.

Table 4: Protocol for glucocorticoid withdrawal (Byyny, 1976).

STEP	INTERVAL	OBSERVATION	RESULT	GLUCOCORTICOID & DOSE
I	VARIABLE	UNDERLYING DISEASE	WORSENING UNDERLYING DISEASE. STEROID WITHDRAWAL SYMPTOMS	GRADUAL DECREMENTS OF 2.5 TO 5mg Δ^1E q. 3 TO 7 DAYS ⟶ 5 mg Δ^1E / DAY ↑ DOSAGE: FLAREUP OF DISEASE. ↑ DOSAGE: STRESS
II	4 wk	8 A M PLASMA F	PLASMA F: < 10 µg / dl	BEGIN Δ^1E 5mg / DAY ⟶ TAPER BY 1.25mg / DAY ONCE / WEEK ⟶ 2.5mg q MORNING ↑ DOSAGE: STRESS
			> 10 µg / dl	STOP MAINTENANCE Δ^1E ↑ DOSAGE: STRESS
III	4 wk – INDEFINITE	8 A.M. 250 µ I.M. ℘ 1-24 ACTH	PLASMA F INCREMENT < 6 OR MAXIMUM < 20 µg / dl (OR BOTH)	SUPPL. FOR STRESS
IV	4 wk – INDEFINITE	8 A.M. 250 µ I.M. ℘ 1-24 ACTH	PLASMA F INCREMENT > 6 OR MAXIMUM > 20 µg / dl	STOP SUPPL. FOR STRESS (RECOVERY HPA AXIS)

The major problem in GC withdrawal is the difficulty in determining when the patient has satisfactorily recovered form the steroid suppression. Recovery of basal adrenocortical function can be evaluated by the determination of the morning plasma F. However, this value does not indicate that the cortex has sufficiently recovered to increase cortisol secretion adequately in response to stress. The latter could be evaluated, as previously mentioned, by the ITT. From the knowledge that adrenal cortex recovery lags behind that of the pituitary in the early recovery phase, it can be expected that the acute hypoglycemic stress will result in an increment of ACTH while the cortex continues to be unresponsive. On this basis, one can usually assume that complete recovery has occurred when the adrenal gland is capable of a F secretory response after a brief pulse of exogenous ACTH.[29] It should therefore be possible to establish a protocol for GC withdrawal with minimum symptoms, relative convenience for the patient and relative certainty for the physician (Table 4).

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