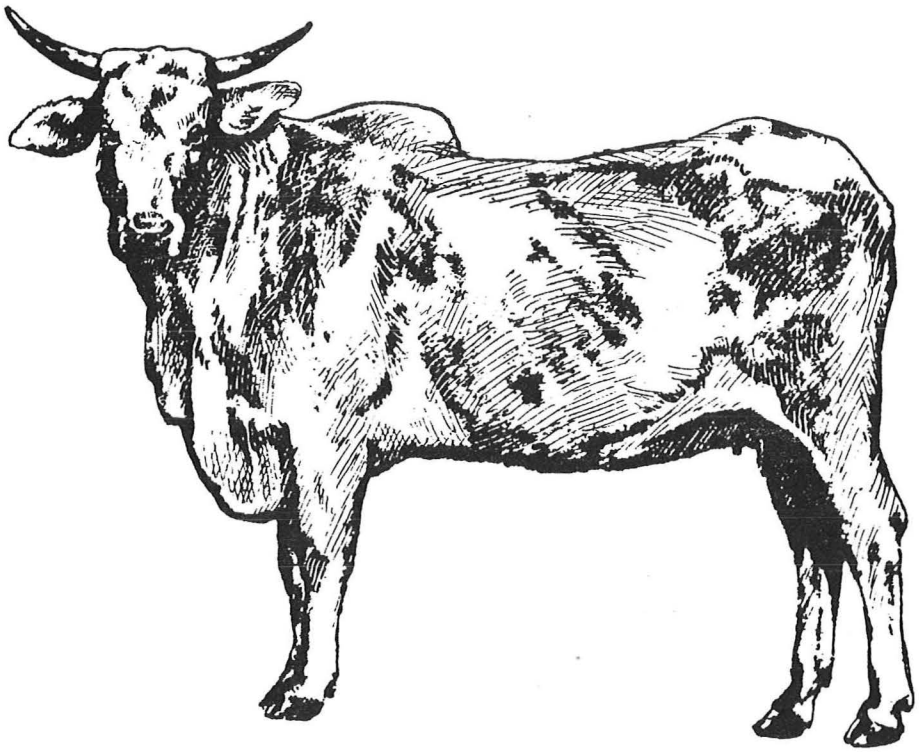
Endocrine - Diabetes

MEDICAL GRAND ROUNDS

UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT DALLAS

APRIL 14, 1983

# THE SOMOGYI PHENOMENON:



SACRED COW OR BULL???

Philip Raskin, M.D.

# INTRODUCTION

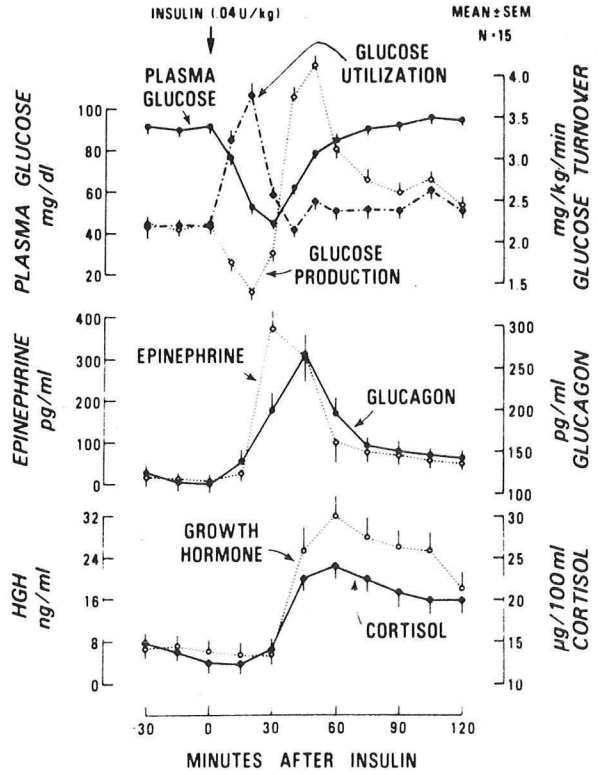
Rebound hyperglycemia, (the Somogyi phenomenon) is the bane of patients with diabetes and their physicians. This phenomenon was originally described by Michael Somogyi, a biochemist, who was interested in the relationship between the dose of insulin administered and the subsequent effect on the amount of carbohydrate utilized. Dr. Somogyi was astonished to learn (something any patient with diabetes could tell you) that the "blood sugar and glycosuria of diabetic patients often show wide fluctuations even when both the carbohydrate content of the diet and the insulin dosage are unchanged". In an attempt to investigate this problem he studied the effect of insulin administration on diabetic control, (most easily done in those days by measuring glucose excretion in the urine) and published these findings in an often quoted paper in the American Journal of Medicine in 1959. In this manuscript Dr. Somogyi promulgated his hypothesis that hypoglycemia even when it is mild and asymptomatic can result in subsequent hyperglycemia. He suggested that the hyperglycemia which follows hypoglycemia is the direct result of a release of counterregulatory hormones from the pituitary and adrenal glands. Dr. Somogyi's conclusions were hardly based on crisp experimental data. In fact, his paper is really a collection of anecdotal case reports in which patients seemed to have less glycosuria on a smaller daily dose of insulin. Based on these observations he was the first to suggest that a possible cause for "brittle" diabetes was an excessive dose of insulin.

This thought that "hypoglycemia begets hyperglycemia" is one of the most widespread concepts in clinical medicine. In fact, on our medicine service, confronted with an insulin treated patient with a markedly elevated fasting blood glucose level our usual reaction to this clinical situation is to lower the patient's insulin dose. We confidently tell housestaff and students that the patient must surely have been hypoglycemic during the night. Thus, the fasting hyperglycemia is "rebound hyperglycemia", and the appropriate course of action is to decrease the insulin dose rather than raise it.

It is my purpose to look carefully at the "Somogyi phenomenon". Is it real? Are we more often right than wrong in suggesting a lower insulin dose in the aforementioned clinical circumstance? Does hypoglycemia, asymptomatic or otherwise, result in subsequent hyperglycemia? If so what is the mechanism by which it occurs?

## Glucose Counterregulation in Non-diabetic Humans

An adequate plasma glucose concentration is crucial to survival. Insulin has long been recognized as the hormone which regulates glucose removal from the extracellular space, both by its effect on increasing glucose clearance and also via its effect on suppressing glucose production. How does recovery from hypoglycemia occur? What are the mechanisms? Figure 1 shows the counterregulatory hormone response to insulin induced hypoglycemia in non-diabetic humans. It is clear that the secretion of epinephrine and glucagon preceed that of growth hormone and cortisol after the induction of hypoglycemia.




Counterregulatory hormone responses to insulin-induced hypoglycemia in normal persons. From Gerich and associates (19); reproduced with permission. HGH = human grown hormone.

(Figure 1, Wilson et al, 1983)

Cryer who has recently reviewed this problem suggests that glucose counterregulation could result by either hormonal signals, neural signals, glucose autoregulation, or some combination of the above. Figure 2 summarizes a series of studies in which Cryer and his associates examined the effect of the isolted deficiency of potentially important glucose counterregulatory hormones on the recovery from insulin induced hypoglycemia in nondiabetic subjects. They demonstrated that recovery from insulin induced hypoglycemia is essentially normal when glucagon secretion is intact and is partially impaired (by 40%) when glucagon secretion is impaired. (Fig. 2B) Recovery from moderate hypoglycemia is normal during pharmacologic adrenergic blockade and in the complete absence of epinephrine. (Fig. 2D) This is also true if

the nerve impulses are impaired as occurs in spinal cord injury. However, if glucagon secretion is inhibited, then recovery from hypoglycemia is markedly impaired during adrenergic blockade (Fig. 2E) and fails to occur at all in the absence of epinephrine. (Fig. 2F) Thus, glucagon plays the primary role in non-diabetics in the recovery from insulin-induced hypoglycemia. Glucagon deficiency is compensated for by enhanced epinephrine secretion. Recovery from hypoglycemia fails to occur only in the absence of both glucagon and epinephrine. The acute release of cortisol and/or growth hormone is not critical. Finally, Cryer feels that neither the release of sympathetic neural norepinephrine nor glucose autoregulation is sufficiently potent to promote glucose recovery from hypoglycemia. Neither is needed to be involved to explain glucose recovery from insulin induced hypoglycemia.

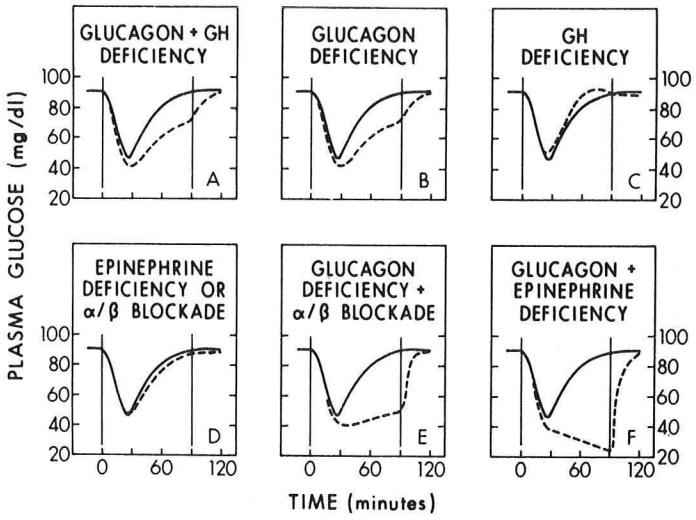



Fig. 2. Plasma glucose curves during insulin-induced hypoglycemia in normal subjects during control studies and as modified (dashed lines)by: a)somatostatin infusion b)somatostatin plus growth hormone infusion, c)somatostatin plus glucagon infusion; d) phentolamine plus propranolol infusion; e)somatostatin plus phentolamine and propranolol infusion; f)somatostatin infusion in bilaterally adrenalectomized patients. (Cryer, 1981)

It is of interest that there appears to be no absolute plasma glucose theshold for the activation of hormonal glucose counterregulatory systems. There is some controversy regarding this issue, as DeFronzo et al have shown that release of counterregulatory hormones fails to

occur in nondiabetics subjects until the plasma glucose level falls below 50 mg/dl even if it falls from elevated levels. Cryer feels that neither the absolute glucose decrement nor the rate of glucose decline are the primary determinants of the magnitude of the counterregulatory response. In his view the magnitude of the response is an inverse function of the absolute glucose concentration (Figure 3). Thus, glucose decrements to hypoglycemic levels trigger the largest hormonal response. An intermediate response is seen when the blood glucose level falls from high to low physiological levels. A fall from hyperglycemia to normal levels results in a much smaller hormonal response.

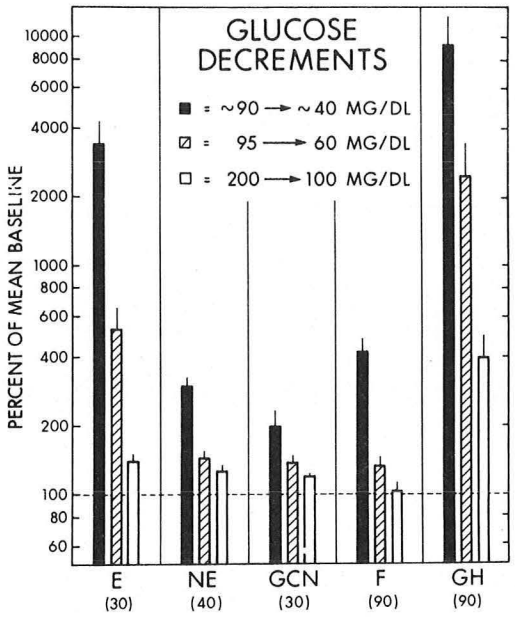



Fig. 3. Mean (±SE) maximal plasma concentrations of epinephrine (E), norepinephrine (NE) glucagon (GCN), cortisol (F), and growth hormone (GH resulting from insulin-induced hypoglycemia (solid columns), plasma glucose decrements from 95 to 60 mg/dl (cross hatched columns), and plasma glucose decrements from 200 to 100 mg/dl (open columns). The numbers in parentheses indicate the time, in minutes, after initiation of the change in plasma glucose. (Cryer, 1981)

## Glucose Counterregulation in Humans with Diabetes Mellitus

Unfortunately the mechanisms for glucose counterregulation have not been well worked out in people with diabetes mellitus. DeFronzo et al, in a beautiful set of studies, (Figure 4) examined the effect of

a falling glucose concentration from one hyperglycemic level (201 ± 22 mg/dl) to a physiological level (100-110 mg/dl) on the release of counterregulatory hormones in 9 subjects with diabetes. During the time when the plasma glucose concentration was falling rapidly or shortly thereafter while the plasma glucose level was being maintained at 100 mg/dl or above, 8 of 9 subjects released growth hormone, 5 of 9 released cortisol, 6 of 9 released epinephrine and 5 of 9 released norepinephrine. None of the subjects released glucagon in response to a falling plasma glucose concentration. In fact, one subject experienced symptoms compatible with a hypoglycemic reaction at a plasma glucose concentration of 150 mg/dl. (Figure 4) Lilavivathana et al, found similar results in studies done in 8 Type I diabetic patients. They lowered blood glucose levels from 350 mg/dl to approximately 100 mg/dl 90 minutes with an intravenous bolus of insulin. Both epinephrine and cortisol levels increased while the plasma glucose levels were falling but still in the hyperglycemic range. No consistent changes in the other hormones (as a group) was seen. Thus, hyperglycemic diabetic patients seem to have a higher "set" for the release of counterregulatory hormones. The clinical lesson from this is that the poorer the antecendant diabetic control the more sensitive the patients are to falling blood glucose levels in terms of symptoms of hypoglycemia. Thus patients can have hypoglycemic symptoms at plasma glucose levels that are not in hypoglycemic range. It therefore is important to document the plasma glucose level during "hypoglycemic" episodes whenever possible. Improvement in overall diabetic control will decrease the frequency of "reactions" at nonhypoglycemic glucose levels. In fact, patients who have achieved long term near normal

glycemia, not only no longer have symptoms of hypoglycemia at nonhypoglycemic levels, they often do not have symptoms when the blood glucose level is in the hypoglycemic range. They are able to tolerate chemical hypoglycemia without symptoms. Although patients are delighted not to have to suffer the unpleasant symptoms of hypoglycemia this is not good news in terms of patient safety. The first symptoms of hypoglycemia is some of these patients are often related to central nervous system dysfunction.

Figure 4
(DeFronzo et al, 1980)

Time course of change in plasma glucose, glucagon, cortisol, and growth hormone concentrations after sustained hyperglycemia in diabetic subjects.

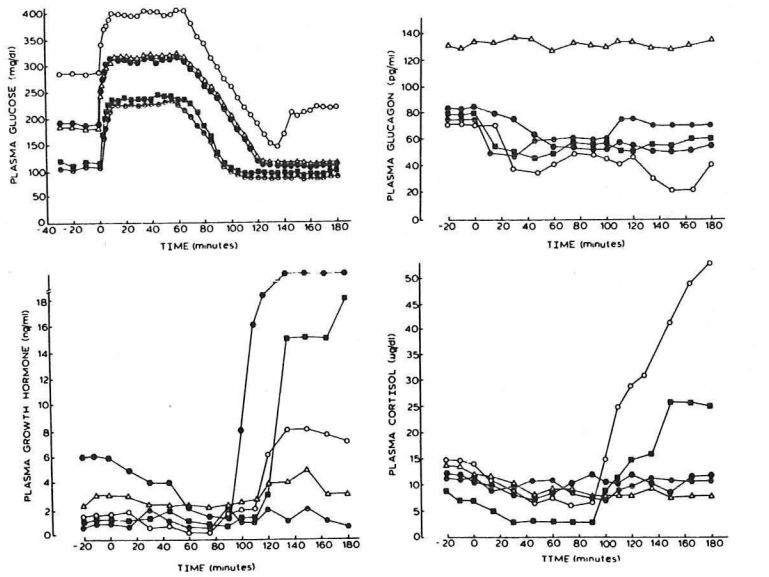
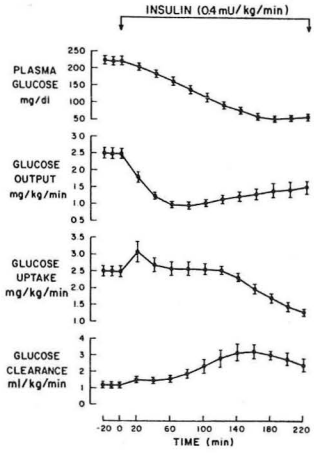



Figure 5 shows the glucose kinetics and couterregulatory response to constant insulin infusion (0.4 mU/kg/min or 1.6 U/hr for a 70 kg person) in a group of patients with Type I diabetes mellitus. There are several things to note. First of all, the plasma glucose level stabilizes (<u>does not rebound</u>) at approximately 60 mg/dl despite the ongoing infusion of insulin. Secondly, in the patients with diabetes

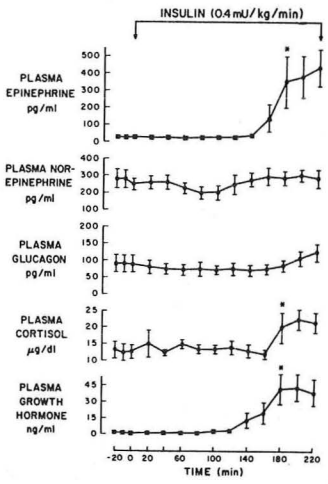
the decline in the plasma glucose concentration is the result of an exaggerated suppression of hepatic glucose output (as compared to nondiabetics), whereas the stabilization of plasma glucose occurs primarily as a consequence of an exaggerated fall in glucose uptake. The exaggerated suppression of hepatic glucose output is probably the result of the failure of glucagon and norepinephrine to increase with hypoglycemia in the patients with diabetes.

Fig. 5A. Effect of insulin infusion (0.40 mU/kg per min) in diabetic subjects on plasma glucose and glucose kinetics.

Fig. 5B. Effect of insulin infusion (0.40 mU/kg per min) in diabetic subjects on plasma epinephrine, norepinephrine, glucagon, cortisol, and growth hormone. The asterisks indicate the first determination that was significantly greater that the basal preinfusion values ($P<0.005$). In the case of norepinephrine and glucagon no significant rise was observed at any time during the insulin infusion. (Sacca et al, 1979)




5A




5B

It has been recently recognized that many patients with diabetes mellitus often have an impaired counterregulatory hormone response to insulin induced hypoglycemia. As early as 1973 Gerich et al, recognized that insulin dependent diabetic patients had a defective glucagon response to hypoglycemia, whereas they had an exaggerated glucagon response to arginine. (Figure 6)

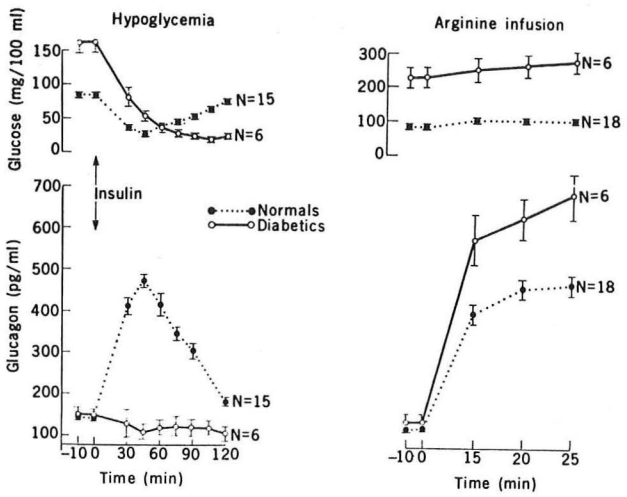


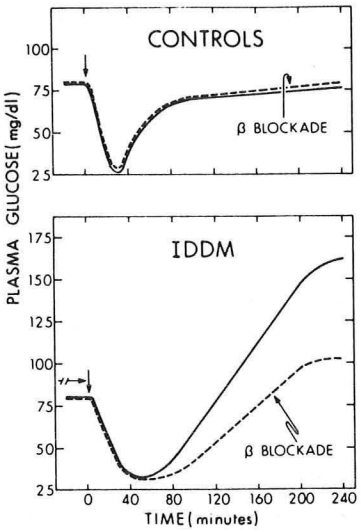

Fig. 6. Plasma glucose and glucagon responses to insulin-induced hypoglycemia (left) and to intravenous arginine infusion (right) in juvenile-type diabetics (——) and in normal controls (- - -). Vertical bars indicate standard erros; N is the number of patients. (Gerich et al, 1973)

Thus, diabetic patients because of their impaired glucagon response to hypoglycemia have an increased dependence on epinephrine mediated beta adrenergic mechanisms to allow blood glucose recovery from hypoglycemia. Popp, Shah, and Cryer, studied the glucose recovery from insulin induced hypoglycemia during beta adrenergic blockade with propanolol in patients with insulin dependent diabetes mellitus and in nondiabetic subjects. In nondiabetics the glucose counterregulation was unaffected by beta blockade, whereas in the patients with diabetes glucose recovery from hypoglycemia was significantly impaired. (Figure 7) Thus, any impairment in the insulin dependent diabetic patient's ability to secrete epinephrine in response to hypoglycemia could potentially lead to severe hypoglycemia.

Since the work by Gerich in 1973, it has become increasingly clear that defective counterregulatory hormone responses are present in many patients with Type I diabetes. Table 1 shows a summary of stu-

dies done by Polonsky et al. They studied 16 patients with Type I diabetes and compared them to 8 non-diabetic controls in terms of the counterregulatory hormone response to insulin induced hypoglcyemia. As a group, the diabetic patients had significant abnormalities in the counterregulatory hormone responses to insulin induced hypoglycemia.

Figure 7
(Popp et al, 1982)




Plasma glucose curves before and after the rapid intravenous injection of regular insulin (0.075 U/kg, arrows) into nondiabetic controls and initially euglycemic (overnight insulin infused) patients with IDDM during infusion of saline (*solid lines*) and the nonselective β-adrenergic antagonist propranolol (*dashed lines, β blockade*). These idealized curves were derived from data published in ref. 20.

TABLE 1

**Basal and Peak Levels of Counterregulatory Hormones in Normal Controls and Diabetics.***

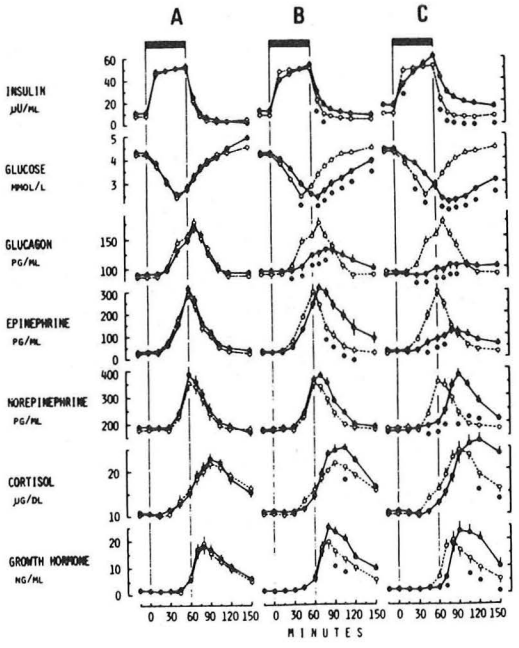
| | Controls N = 8 | Diabetics N = 16 | P Value |
|---|---|---|---|
| Glucagon (pg/ml) | | | |
| Basal | 62.4±14.9 | 71.1±12.9 | |
| Peak | 194.9±26.2 | 92.9±18.1 | <0.0001 |
| Epinephrine (pg/ml) | | | |
| Basal | 60.6±9.0 | 68.8±8.7 | |
| Peak | 1060.9±177.7 | 653.4±136.8 | <0.113 |
| Norepinephrine (pg/ml) | | | |
| Basal | 199.9±26.3 | 208.7±16.6 | |
| Peak | 655.6±68.5 | 587.6±61.4 | NS |
| Growth hormone (ng/ml) | | | |
| Basal | 1.9±0.3 | 4.7±1.3 | |
| Peak | 63.3±8.1 | 37.2±5.1 | <0.006 |
| Cortisol (μg/dl) | | | |
| Basal | 5.2±1.2 | 7.2±1.4 | |
| Peak | 19.6±1.7 | 19.6±2.2 | NS |

*The significance of differences in the peak levels was assessed by analysis of covariance. Differences in basal levels were not significant by the t-test.

(from Polonsky et al, 1982)

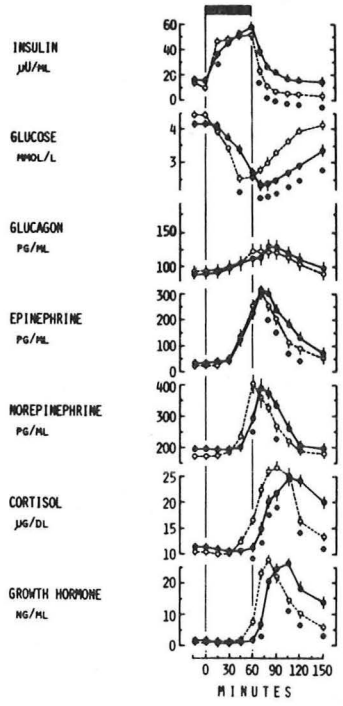
Bolli et al, (Figure 8) studied the effect of duration of diabetes and the presence of insulin antibodies on the abnormal glucose counter-regulation in insulin dependent diabetes mellitus. They showed that impaired alpha cell secretion is the predominant mechanism for the delayed glucose response after insulin induced hypoglycemia in Type I diabetic patients who did not have insulin antibodies circulating in their serum and who had a normal epinephrine response to hypoglycemia. Slowed disappearance of insulin due to the presence of insulin antibodies further delays the restoration of normoglycemia. (Figure 9) The plasma glucagon response to hypoglycemia was inversely correlated to duration of the diabetes. (Figure 10) Patients with long standing diabetes and autonomic neuropathy also exhibit decreased epinephrine secretion in response to hypoglycemia which leads to an additional retardation of glucose recovery from hypoglycemia. Since the glucagon and epinephrine responses were normal early in the course of diabetes but diminished in long term diabetes, it appears that the impaired glucagon and epinephrine response to insulin-induced hypoglycemia are acquired defects that develop subsequent to beta cell failure.

Figure 8
(Bolli et al, 1983)



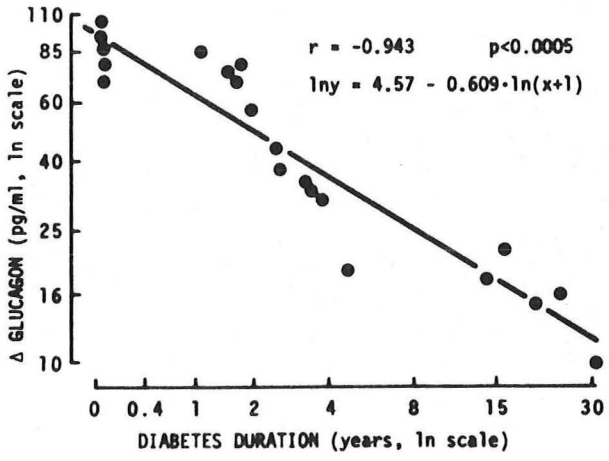

**Plasma insulin, glucose, and counterregulatory hormone concentrations in response to insulin-induced hypoglycemia in diabetic patients (●——●) and in 10 nondiabetic subjects (○----○). Insulin was infused from 0 through 60 min (▬▬, 28 mU/m² · min). Diabetic patients were rendered euglycemic by overnight i.v. infusion of insulin, and the basal insulin infusion rate required to maintain euglycemia from −60 to 0 min was continued through 60 min (A, group A: 5 diabetic patients, diabetes duration less than 1 mo; B, group B: 11 diabetic patients, duration 1–5 yr; C, group C: 5 diabetic patients, duration 14–31 yr). *P < 0.05, diabetics versus nondiabetics.**

Figure 9
(Bolli et al, 1983)




**Plasma insulin, glucose, and counterregulatory hormone concentrations in response to insulin-induced hypoglycemia in six diabetics without insulin antibodies (○---○, group $B_1$) and in five diabetics with insulin antibodies (●——●, group $B_2$). The study was performed as described in the legend to Figure 1. *$P < 0.05$, group $B_1$ versus group $B_2$.**

Figure 10
(Bolli et al, 1983)




**Correlation between maximal increment in plasma glucagon concentration following insulin-induced hypoglycemia and duration of diabetes.**

## The Somogyi Phenomenon

The hyperglycemia that follows hypoglycemia, (the Somogyi Phenomenon) from a clinical point of view, is well demonstrated in Figure 11 which shows blood glucose concentrations, quantitative glycosuria and the presence or absence of urinary ketones over a 48 hour period in a 12 year old patient with Type I diabetes mellitus. Note the sustained hyperglycemia, glycosuria and acetonuria which followed a decline in the plasma glucose level to approximately 60 mg/dl. This type of clinical picture is identical to that described by Somogyi, and in fact, this patient like those of Dr. Somogyi responded to a gradual decrease in insulin dosage.

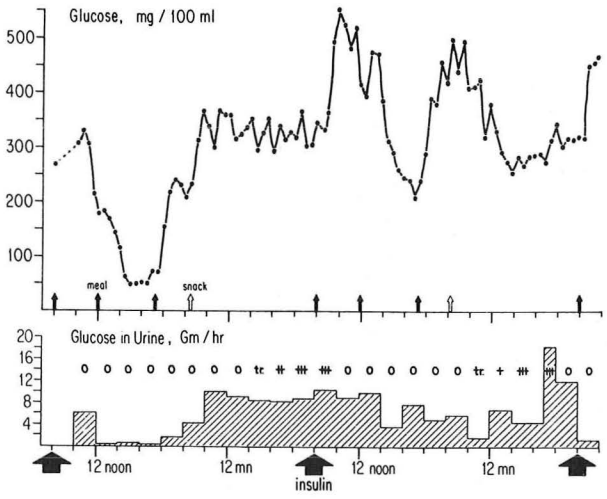



Fig.11 Glucose in blood qualitative reactions for sugar and acetone, and quantitative amount of glucose in timed urine specimens. (Bruck et al, 1974)

Bloom et al, suggested from their studies that posthypoglycemic hyperglycemia was an important cause of "brittle diabetes". They studied 6 patients with insulin dependent diabetes on their clinical research unit, all of whom apparently "did better" on less insulin. They also made the point that if excessive insulin is being administered, the dose should be gradually reduced, as a rapid reduction

tends to lead to excessive hyperglycemia. Figure 12 is an example of one patient reported by Bloom et al. Although it is true that glycosuria was diminished on a smaller daily dose of insulin and the plasma glucose concentrations seemed more stable (this a tough call with only 3-4 measurements per day), diabetic control on the lower insulin dose is not what I would consider adequate. I also would like to point out that in addition to reducing the total daily dose of insulin they also divided the daily dose of insulin into two injections. A manuever which would help smooth things out.

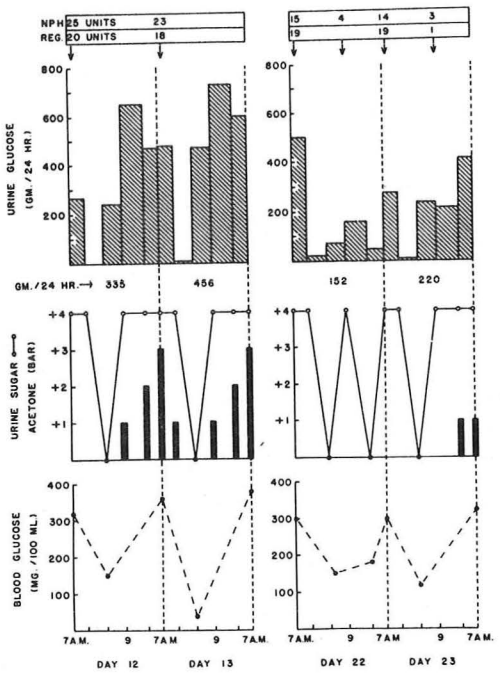



Fig. 12. Quantitative glycosuria, qualitative urine tests for glucose and acetone, and blood glucose on hihg dose insulin, days 12 and 13 and on a lower dose, days 22 and 23, showing better control of these parameters on the lower dose. (Bloom et al, 1969)

Rosenbloom and Giordano have long been proponents that "the most common cause for poor diabetic control in children and adolescents is the chronic overtreatment with insulin." Their data is based on treatment of 101 pediatric patients ages 2 - 21 years old over a 2

year period. They found that overtreatment occured in 70% of their patients overall and in 90% of those patients who were referred to them because of diabetic instability. On the average the daily insulin dosage was reduced by 38%. Unlike Somogyi and Bloom et al, they found that persistent glycosuria, ketonuria and exacerbation of hypoglycmic symptoms were more frequent with slow rather than with rapid reduction in insulin dosages. Table 2 gives some clinical clues to overinsulinization.

TABLE 2

CLINICAL CLUES OF OVERINSULINIZATION

| |
|---|
| I. Clues of nocturnal hypoglycemia |
| A. Morning ketonuria disproportionate to glycosuria |
| B. Soaked bedsheets from nocturnal sweating |
| C. Bad dreams or nightmares |
| D. Morning grumpiness, belly ache, headache |
| E. Hypothermia |
| F. Minimal glycosuria in overnight quantitative urine collection |
| G. Elevated cortisol/creatinine ratio in early morning urine specimen |
| II. Other clues of Somogyi reactions |
| A. Rapid (4–6 h) swings in urine glucose and acetone from negative to large spills |
| B. Wide swings in blood glucose, unrelated to meals |
| C. Glycosuria much of the day with evidence of nocturnal hypoglycemia |
| III. Other clues of overinsulinization |
| A. Insulin dosage that significantly exceeds 1.0 U of insulin per kilogram of body weight per day |
| B. Headaches |
| C. Rapid weight gain |
| D. Lethargy, depression |
| E. Hepatomegaly |

This now brings us to the most important issue of all, that of nocturnal hypoglycemia. Nocturnal hypoglycemia because it usually is asymptomatic is thought by most to be the most frequent cause of the Somogyi Phenomenon. How common is nocturnal hypoglycemia? Table 3 shows the incidence of nocturnal hypoglycemia in three separate studies.

TABLE 3

INCIDENCE OF "ASYMPTOMATIC" NOCTURNAL HYPOGLYCEMIA

| | NUMBER OF PATIENTS | AGE GROUP | NUMBER HYPOGLYCEMIC | REF. |
|---|---|---|---|---|
| | 34 | CHILDREN | 6 (18%) | WINTER |
| | 62 | ADULTS | 8 (13%) | MOORE, ET. AL |
| | 39 | CHILDREN ADULTS | 22 (56%) | GALE AND TATTERSALL |
| TOTAL | 135 | | 36 (27%) | |

"Asymptomatic" nocturnal hypoglycemia is a common finding in insulin treated diabetic patients occuring in approximately 27% of pattients. Although nocturnal hypoglycemia is more common in patients treated with intensive treatment programs, it also occurs quite often in patients treated with even a single daily dose of insulin. With the recent increase in the use of patient self monitoring of blood glucose levels patients and physicians have discovered that nocturnal asymptomatic hypoglycemia is very common in insulin treated diabetic patients. However, the question is not that nocturnal hypoglycemia does occur but does asymptomatic nocturnal hypoglycemia result in the clinical "posthypoglycemic hyperglycemia syndrome" described by Somogyi? This question is addressed in the following paragraphs.

Winter, performed 24 hour glucose and counterregulatory hormone profiles on 34 randomly selected children with Type I diabetes. Asymptomatic nocturnal hypoglycemia was present in 18% (6/34). In these patients the nocturnal plamsa glucose declined at a rate of 20-25 mg/dl/hr to a nadir of 50 mg/dl. The subsequent glucose incre-

ment was 220 ± 38 mg/dl and it occurred only after breakfast. Although it was greater than the glucose increment of 105 ± 11 mg/dl in a group of children with daytime symptomatic hypoglycemia, or in 23 children with non-hypoglycemic profiles the level of hyperglycemia that occurred in the group with nocturnal hypoglycemia never exceeded values seen in the other two groups. In those patients with nocturnal hypoglycemia the only counterregulatory hormone released in excess was growth hormone. Thus, in this study, asymptomatic nocturnal hypoglycemia was followed by a "rebound" of 220 mg/dl in glucose concentration. This rebound required the ingestion of a meal and the blood glucose levels never exceeded 300 mg/dl. This seems a far cry from the syndrome described by Somogyi or that clinical picture as reflected in the patient seen in Figure 11.

Gale and Tattersall measured hourly blood glucose levels throughout the night in 39 unselected patients with insulin dependent diabetes melltius. Hypoglycemia (blood glucose level < 2 mmol/l or 36 mg/dl) occurred in 22 patients and lasted 3 hours or longer in 17 patients. Figure 13 shows profound hypoglycemia lasting 8 hours in a 15 year old boy treated with two daily insulin injections. They reported that hypoglycemic symptoms were very mild or absent but 19 of their 22 patients had other features of overtreatment with insulin. These included lethargy, depression, night sweats, morning headaches, seizures (3 patients), glycogen-laden hepatomegly and an acquired tolerance to high doses of insulin.

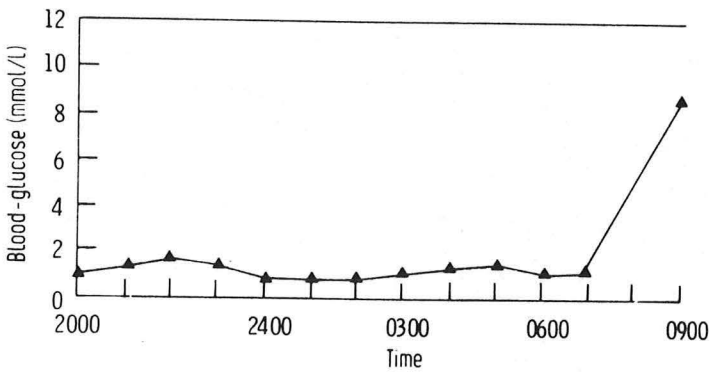



Fig. 13. Prolonged nocturnal hypoglycemia in a 15-year-old boy on twice daily insulin who was taking soluble 12 units and isophane 28 units as an evening dose. (Gale, et al 1979)

The best study, in my opinion, which casts doubt on the importance of nocturnal hypoglycemia resulting in subsequent marked hyperglycemia comes from Gale, Kurtz, and Tattersall which was an outgrowth of the above mentioned study. They studied 15 patients (17 episodes) of asymptomatic untreated hypoglycemia (blood glucose less than 2 mmol/l [36 mg/dl]) that occurred between 11 p.m. and 3 a.m. After nocturnal hypoglycemia, the mean fasting blood glucose level at 7 o'clock in the morning ranged from 0.7 - 17 mmole/l (13-309 mg/dl) and was greater than 7.0 mmol/l (127 mg/dl) in 6 patients. (Fig. 14) The 6 patients with apparent "rebound" hyperglycemia" did not have higher levels of growth hormone, cortisol or glucagon than those who had little or no recovery of blood glucose levels. (Fig. 15) There was a close inverse correlation ($r=0.996$ $p<0.001$) between blood glucose and free insulin levels suggesting that hyperglycemia, when it occurred after nocturnal hypoglycemia, was due to relative insulin deficiency in the latter part of the night. These data have lead these workers to suggest that fasting diabetics often have an <u>impaired</u> rather than excessive recovery of blood glucose after asymptomatic hypoglycemia.

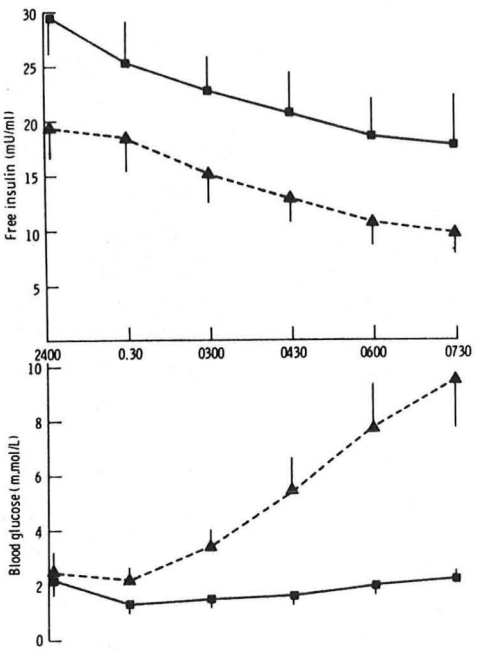



Fig. 14. Blood-glucose and free-insulin concentrations (mean ± SEM)

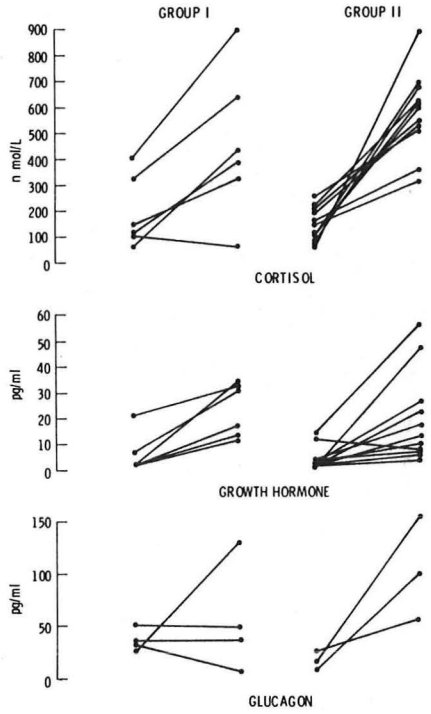



Fig. 15 Plasma concentration of growth hormone, cortisol, and glucagon in group 1 and group 2 patients at onset of hypoglycaemia and the highest value reached in the nex 3 h. (Gale et al, 1980)

Thus it seems clear, that under most circumstances, unless food is taken to relieve the symptoms, nocturnal hypoglycemia does not lead to a rapid and marked increase in the blood glucose level despite the release of counterregulatory hormones. In fact, hypoglycemia in a fasting, insulin treated patient can persist for hours. The eventual increase in the blood glucose concentration to hyperglycemic levels seems related more to a fall in free insulin concentrations than to a rise in counterregulatory hormone levels. (Figures 16 & 17)

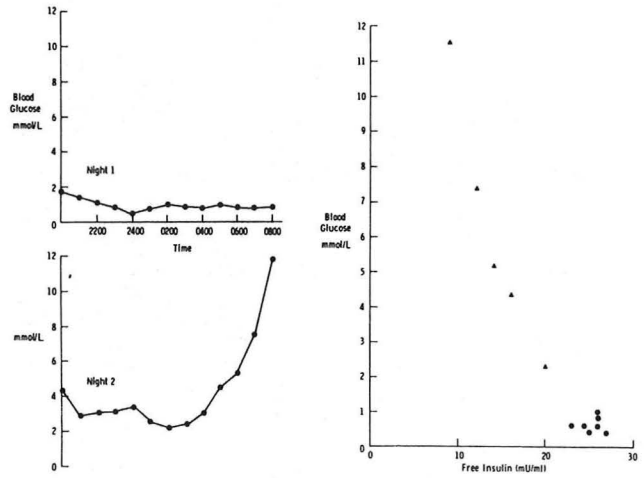



Fig. 16. Relation between glucose and free insulin in a patient studied on two occassions. (Gale et al, 1980)

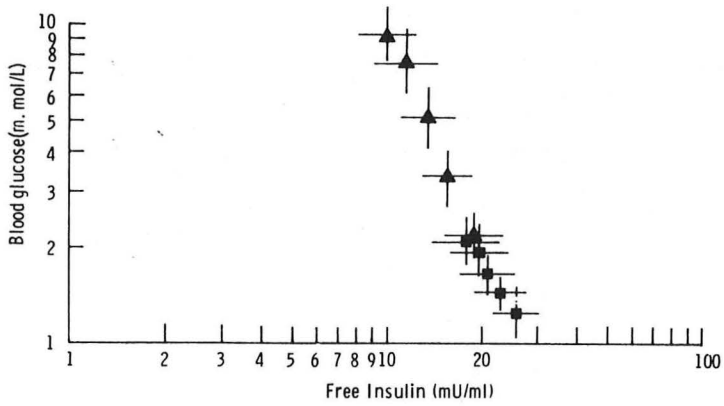



Fig. 17. The relationship between glucose and free insulin (mean $\pm$ SEM) after nocturnal hypoglycaemia in group 1 (triangles) and group 2 (squares) (Gale et al, 1980)

The importance of the free insulin levels with regard to the blood glucose response to counterregulatory hormones is well shown in a study by Shamoon et al. These authors studied the mechanisms of rebound hyperglycemia in Type I diabetic patients who were receiving a constant infusion of insulin prior to and during an infusion of cortisol, epinephrine, and glucagon in doses designed to simulate the increments observed following insulin induced hypoglycemia. (Fig. 18, 19, 20) Although the increment in plasma glucose that occurred with infusion of the counterregulatory hormones was five to seven fold

greater in the diabetics than it was in the normals, the plasma glucose level never exceeded 200 mg/dl. The mechanism for the observed increase in blood glucose level was thought to be an altered response of the liver to these hormones.

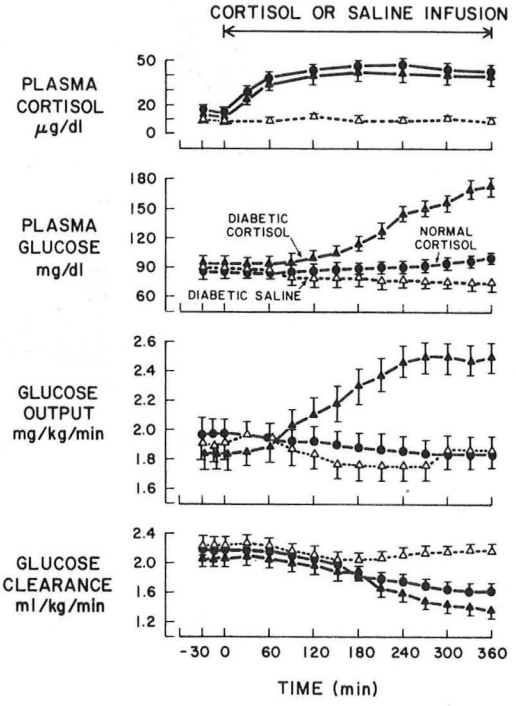



Fig. 18 Influence of diabetes on the response of glucose kinetics to cortisol infusion. Plasma glucose, glucose production, and glucose clearance were normalized in the diabetics before cortisol administration by insuion of insulin which was then continued for the remainder of the study. Changes in glucose kinetics in insulin-infused diabetics given cortisol (closed triangles) are compared with those observed in insulin-infused diabetics given saline (open triangles) and in normal subjects given cortisol (closed circles). (Shamoon et al, 1980)

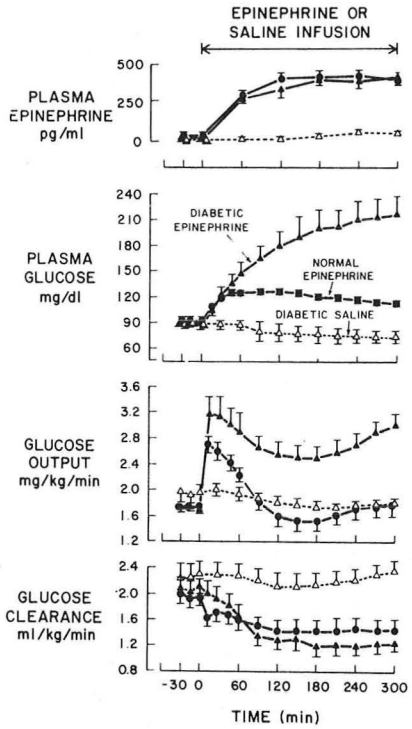



Fig. 19 Effect of cortisol and epinephrine infusion on the plasma concentrations of other anti-insulin hormones in insulin-infusion diabetic subjects O, cortisol; Δ, epinephrine; Δ, saline. (Shamoon et al, 1980)

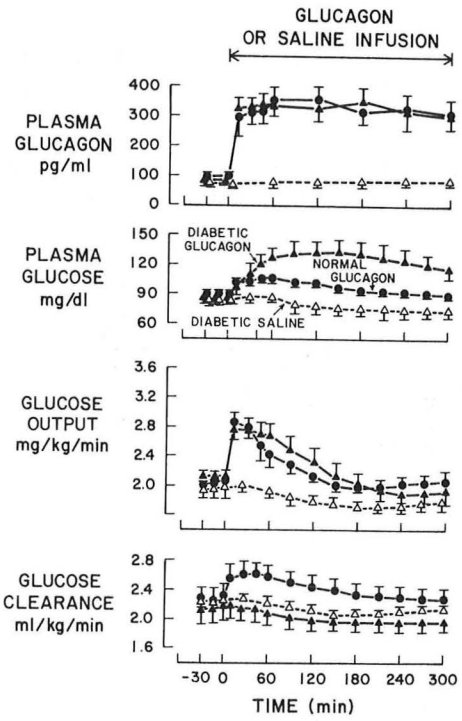



Fig. 20 Changes in plasma glucagon concentration and glucose kinetics in response to the infusion of glucagon in normal (closed circles) and insulin-infused diabetic subjects (closed triangles) (Shamoon et al, 1980)

## POSSIBLE MECHANISMS FOR THE FAILURE TO OBSERVE THE SOMOGYI PHENOMENOM

What are the possible explanations for the failure of hypoglycemia to provoke true rebound hyperglycemia in insulin treated diabetic patients? The first and most obvious explanation for this is some failure of the counterregulatory mechanisms in patients with insulin dependent diabetes. As described previously, Gerich et al, first described the defective glucagon response to insulin induced hypoglycemia in diabetics as compared to normals. Maher et al, confirmed the defective glucagon release to hypoglycemia in patients with diabetes and further showed that defective glucagon secretion was even worse in patients with diabetic autonomic neuropathy. Hoeldtke et al, showed that two-thirds of patients with autonomic neuropathy have moderate to severe deficits in epinephrine secretion in response to hypoglycemia. As a result, these patients have a diminished or delayed glucose response following hypoglycemia, confirming the previously mentioned

work of Polonsky. Finally, Boden et al, recently reported the tragic case of a 46 year old man with Type I diabetes who was capable of synthesizing and releasing all of the counterregulatory hormones (Table 5) but did not secrete them appropriately in response to insulin induced hypoglycemia. (Figure 21) As a result, this patient had many severe and protracted hypoglycemia episodes which resulted in permanent brain damage.

TABLE 5

| Variable | Arginine Test | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ARGININE | | | | | | | |
| Time (min) → | *−30* | *−15* | *0* | *10* | *20* | *30* | *45* | *60* | *90* | *120* |
| Glucagon (pg/ml) | 72 | 74 | 64 | 178 | 288 | 290 | 256 | 200 | 152 | 150 |
| Growth hormone (ng/ml) | 2.2 | 2.2 | 2.2 | 1.6 | 1.6 | 2.4 | 1.6 | 2.6 | 1.6 | 2.2 |

| | Treadmill-Exercise Test | | | | |
|---|---|---|---|---|---|
| | EXERCISE | | | | |
| Time (min) → | *0* | *7.5* | *15* | *20* | *30* |
| Epinephrine (pg/ml) | 61 | 666 | 1791 | 157 | 77 |
| Norepinephrine (pg/ml) | 576 | 2580 | 7584 | 2082 | 617 |
| Cortisol (μg/dl) | 8.7 | 7.8 | 6.8 | 7.6 | 12.3 |
| Growth hormone (ng/dl) | <2.0 | <2.0 | <2.0 | <2.0 | <2.0 |

GLUCAGON AND GROWTH HORMONE RESPONSES TO INTRAVENOUS ARGININE HYDROCHLORIDE (30 g INFUSED OVER 24 MINUTES) AND EPINEPRHINE, NOREPINEPHRINE CORTISOL AND GROWTH HORMONE RESPONSES TO TREADMILL EXERCISE (6 km PER HOUR FOR 15 MINUTES)

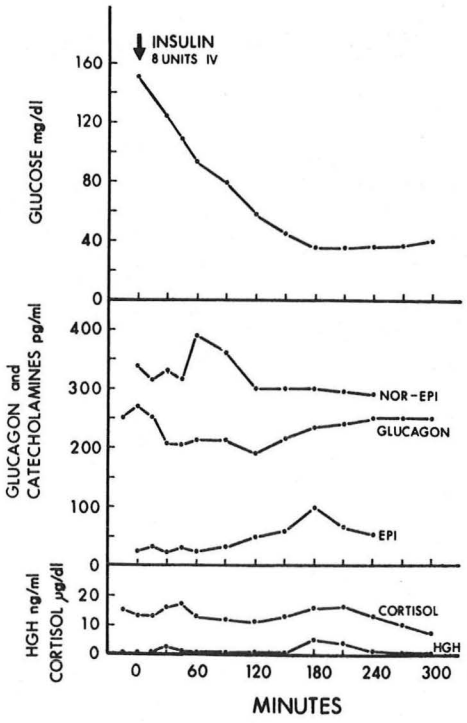


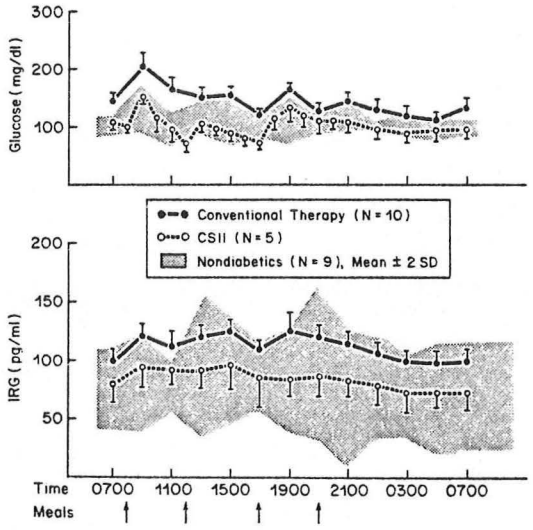

Fig. 21. Effect of intravenous (IV injection of insulin (0.1 U per kilogram of body weight) on plasma concentrations of glucose, epinephrine (EPI), norepinephrine (NOR-EPI), glucagon, cortisol, and human growth hormone (HGH) in a patient with diabetes. (Boden et al, 1981)

The future therapy of Type I diabetes mellitus is likely to involve the expanded use of intensive and innovative treatment programs which include the use of portable insulin infusion devices. All of these treatments improve the possibility of establishing and maintaining long-term normoglycemia. I feel it is important to recognize that chronic euglycemia achieved with portable insulin infusion devices may also effect the ability of the patient to "rebound" from hypoglycemia. First of all, unlike conventional insulin therapy where free insulin levels tend to wane in the middle of the night and thus may be the direct cause for the typically observed early morning increase in blood glucose levels ("The Dawn Phenomenon"), the use of infusion devices results in constant insulin levels. Thus, these patients are particularly at risk to prolonged nocturnal hypoglycemia should glucose counterregulation be defective. Figure 22 shows the plasma IRG profiles in Type I diabetic patients treated for several

weeks with either aggressive conventional therapy or with continuous subcutaneous insulin infusion using a portable insulin infusion device. Note the marked difference in the plasma IRG profile in the patients treated with CSII as compared to conventional treatment. Thus, in Type I diabetic patients who may have a defective glucagon response to hypoglycemia to begin with, treatment with portable insulin infusion devices, with subsequent long-term near normoglycemia, causes in a further suppression of steady-state glucagon levels as compared to an aggressive conventional treatment program. Although the counterregulatory hormone responses to hypoglycemia have not as yet been studied in detail it has been shown by Bolli et al, that near normoglycemia for periods up to 20 days does not restore the glucagon response to hypoglycemia. It is possible also that long term normoglycemia might even impair the epinephrine response to hypoglycemia, thus making recovery from hypoglycemia even more of a problem.

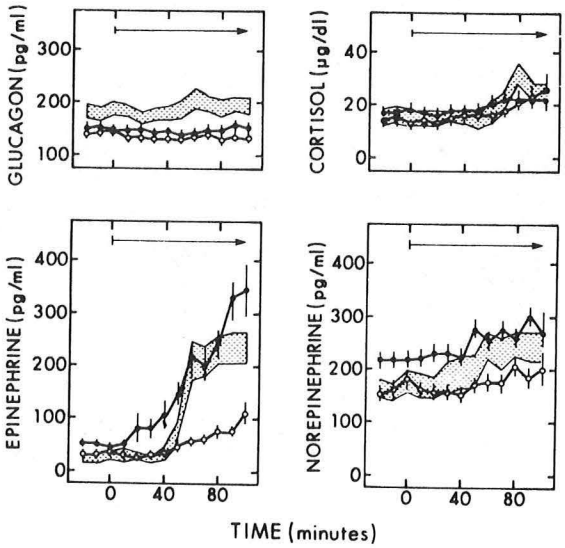
Figure 22

PLASMA GLUCOSE AND IRG LEVELS
IN TYPE I DIABETICS DURING A 24 HOUR PERIOD
OF OPTIMAL CONTROL WITH EITHER
CONVENTIONAL INSULIN TREATMENT OR CSII



In an attempt to identify Type I patients who might be at an increased risk to severe hypoglycemia during intensive therapy, White et al, compared the response to hypoglycemia produced by a 60 minute infusion of regular insulin at a rate of 40 mU/kg body weight in 22 Type I diabetic patients and 10 non-diabetic controls. Counterregulation was defective in 13 of the 22 patients (Figure 23), and in 3 of the patients with inadequate glucose counterregulation the study had to be terminated because of the development of neurologic symptoms of hypoglycemia. The presence or absence of peripheral or autonomic neuropathy and/or a history of previous severe hypoglycemia during conventional therapy were poor predictors as to the adequacy of glucose counterregulation. (Table 6) After completion of this study all 22 patients were placed on an intensive treatment program. During 243 patient months of intensive therapy one of the 13 patients classified as having adequate glucose counterregulation had 2 episodes of severe hypoglycemia. On the other hand, in the other group in 224 months of intensive therapy had a total of 46 episodes of severe hypoglycemia. These occurred in 8 of the 9 patients judged as having inadquate glucose counterregulation. Forty of these episodes occurred between 1:00 - 5:00 AM and required the administration of subcutaneous glucagon or intravenous glucose.

Figure 23
(White et al, 1983)




Plasma Concentrations of Glucagon, Epinephrine, Norepinephrine, and Cortisol (Means ±S.E.) during Infusions of Regular Insulin (40 mU per Kilogram per Hour, Arrows) in 10 Normal Controls (Stippled Areas), in 13 Insulin-Dependent Patients with Diabetes Mellitus (IDDM) Who Had Adequate Glucose Counterregulation (●), and in 9 Insulin-Dependent Patients Who Had Inadequate Glucose Counterregulation (○).

To convert values for cortisol to micromoles per liter, multiply by 0.029. To convert values for epinephrine and norepinephrine to nanomoles per liter, multiply by 0.0055 and 0.0059, respectively.

TABLE 6
(White et al, 1983)

**Characteristics of 22 Patients with Insulin-Dependent Diabetes Mellitus at the Time of the Insulin-Infusion Test, According to the Adequacy of Glucose Counterregulation.**

| | ADEQUATE COUNTERREGULATION (N = 13) | INADEQUATE COUNTERREGULATION (N = 9) |
|---|---|---|
| Age (yr) | 28.9±2.1 * | 34.6±4.1 |
| Duration of disease (yr) | 9.8±2.1 | 15.9±2.8 |
| Neuropathy | | |
| Peripheral | 4 patients | 3 patients |
| Overt autonomic | 1 patient | 2 patients |
| History of severe hypoglycemia during conventional therapy | 4 patients | 5 patients |

*Mean ±S.E.M.

Another study by Polonsky et al, found no relation between the presence or absence of a history of severe clinical hypoglycemia and the plasma glucose or counterregulatory hormone response in 16 Type I diabetic patients. Although the insulin protocol was different (higher doses of insulin) there were no differences in the peak level of counterregulatory hormones in the 7 patients with a history of clinical hypoglycemia and in the 9 who did not have a past history of clinical hypoglycemia. (Table 7)

TABLE 7
(Polonsky et al, 1982)

Basal and Peak Levels of Counterregulatory Hormones and Rates of Glucose Production in Diabetics with and without Clinical Hypoglycemia.*

| | Diabetics with Clinical Hypoglycemia N = 7 | Diabetics without Clinical Hypoglycemia N = 9 |
|---|---|---|
| Ra † (mg/kg/min) | | |
| Basal | 2.35±0.48 | 1.99±0.18 |
| Peak | 2.98±0.51 | 2.18±0.20 |
| Glucagon (pg/ml) | | |
| Basal | 73.6±2.34 | 69.2±15.2 |
| Peak | 98.3±34.7 | 88.8±19.6 |
| Epinephrine (pg/ml) | | |
| Basal | 73.6±10.1 | 64.9±13.6 |
| Peak | 613.3±252.1 | 684.6±158.2 |
| Norepinephrine (pg/ml) | | |
| Basal | 223.6±29.1 | 197.0±19.6 |
| Peak | 576.7±83.9 | 596.1±91.9 |
| Growth hormone (ng/ml) | | |
| Basal | 2.4±0.4 | 6.5±2.2 |
| Peak | 26.4±5.7 | 45.6±6.8 |
| Cortisol (μg/dl) | | |
| Basal | 8.4±2.6 | 6.4±1.7 |
| Peak | 20.1±4.4 | 19.2±2.3 |

*None of the differences between the peak levels in the groups, assessed by analysis of covariance, or the basal levels, assessed by the t-test, were significant.

†Ra denotes rate of glucose production.

## SUMMARY

Post hypoglycemic hyperglycemia (the Somogyi phenomenon) probably occurs in insulin treated diabetics patients. However, it is not as common as has been suggested. When it does occur it is most likely to be seen in children and adolescents, or other insulin-dependent diabetic patients with a short duration of diabetes. Marked hyperglycemia ( ≥220 mg/dl) after hypoglycemia is usually related to the ingestion of a meal (often too large) in an attempt by the patient to relieve the symptoms of hypoglycemia.

Post hypoglycemic hyperglycemia correlates best with falling plasma insulin levels, rather than increasing blood concentrations of counterregulatory hormones, whose secretion may be defective in insulin dependent diabetics. In fact, the failure of the Somogyi phenomenon to occur, may put insulin-dependent diabetic patients at an increased risk to the potential lethal consequences of nocturnal hypoglycemia.

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