Roger Unger

MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

[Roger H. Unger]

STRESS HYPERGLYCEMIA

November 21, 1974

CASE REPORTS

Case #1 - A 15 year old, [redacted], male was admitted to [redacted] with extensive gunshot wounds of the chest and abdomen. He was not a known diabetic. On admission, his blood pressure was 70/0, his plasma glucose was 326. There was no personal or family history of diabetes.

Case #2 - A 48 year old, [redacted] was admitted with crushing precordial pain. On admission, his blood pressure was unobtainable. Plasma glucose was 306 mg%. He denied personal or family history of diabetes.

Case #3 - A 62 year old, [redacted], non-diabetic, female was admitted to [redacted] on [redacted] 1974, after having been found in bed in an obtunded state. In [redacted] Emergency Room, her temperature was 110° and her blood pressure was 60 mm Hg. She was placed in an ice bath and given 1000 cc. of saline and 1000 cc. of D5W with aramine and 50 mg. thorazine. On the next day, a glucose of 242 mg% was noted and subsequent values during her stormy five day survival were as high as 439 mg%.

Case #4 - A 60 year old, [redacted], previously non-diabetic, female with chronic pyelonephritis developes unexplained fever and chills and blood pressure of 70/0. Glucose at that time was 308 mg%.

Case #5 - A 35 year old, [redacted] with chronic peptic ulcer disease enters the [redacted] Hospital with fever, hematemesis and tarry stools. Blood pressure is 80/60, blood glucose 220 mg%.

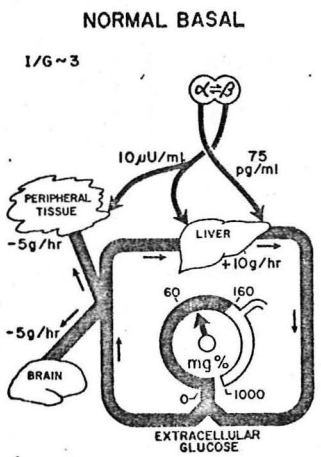
NORMAL GLUCOREGULATION

Defined as the ability to meet changes in glucose need and availability without major perturbations in glucose concentration. Mediated by proper responses of the α - β cells functional unit to various challenges.

I. CHALLENGE OF FOOD:

Figure I

A



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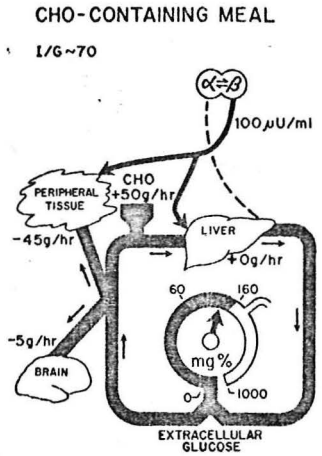
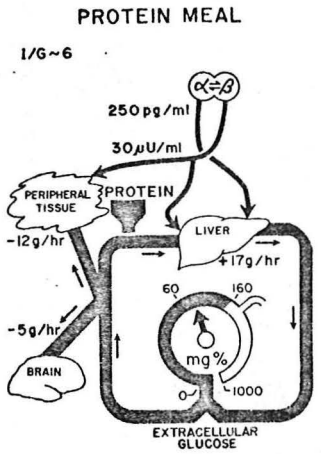


C



GLUCOSE EFFLUX (g/hour):

A	B	C
AUTONOMOUS (CNS) = 5	AUTONOMOUS (CNS) = 5	AUTONOMOUS (CNS) = 5
INSULIN - DIRECTED = 5	INSULIN - DIRECTED = 45	INSULIN - DIRECTED = 12
10	50	17

GLUCOSE INFLUX (g/hour):

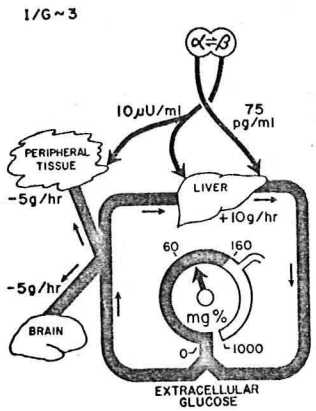
A	B	C
EXOGENOUS = 0	EXOGENOUS = 50	EXOGENOUS = 0
ENDOGENOUS = 10	ENDOGENOUS = 0	ENDOGENOUS = 17
10	50	17

II. CHALLENGE OF NO FOOD:

Figure 2

A

NORMAL BASAL



GLUCOSE EFFLUX (g/hour):

AUTONOMOUS (CNS) = 5
INSULIN - DIRECTED = 5

10

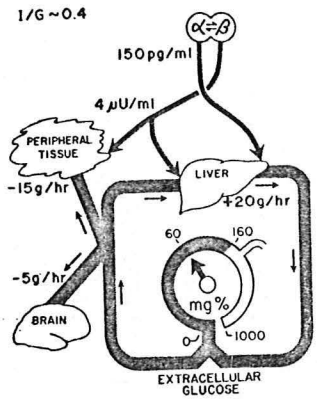
GLUCOSE INFLUX (g/hour):

EXOGENOUS = 0
ENDOGENOUS = 10

10

B

EARLY STARVATION
NON-BASAL



AUTONOMOUS (CNS) = 5
INSULIN - DIRECTED
PLUS OTHER = 15

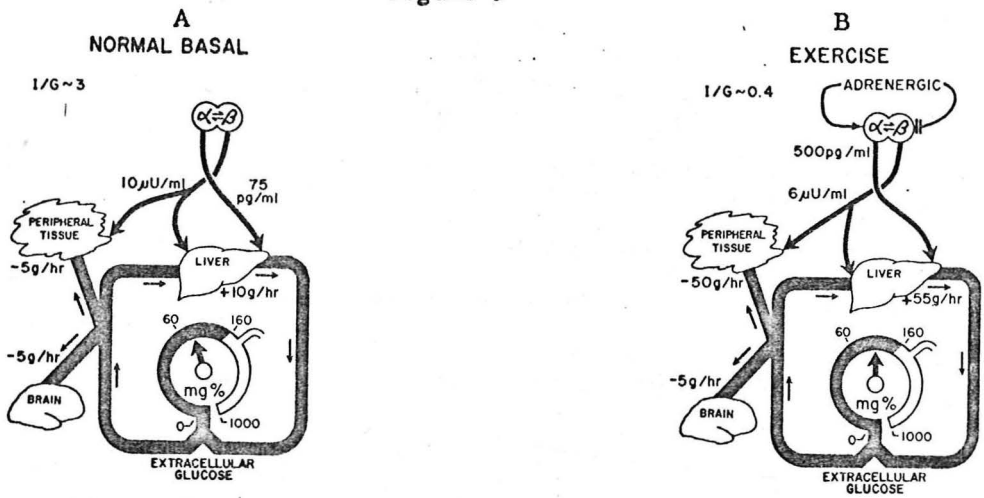
20

EXOGENOUS = 0
ENDOGENOUS = 20

20

III. CHALLENGE OF STRENUOUS EXERCISE

Figure 3



GLUCOSE EFFLUX (g/hour):

AUTONOMOUS (CNS)	=	5
INSULIN - DIRECTED	=	5
		10

GLUCOSE INFLUX (g/hour):

EXOGENOUS	=	0
ENDOGENOUS	=	10
		10

AUTONOMOUS (CNS)	=	5
INSULIN - DIRECTED PLUS OTHER	=	50
		55

EXOGENOUS	=	0
ENDOGENOUS	=	55
		55

IV. CHALLENGE OF ACUTE INJURY AND SHOCK

A. TRAUMA

1. Surgery (Deliberate trauma without shock)

a. Although K value for glucose drops during and for eight days or more post-operatively with all major surgery, fasting hyperglycemia is not usually observed in the absence of shock (Wright et al, 1974).

b. Insulin response to glucose is diminished in surgery.

c. Catecholamine excretion increases and is correlated with K impairment.

d. Cortisol is generally normal in all uncomplicated surgery.

2. Accidental Trauma With Shock

a. Impaired glucose tolerance and insulin resistance (Howard, 1955).

b. Carey et al (1970) report that, in traumatic hemorrhagic shock in non-diabetic patients in Viet Nam, glucose averaged 215 mg% 30 minutes after wounding. The highest level at 30 minutes was 420 mg%. One patient reached 622 mg% in two hours without having received IV glucose. In survivors, it returned to normal in 12 - 24 hours, but in most of the dying, it rose until death, although in one it dropped from 622 to 25 in 10 hours. Good relationship between the severity of hyperglycemia and the severity of shock.

B. THERMAL INJURY WITH SHOCK (Allison et al, 1968)

1. Glucose intolerance and spontaneous hyperglycemia.
2. ↑ FFA → massive hepatic fat accumulation.
3. Impaired insulin response to glucose.
4. ↑ adrenaline.
5. "Insulin resistance" - sick cell syndrome.

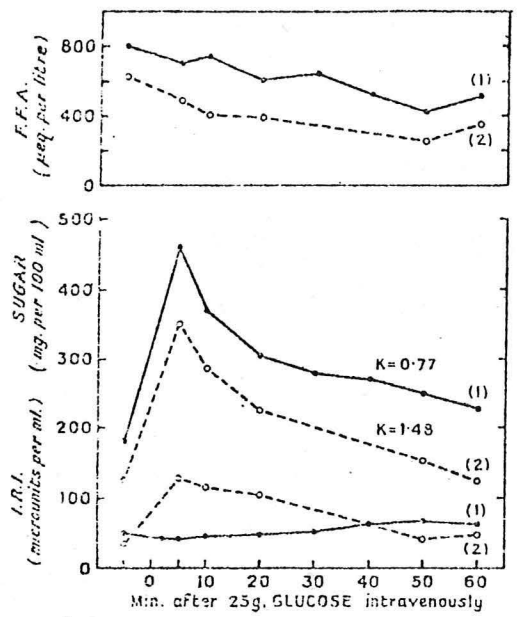


Fig. 4—Patient no. 1, age 44, with burns of 60% body area. (1) acute study; (2) follow-up study 1–4 weeks later.

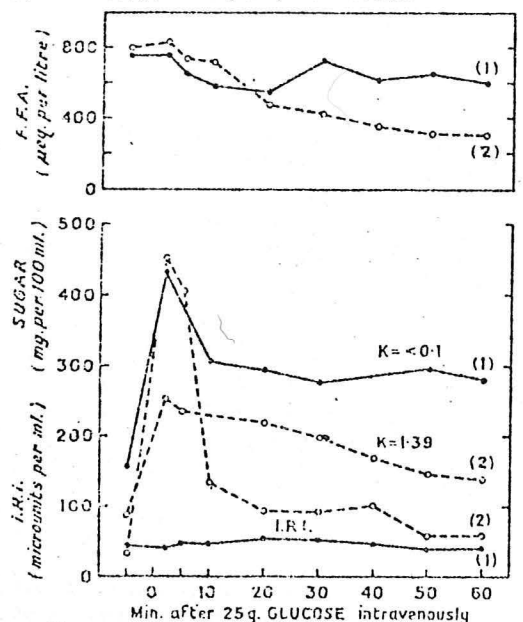


Fig. 5—Patient no. 2, age 19, with burns of 40% body area. (1) and (2) as in fig. 1.

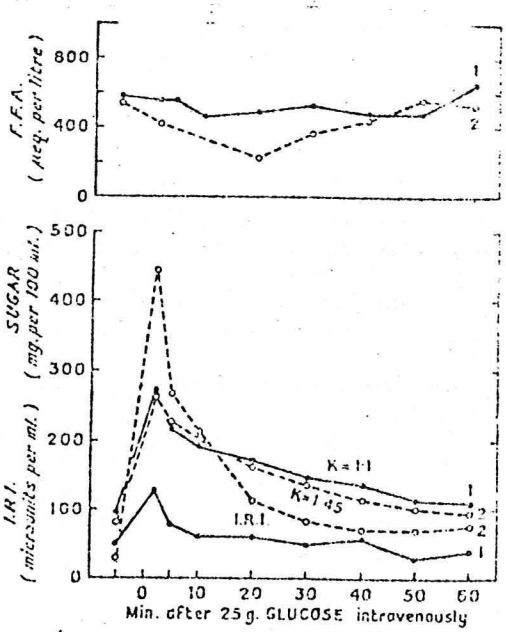


Fig. 6—Patient no. 3, age 42, with burns of 21% body area. 1 and 2 as in fig. 1.

C. ISCHEMIC INJURY

1. Myocardial Infarction with Shock

Lebovitz et al (1969) found increased circulating catecholes in cardiogenic shock together with decreased insulin response. In the absence of shock, these changes are much less prominent, although glucose tolerance is almost always impaired.

SHOCK WITHOUT INJURY

A. HEMORRHAGIC SHOCK IN PRIMATES

1. Hemorrhagic Shock with Sustained Hypotension (Coran et al, 1972):

When cardiac output falls from 3.2 to 0.9 L/minute:

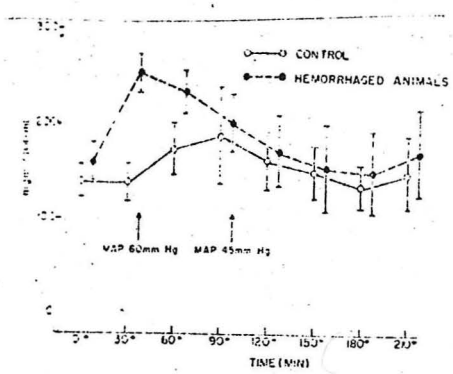


Fig. 7. Serum glucose levels in control and hemorrhaged baboons (mean ± S.E.M.).

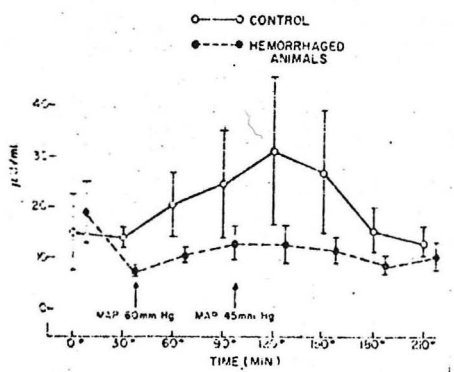


Fig. 8. Serum insulin levels in control and hemorrhaged baboons (mean ± S.E.M.).

a. Lactate increases from 20 to 80 mg%.

b. pH falls but is not statiscally significant.

c. Glucose averages 252 + 20 mg% 30 minutes after the onset of shock but ultimately declines, sometimes to hypoglycemic levels.

d. Insulin falls promptly and remains low.

e. Glucagon was not measured (but we know it must have been extremely high).

f. FFA ↑.

Starvation before shock shortens the magnitude and duration of hyperglycemia in prolonged hypovolemia and hastens hypoglycemia (Moffat et al, 1968). If glucose is infused, survival is prolonged significantly; sucrose also helps but less dramatically.

Conclusion: With continuing hypovolemia and shift to anaerobic metabolism, glycogen stores are depleted and exogenous glucose helps prolong life by providing needed fuel. Volume expansion effect is suggested by the beneficial effect of non-metabolizable sucrose.

2. Hemorrhagic Shock from Rapid Exsanguination (Moss et al, 1970)

a. Metabolic acidosis.

b. PO2 normal.

c. 177 mg% average rise in glucose beginning in five minutes.

d. 22 μU/ml fall in insulin.

Is the fall in insulin the result of pancreatic ischemia, islet ischemia or increased insulin destruction? Moss et al (1972) showed that the decline in insulin is not due to decreased pancreatic blood flow but rather to decreased insulin secretion. Associated hyperglucagonemia of hemorrhagic shock (Lindsey et al, 1973, unpublished), attributable in part to increased glucagon secretion, is against islet ischemia. Lau et al (1971) and Hiebert et al (1972) also found, by direct measurement, a reduction in insulin secretory rate in dogs and in primates.

B. GRAM NEGATIVE SEPTICEMIA

a. E. coli septicemia in baboons causes hyperglycemia averaging 187 mg% in 15 minutes and insulin falls (Cryer et al, 1971).

b. Plasma 11-hydroxycosteroids rise but not significantly.

c. Growth hormone occasionally rises (N.S.).

d. Urinary catecholamines increase significantly. In adrenalectomized rats on cortisol endotoxic shock does not deplete glycogen (Sanford, Barnett, 1960), all of which suggests that cortisol at most plays a permissive role in the increased hepatic glucose production induced by other hormones (see below). Its major importance may be in furnishing gluconeogenic substrate, maintaining a higher level of glucagon secretion and hepatic sensitivity to glucagon, but it may also reduce tissue sensitivity to insulin.

C. HEAT STROKE (Monteleone and Keefe, 19)

This is really dehydration hypovolemia with the same mechanisms as above. It responds to fluid replacement.

METABOLIC CHANGES ASSOCIATED WITH SHOCK (Engel, 1952)

Despite reduced splanchnic and muscle blood flow, both hepatic production of glucose and glucose utilization by peripheral tissues are substantially increased. Initially, glucose production must exceed utilization to produce endogenous hyperglycemia, but ultimately, as glycolysis becomes increasingly anaerobic, glucose utilization outstrips a declining glucose production, hypoxia increasing glucose uptake. Lactate and pyruvate rise late and ultimately L/P rises, as does inorganic PO4 (Drucker, 1958).

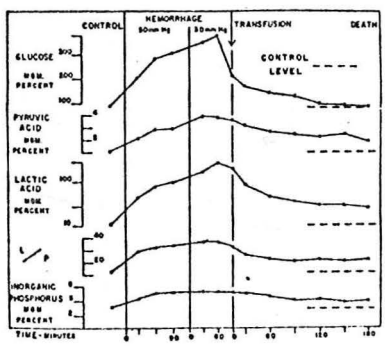


Fig. 9. Metabolic changes during hemorrhage and after blood replacement in dogs under nembutal anesthesia, (average of nine dogs).

Weiner and Spitzer (1974):

a. Glucose turnover increases in post-hemorrhagic hypotension in relation to pool size and % of the glucose turnover oxidized is increased.

b. Both CO_2 and lactate derived from glucose is increased.

c. Glucose from lactate usually increased.

d. Most of the increase in glucose oxidation involves glucose derived from lactate, i.e. a marked increase in Cori cycle activity.

e. Lactate oxidation is twice normal and gluconeogenesis is twice normal, accounting for 91% of lactate turnover. Later, during severe hypoxia, a decline in lactate oxidation may explain terminal lactate rise and irreversible deterioration.

f. FFA turnover is increased but there is a tissue preference for carbohydrate.

HORMONAL CHANGES ASSOCIATED WITH STRESS HYPERGLYCEMIA

1. Catecholamines: Increased epinephrine and nor-epinephrine in shock (Hume, 1958; Jaattela, 1972). Porte et al (1966) showed α -adrenergic inhibition of insulin secretion.

2. Cortisol: Increased in shock. Stress hyperglycemia is blocked by adrenalectomy (Selye, 1941). However, McCormick et al (1969) found that suppression of cortisol secretion does not block shock-induced hyperglycemia; therefore, it is the adrenal medulla, not the cortex, that is most important in the genesis of stress hyperglycemia. Indeed, in vitro studies suggest that cortisol does not itself inhibit glucose utilization by muscle (Herman, 1960), but merely "permits" the epinephrine effect. Since it also "permits" the glucagon effect on hepatic gluconeogenesis, its role may be entirely permissive; i.e. while hyperglycemia would not occur if cortisol were absent, increased levels are not a major factor in causing hyperglycemia.

3. Growth Hormone: It is often high in shock and often normal, whether or not hyperglycemia is present. Probably has no real glucoregulatory role despite its responses to glycemic change. It undoubtedly maintains a normal level of insulin sensitivity in peripheral tissues.

4. Glucagon:

a. Absolute or relative hyperglucagonemia derived from pancreatic and/or extrapancreatic alpha cells has now been identified in every known form of stress hyperglycemia - infection (Rocha et al, 1973), trauma (Lindsey et al, 1974), burns (Wilmore et al, 1974), myocardial infarction (Willerson et al, 1974), fetal distress (Johnston et al, 1972). In fact, hyperglucagonemia has now been identified in all forms of endogenous hyperglycemia studied, including total pancreatectomy.

b. Most forms of endogenous hyperglycemia can be prevented by glucagon blockade.

c. Although catechols may be directly involved in hepatic glycogenolysis at the hepatic level - either via the circulation or the nerve endings or both, this probably requires higher level of adrenergic activity than is needed to cause hyperglucagonemia.

d. Stress hyperglucagonemia is largely blocked by β -adrenergic blockade (Lindsey et al, 1975), and stress hyperglycemia somewhat reduced.

MECHANISMS OF ISLET CELL RESPONSE TO STRESS

1. Hyperglucagonemia and Hypoinsulinemia:

Bernard (1844) found that piqure of the floor of the fourth ventricle causes rapid hyperglycemia. Frohman and Bernardis (1971) found glucoreceptors in the ventromedial hypothalamus (VNM) (figure 10) which, when stimulated electrically, cause a rise in plasma glucose in 2.5 minutes. Fibers from these nerves travel along the floor of the fourth ventricle and via sympathetic fibers through the brain stem, spinal cord and celiac ganglion. Electrical stimulation of pancreatic nerve (Marliss et al, 1973) causes glucagon rise and marked hyperglycemia.

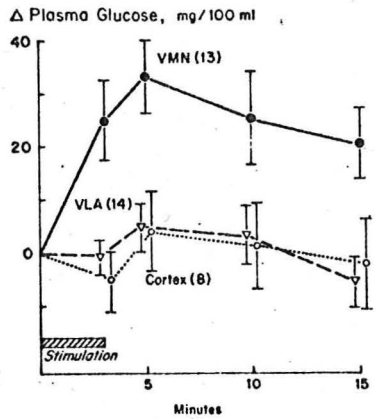


FIG. 10. Effect of electrical stimulation of ventromedial hypothalamic nucleus (VMN), ventrolateral hypothalamus (VLA), and cerebral cortex on plasma glucose. Shown are means ±SE. Numbers of animals in each group are in parentheses. Initial plasma glucose levels of 3 groups were 142 ± 5, 137 ± 6, and 134 ± 8 mg/100 ml, respectively.

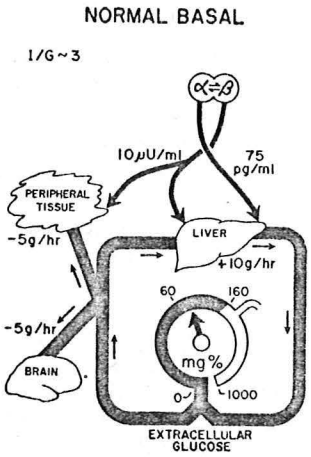
VMN stimulation causes a glucagon rise of 348 pg/ml in 2.5 minutes in intact animals and 253 pg/ml in adrenalectomized animals, suggesting both direct and adrenal medullary mediated glucagon response. In adrenalectomized rats, insulin is not suppressed by VMN stimulation. Therefore, glucagon stimulation is not dependent on adrenal medulla in rats, whereas insulin suppression is. Direct innervation of the liver by postganglionic fibers of the liver may also contibute to glycogenolysis.

Epinephrine, nor-epinephrine and isoproterenol stimulate glucagon in isolated pancreas (Iversen) via beta receptors, while insulin suppression is mediated through an alpha receptor. Glucagon stimulation by catacholamines may well account for more of the glycogenolytic response than do direct catecholamine effects upon the liver.

Cortisol, at high levels, potentiates glucagon response to stimulation (Marco et al, 1973) and permissively enables the full hepatic response to glucagon and catechols.

Figure 11

A



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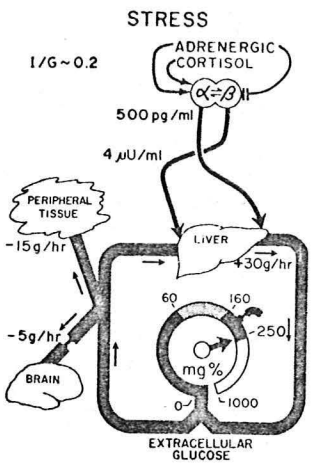

GLUCOSE EFFLUX (g/hour)

AUTONOMOUS (CNS)	=	5
INSULIN - DIRECTED	=	5
		10

AUTONOMOUS (CNS)	=	5
INSULIN - DIRECTED AND/OR OTHER	=	15
		20

GLUCOSE INFLUX (g/hour)

EXOGENOUS	=	0
ENDOGENOUS	=	10

EXOGENOUS	=	? IV
ENDOGENOUS	=	30

TREATMENT OF STRESS HYPERGLYCEMIA

1. During Shock - DON'T CORRECT IT

If you lower glucose during shock, you remove a vital means of cerebral glucose delivery (cerebral blood flow x arterial glucose concentration = cerebral glucose delivery). CBF is low, but, thanks to a high glucose concentration, the brain may get by. If you "correct" hyperglycemia with insulin, as some surgeons have recommended, you reduce glucose delivery to the brain and may decorticate your patient. A second, less convincing reason for maintaining hyperglycemia is that the hyperglycemia is osmotically supporting ECF volume and a major decline in glucose would further reduce ECF - perhaps to the point of no return.

Should you help maintain hyperglycemia by giving exogenous glucose? Your first priority is vigorous correction of the shock and the hyperglycemia will, in an otherwise healthy and well fed person, take care of glucose needs for a while. Giving glucose too fast early in shock could lead to hyperosmolal levels relatively quickly. BUT, if starvation, liver disease, or a glucose level under 200 mg% is present in a patient, you would be wise to give about 10 - 20 g of glucose per hour, or more if needed, to maintain twice the normal glucose concentration.

2. Post-Shock Hyperglycemia

If hyperglycemia persists after correction of shock, this could signify a catabolic state or diabetes and a high insulin; glucagon ratio is theoretically valuable. In burn patients and other severely catabolic conditions, hyperalimentation, though not without its own hazards, may promote the anabolic changes required for healing.

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