MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

April 9, 1970

COMMON DISEASES OF GLUCAGON SECRETION IN MAN

I. CURRENT CLASSIFICATION OF ALPHA CELL DISEASE

A. Hyperglucagonism

1. Chronic

a. Glucagonoma - Autonomous or semiautonomous glucagon-producing alphacytoma. Islet of Langerhans

b. Diabetes mellitus - Constant inappropriate hyperglucagonemia, not suppressible by hyperglycemia.

2. Transient

a. Acute pancreatitis - Presumably a glucagon leak secondary to alpha cell injury.

b. Chronic hypercalcemia of any cause (hyperparathyroidism, Gellhorn-Plimpton Syndrome, leukemia)

B. Hypoglucagonism

a. Chronic pancreatitis or any extensive destructive disease of the pancreas.

b. Absence or hypofunction of alpha cells (McQuarrie, Grollman) not yet proven by specific glucagon assay to exist.

II. THE FUNCTION OF THE ISLETS OF LANGERHANS

Alpha and beta cells constitute a single bihormonal functional unit which shepherds the major nutrient substrates into and out of the various tissues in a manner appropriate to tissue needs and to the available supply of exogenous nutrients. When the flux of nutrients into and out of cells is thus appropriately regulated, nutrient concentration in extracellular fluid is restricted to within a relatively narrow range, considering the enormous differences in nutrient supply and demand. Whereas Insulin should be regarded as the hormone of storage for exogenous nutrients, glucagon functions as a hormone of distribution of nutrients which maintains their flow from storage sites to the vital organs during times when exogenous nutrients are not available.

III. KNOWN PHYSIOLOGIC ACTIONS OF GLUCAGON

A. Glucagon increases hepatic glucose production (1, 2).

1. By enhancing glycogenolysis (3, 4, 5).

2. By enhancing gluconeogenesis (6, 7)

MECHANISMS: It is believed that both effects result from direct activation by glucagon of the enzyme adenyl cyclase, which increases the formation of hepatic cyclic AMP (CAMP) from ATP. CAMP, in turn, activates the enzyme phosphorylase, which promotes glycogen breakdown to glucose-1-PO_4, etc. (8, 9).

CAMP also promotes gluconeogenesis (10, 11) in two ways:

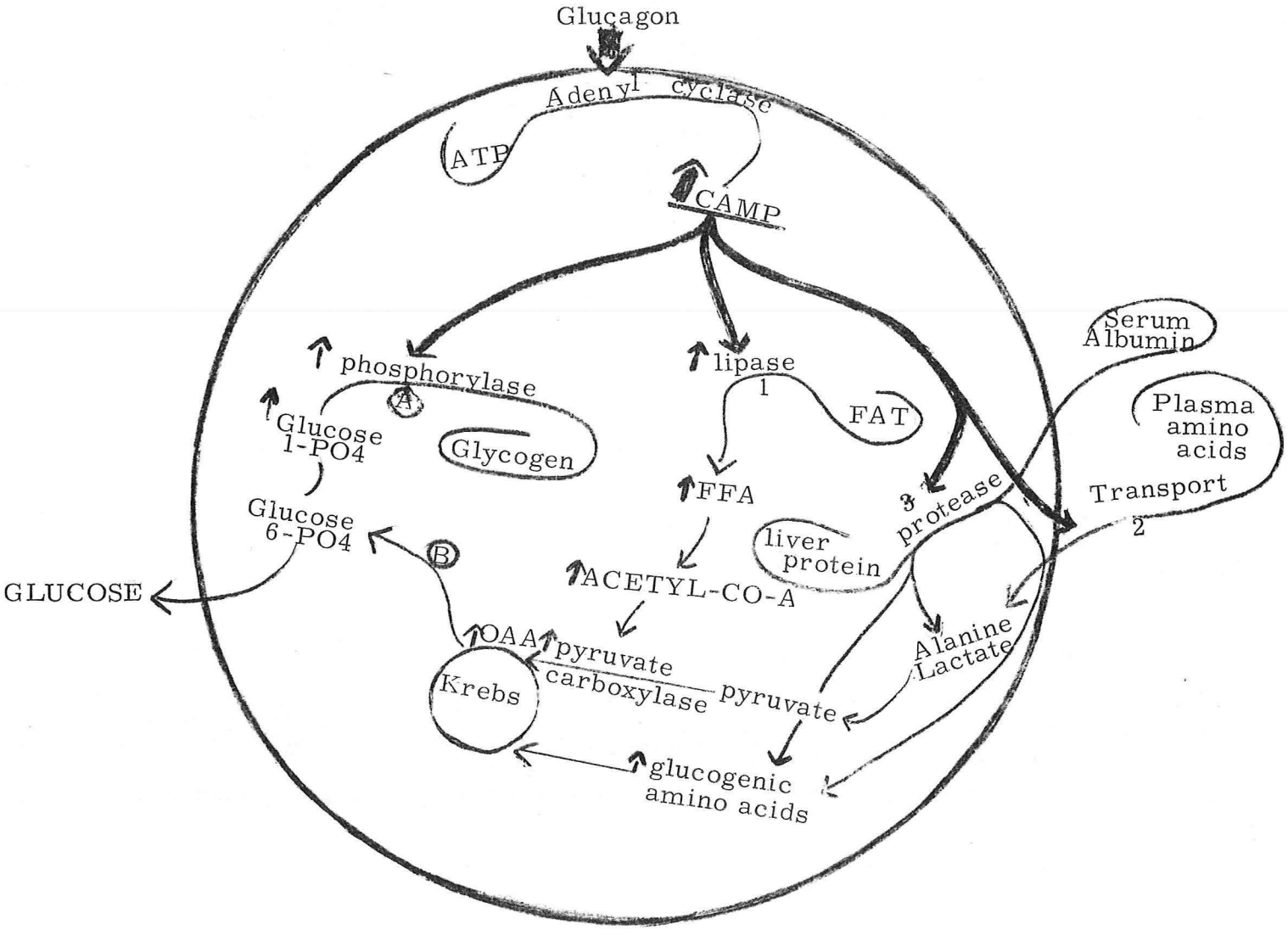
1. It activates hepatic lipase (12) thus increasing intrahepatic lipolysis and consequently, the oxidation of FFA to acetyl CoA; acetyl CoA allosterically increases pyruvate carboxylase activity, a rate-limiting point in the gluconeogenesic sequence (pyruvate $\longrightarrow$ oxaloacetate) (13).

2. It increases the intrahepatic pool of glucogenic amino acids a) by enhancing their transport into the liver cells, and b) by increasing proteolysis from plasma protein and from hepatic cellular protein (14).

NOTE: Although its glycogenolytic activity is too well appreciated to require emphasis, glucagon's gluconeogenic activity is less well recognized. It is now clear that glucagon is THE gluconeogenic hormone par excellence, having been shown to increase hepatic glucose production from alanine and lactate (15), in the isolated perfused liver, to increase hepatic uptake of all glucogenic amino acids from plasma by the perfused liver (16), as in vivo (17), to derive these subtrates from proteins by increasing proteolysis of intrahepatic and plasma proteins. The glucogenic amino acids thus freed are converted to glucose, and the non-glucogenic amino acids subsequently released. Cahill's group regards alanine as the principle glucogenic precursor and glucagon infused at a rate as low as 100 mμg/minute causes a remarkable reduction in plasma alanine.

NOTE: These hepatic actions of glucagon can be achieved by as little as 10^{-11}m of glucagon or 100 molecules per liver cell. Insulin, which opposes all these actions of glucagon, probably requires a concentration of about 10,000 molecules per liver cell to do so.

EFFECTS OF GLUCAGON ON LIVER CELLS



A. GLYCOGENOLYSIS

B. GLUCONEOGENESIS

1. ↑ lipolysis
2. ↑ transport of amino acids into liver cell
3. ↑ proteolysis from hepatic and plasma protein

B. Glucagon causes an immediate increase in free fatty acid and glycerol release from fat cells by enhancing lipolysis.

MECHANISM: It is believed that glucagon activates adenyl cyclase of fat cells and that the resulting increase in CAMP activates the hormone-sensitive lipase (19).

IV. KNOWN ACTIONS OF GLUCAGON OF DOUBTFUL OR UNCERTAIN PHYSIOLOGIC SIGNIFICANCE

A. Exogenous glucagon, even in physiologic doses, stimulates insulin secretion in vivo (20, 21).

MECHANISM: There is indirect evidence that glucagon enhances beta cell adenyl cyclase activity and that the resulting increase in CAMP promotes insulin release (23).

NOTE: Although insulin release is enhanced by the injection of physiologic quantities of glucagon, the physiologic relevance of this action is questionable, because in real life, glucagon secretion is stimulated by circumstances which suppress insulin release, e.g. glucopenia, and suppressed by substrates which stimulate insulin — with only one exception, i.e. protein ingestion (vide infra). If endogenous glucagon ever stimulates insulin secretion, it must do so only during protein-induced hyperaminoacidemia, this being the one situation in which the secretion of both hormones increases in parallel. But even in this situation, insulin stimulation by glucagon is uncertain.

B. Exogenous glucagon given in pharmacologic doses lowers calcium (24, 25).

MECHANISM: Although Avioli reports abolition of glucagon's hypocalcemic effect in dogs following thyroidectomy, and suggests that glucagon lowers calcium by stimulating thyrocalcitonin secretion (26), others claim that in rats glucagon's hypocalcemic action persists even in the absence of the thyroid, parathyroids, and kidneys. They believe that glucagon promotes bone uptake of calcium (27) (in contrast to thyrocalcitonin which decreases bone resorption).

NOTE: We doubt that this effect of glucagon has any physiologic significance, whatever its mechanism, since in our lab physiologic doses of glucagon failed to alter serum calcium, and calcium infusion failed to stimulate glucagon secretion. However, the effect may have pathophysiologic significance since in hypercalcemic states in man (hyperparathyroidism, Gelhorn-Plimpton, milk-alkali syndrome, leukemia) glucagon levels are elevated (28).

C. Exogenous glucagon in pharmacologic doses allegedly stimulates epinephrine and norepinephrine release in dogs (29).

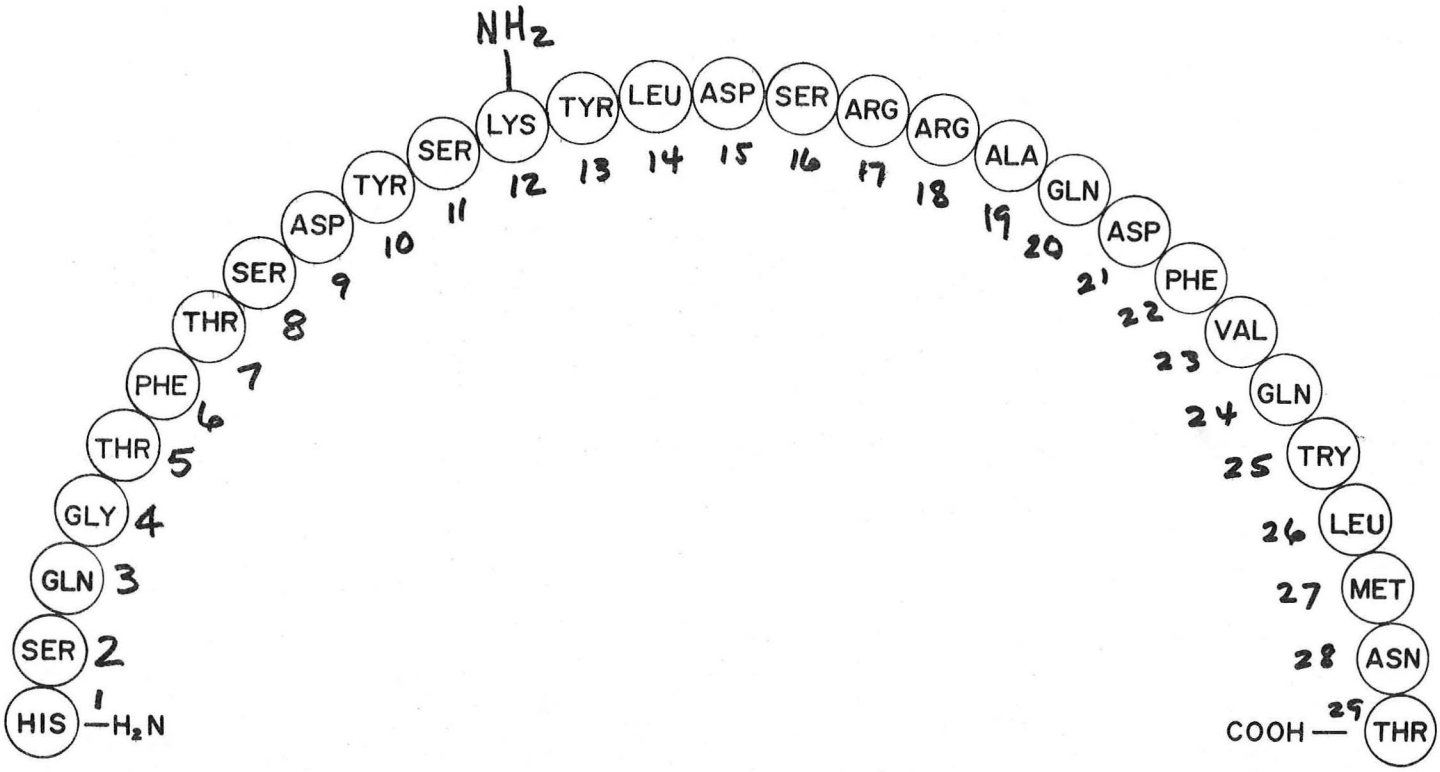
Uncertain significance.

V. GLUCAGON STRUCTURE AND ITS RELATIONSHIP TO FUNCTION

A. Two "glucagon" Peaks in pancreatic extracts

1. True glucagon -- M.W. 3485 -- largely a random coil with some structure between amino acids 14 and 25.

Bromer sequence (30):



a. Immunoreactive site from 14 - 25 (30a).

b. Biologically active site from 1 - 27 (31).

2. "Large glucagon immunoreactivity" (LGI) makes up about 5% of the total extractable immunoreactivity of plasma. M.W. about 7,000 (32).

a. Immunoreactivity indistinguishable from true glucagon.

b. No glycogenolytic activity.

c. Converted by limited tryptic hydrolysis to a product smaller than true glucagon, immunologically indistinguishable therefrom, devoid of glycogenolytic activity; this fragment could well be the same as the immunoreactive tryptic product of true glucagon (probably fragment 18-29).

NOTE: Two important questions: 1) Is LGI a "proglucagon"?

2) Does plasma contain immunoreactive derivatives or precursors of glucagon devoid of biological activity yet measured in the radioimmunoassay for glucagon? (vide infra)

VI NORMAL CONTROL OF ALPHA CELL SECRETION

NOTE: Glucagon secretion, like that of many other hormones, is under the primary feedback control of the products and precursors of the biologic reactions which it activates. A rise in the arterial plasma concentration of a precursor (glucogenic amino acids) (33) or a fall in the concentration of a product (glucose [34, 35], FFA [36,37]) stimulates its release, while a rise in the concentration of a product will feed back negatively to suppress glucagon secretion (34, 35, 36).

A. Rise of glucose concentration and glucose availability:

1. Experimental Conditions.

Glucose concentration appears to be a primary regulator of glucagon secretion (38).

a. Glucose concentrations raised acutely >160 mg% normally will always suppress glucagon secretion (38, 39).

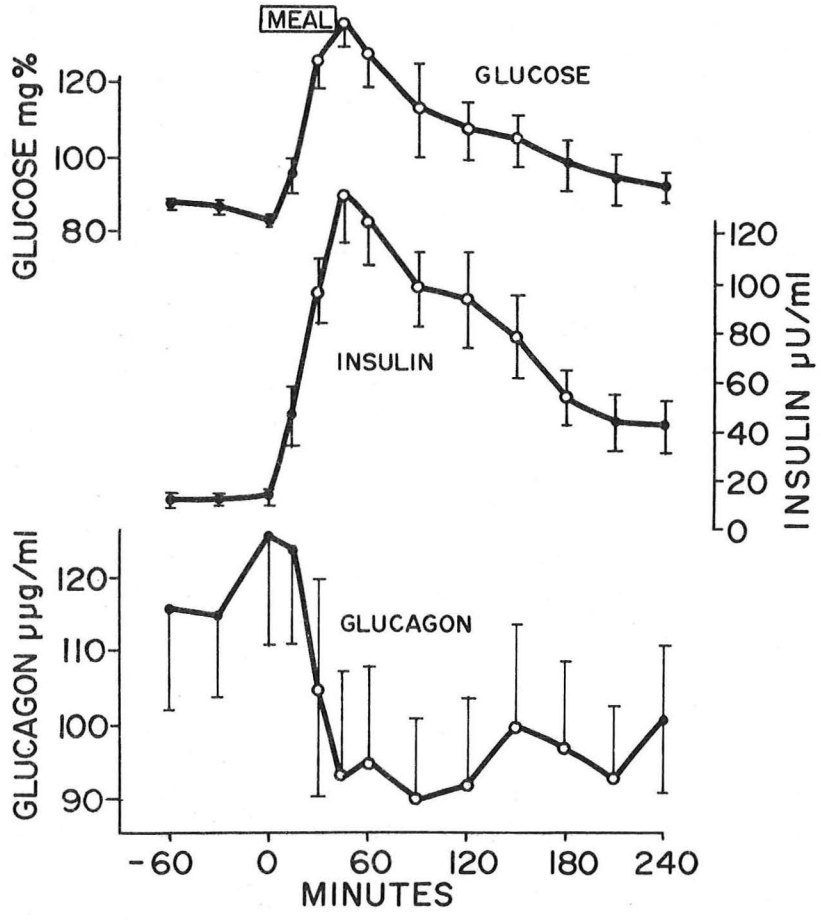
b. Glucose concentrations lowered <60 mg% normally will almost always stimulate glucose concentration, irrespective of the cause of the hypoglycemia (insulin, sulfonylurea, phloridzin) (38, 39, 40).

c. Between these two extremes, glucagon secretion will be influenced by other variables.

2. Physiologic Conditions:

a. Carbohydrate Feeding: The ingestion of a carbohydrate meal causes, in normal subjects, a prompt fall in plasma glucagon as insulin rises (45). The decline in glucagon is vital to permit a maximum insulin-directed storage of the ingested glucose, the resulting "glucose tolerance curve" reflecting the net response of the two hormones. In other words, if the same insulin response was accompanied by less complete glucagon suppression, storage of glucose would be retarded and "glucose tolerance" less "normal".

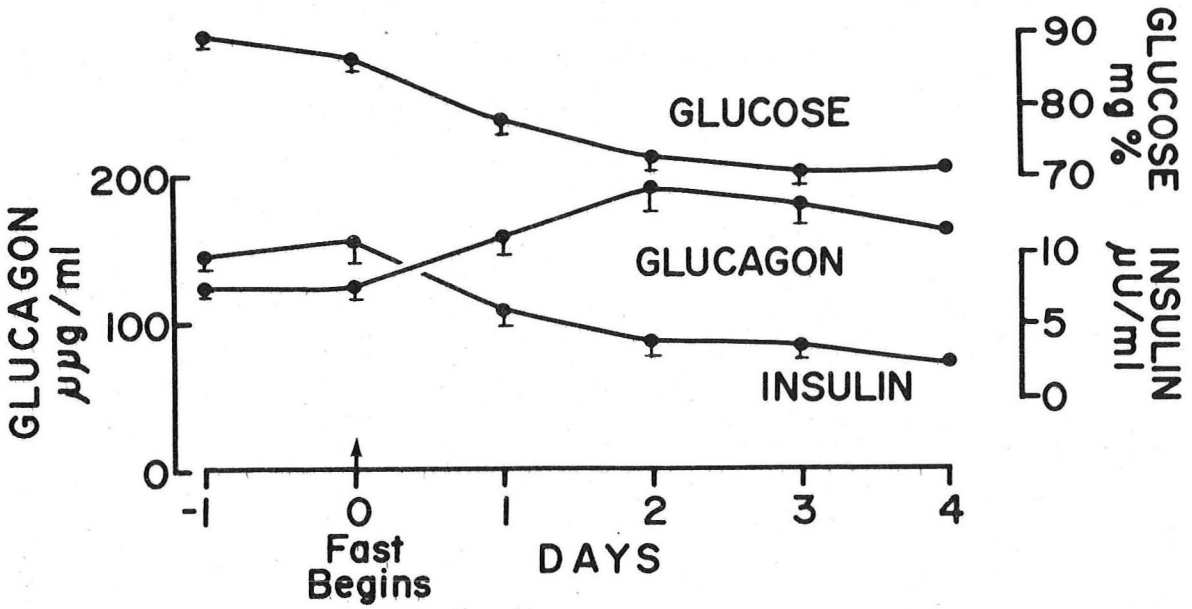
GLUCAGON RESPONSE TO A CARBOHYDRATE MEAL IN 11 NORMAL SUBJECTS



b. Glucose Deprivation. In starvation, which is the only natural non-pathologic and non-experimental form of glucose need, glucagon rises during the first 5 days and insulin falls reciprocally. This bihormonal adjustment does the following: 1) it increases production of amino acids, primarily alanine, in muscle; 2) it increases uptake of amino acids by the liver; and, 3) glucose production from amino acids is increased (41).

This 3-5 day period of hyperglucagonemia coincides precisely with the period of maximal gluconeogenosis, as reported by Cahill's group (42). If starvation continues past 5 days, the brain turns from glucose to ketones as its major energy source so as to spare body protein (43); glucagon secretion during this period declines (44). If during prolonged starvation, small doses (100 mμg/minute) of glucagon are infused at this time and the glucagon concentration raised to the previous levels, plasma alanine falls and gluconeogenesis is dramatically stimulated. It would appear that glucagon is a major force in controlling the metabolic response to starvation, i.e. to glucose deprivation.

EFFECT OF TOTAL STARVATION ON PLASMA GLUCAGON AND INSULIN



B. Role of Free Fatty Acid Concentration.

In dogs a rise in FFA, brought about by administering heparin during the infusion of a triglyceride emulsion, causes a fall in glucagon and a rise in insulin, which are reciprocal to each other (46). The changes of both hormones are small. Luyckx and LeFebvre report that a fall in FAA is associated with a rise in glucagon, and they regard glucagon as an important lipolytic hormone influenced importantly by FFA concentration (47).

MECHANISM OF INHIBITION OF GLUCAGON SECRETION BY PRODUCTS OF GLUCAGON-STIMULATED REACTIONS (Glucose, FFA).

Glucose, FFA, and ketones inhibit glucagon release from isolated islets of Langerhans in vitro (48, 49). In vivo and in vitro work suggest that the alpha cells are, in the basal state, "set" to secrete, just as the beta cells are "set" not to secrete. Just as nutrients are required to turn beta cells on, nutrients are required to turn alpha cells off. If one blocks glucose metabolism in a dog by infusing 2-deoxy-glucose, a non-metabolizable glucose analog which stops the Emden-Meyerhoff pathway at 2-deoxy-glucose-6 $-PO_4$, glucagon rises despite associated hyperglycemia (50). This suggests that metabolism of glucose within the alpha cell is essential to turn off glucagon secretion. Edwards and Taylor (49), report 1) that in vitro FFA and ketones are even more potent than glucose as inhibitors of glucagon release and 2) that inhibition of glucagon release by these fuels can be blocked by metabolic inhibitors such as cyanide, malonate, dinitrophenol, and iodoacetate. They believe that energy production within the alpha cell turns off glucagon release, just as it turns on insulin release, and that lack of energy in the alpha cell has the opposite effect, a unique but highly useful arrangement for a cell designed for maximum function during shortages of exogenous sources of energy (starvation).

C. Role of Amino Acid Concentration.

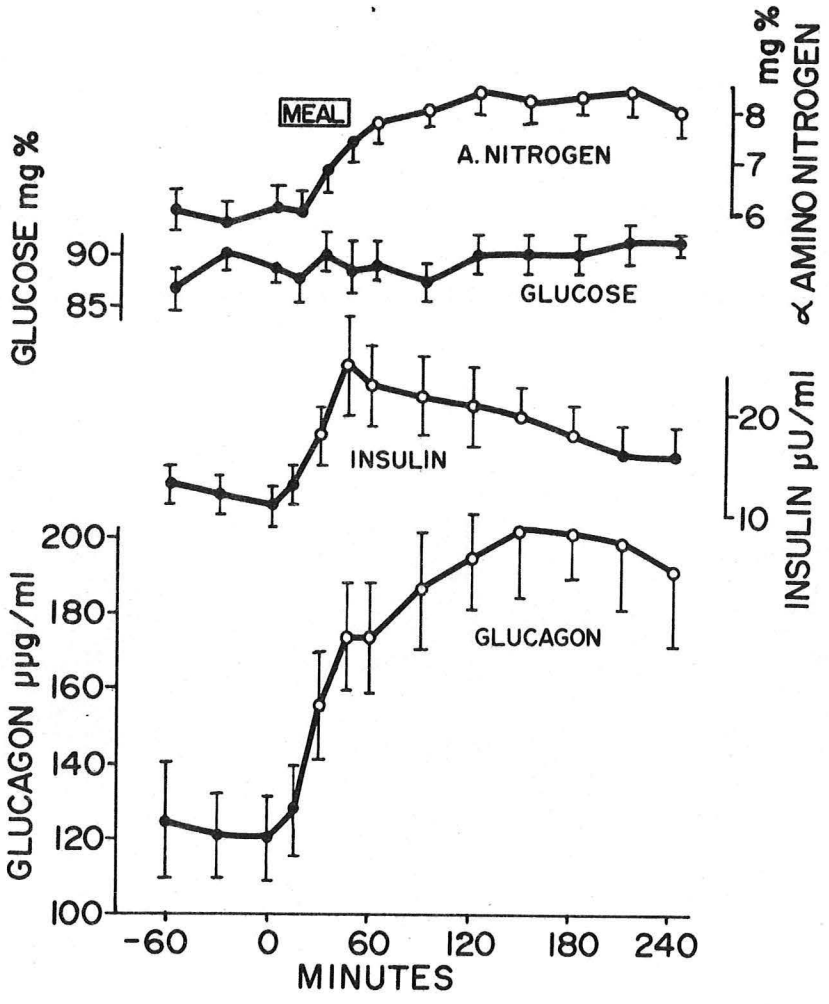
1. Experimental Conditions.
Infusion of amino acid mixtures stimulate glucagon in parallel with insulin (51, 52). The glucogenic amino acids alanine (53), and arginine (54) are potent stimuli, in contrast to the non-glucogenic branch chained amino acids. The metabolic results of this pattern of bihormonal secretion are thought to be as follows:

a. Insulin secretion facilitates net "storage" of amino acids, i.e. incorporation into protein; specifically, it reduces hepatic gluconeogenesis and causes a net uptake of amino acids by muscle and other tissues.

b. Glucagon's gluconeogenic effect on liver is minimized by the insulin, but its glycogenolytic effect prevents aminogenic hypoglycemia by replacing from hepatic glycogen the glucose which, together with amino acids, moves into tissues under the impact of insulin (52) [glucose is necessary for incorporation of amino acids into protein (56)] . If you infuse exogenous glucose together with the amino acids, aminogenic glucagon secretion is abolished -- it is unnecessary when exogenous glucose is readily available.

2. Physiologic Conditions: Ingestion of a large protein meal (60 g of lean beef) elicits a prompt rise in glucagon and insulin which reaches a plateau peak between 45 and 90 minutes and persists for 3 hours (45).

GLUCAGON RESPONSE TO A PROTEIN MEAL IN 14 NORMAL SUBJECTS



The function of this glucagon response is thought to be that described above, i.e. to facilitate incorporation of amino acids into protein by replacing glucose moving into tissues with amino acids. (If you eat potatoes with the beef, glucagon secretion is suppressed --- it obviously wouldn't be needed.)

NOTE: The glucagon response anticipates the rise in aminoacidemia and is somewhat greater than is observed with an identical level of amino acids delivered intravenously (58). This anticipatory and potentiating effect of ingested protein can be explained by protein-induced pancreozymin and secretin release. Pancreozymin is a potent stimulator of glucagon and insulin (59), while secretin stimulates insulin secretion only (60). Together these gut hormones are believed to provide advance warning to the islets concerning the magnitude of an incoming nutrient load, thus preparing the islet cells for a secretory response timed to meet, rather than follow, the incoming load. This so-called "enteroinsular axis" is believed to provide a "fine tuning control" of nutrient homeostasis (61), and thereby reduce hypernutrientemia after large nutrient loads.

CONTROL OF ISLET HORMONES BY NUTRIENTS AND GUT HORMONES

	NUTRIENTS			GUT HORMONES			
				PROTEIN-RESPONSIVE			GLUCOSE RESPONSIVE
	Glucose	Amino Acids	FFA	Pancreozymin	Secretin	Gastrin	Unidentified Factor
Insulin	↑	↑	↑	↑↑	↑	↑ ±	↑
Glucagon	↓	↑	↓	↑↑	—	—	—

VII. THE STATE AND BIOLOGICAL ACTIVITY OF IMMUNOASSAYABLE PLASMA GLUCAGON.

A. More than 90% extractable immunoreactive glucagon present in plasma after stimulation of alpha cell secretion by amino acids is present in free form and has a molecular size, as determed by gel filtration, which is indistinguishable from crystalline glucagon (MW 3485) (62). Less than 10% is in the >7000 M.W. zone indistinguishable in molecular size from "LGI". Thus, plasma glucagon appears not to differ from pancreatic glucagon in molecular size.

B. The glucagon-sized plasma fraction has the full glycogenolytic activity of crystalline glucagon when perfused into the isolated rat liver (62).

VIII. GLUCAGON VALUES IN NORMAL SUBJECTS.

	Glucagon mμg/ml (S.E.M.)
Fasting	108 ± 10 (50 - 220)
During Glucose Infusion (Glucose >200 mg%)	57 ± 8
Maximal Glucagon Fall below Fasting During a Carbohydrate Meal	↓ 54 ± 9
Maximal Glucagon Rise above Fasting During Arginine Infusion	239 ± 19 (100 - 400)
Maximal Glucagon Rise During a Protein Meal	↑ 121 ± 11

IX. COMMON DISORDERS OF GLUCAGON SECRETION

Case #1 - A 60-year old [redacted] male with a history of diabetes dating back 24 years. He receives 3.0 g of Orinase and 100 mg of DBI daily. His fasting glucose levels have ranged between 180 and 270 mg%.

Test of islet cell hormone function revealed the following:

	Glucose (mg%)	Insulin (μU/ml)	Glucagon ($\mu\mu$g/ml)
Fasting	286	8	190
Arginine Infusion	298	26	1100
Maximal Rise			810
Carbohydrate Meal	350	65	200
Maximal Fall			0
Protein Meal	324	45	580
Maximal Rise			390

This patient, like almost all genetic diabetics, demonstrates four abnormalities:

1. Relative fasting hyperglucagonemia. His glucagon is in the normal range, but a normal fasting glucagon level is intended to prevent hypoglycemia (if you give antiglucagon serum to fasted rats they become hypoglycemia [62]). This patient, whose glucose level is 286 mg%, is in no danger of hypoglycemia. In non-diabetic

subjects if one induces a blood glucose level of >200 mg% by means of a glucose infusion, the glucagon level falls below 60 mg%. Therefore, this patient has relative hyperglucagonemia. Marco found that extracts of his plasma contained a level of glycogenolytic activity by rat liver perfusion assay commensurate with the immunoassayable concentration of glucagon — therefore, it is biologically active glucagon, and it is maintaining a level of hepatic glucose production which, together with inappropriately low insulin level, is contributing to the steady state hyperglycemia.

2. Excessive Response of Glucagon Secretion to Arginine. Arginine provoked a massive outpouring of glucagon in this patient despite the hyperglycemia.

3. Non-Suppressibility of Glucagon in Response to a Carbohydrate Meal.

The relatively high fasting glucagon failed to decline in normal fashion during the first hour after a carbohydrate meal, despite increasing hyperglycemia >350 mg%. The inappropriately high glucagon, coupled with a subnormal rise in insulin, must combine (as in starvation) to maintain an inappropriately high net hepatic glucose output, and thus contribute to the abnormal glucose tolerance and to the subnormal FFA fall, which characterizes the diabetic state.

4. Excessive Response of Glucagon Secretion to a Protein Meal. Glucagon rose about 3 times as high as the maximal response of normal subjects, despite a glucose of 324 mg%, which, if induced in non-diabetics by glucose infusion, completely aborts the protein-induced glucagon secretion.

Thus, although there were excessive amounts of glucose in the ECF available to facilitate incorporation of the ingested amino acids into protein, etc., making additional hepatic glucose production quite unnecessary, glucagon was secreted anyway, and in supernormal amounts. The reduced insulin response to the meal would tend to limit incorporation of amino acids into protein, and permit an increased level of gluconeogenosis, which glucagon would further encourage.

A. SUMMARY OF ALPHA CELL ABNORMALITIES IN DIABETES MELLITUS (63, 64).

	Non-Diabetics	Adult-type Diabetics	Juvenile-type Diabetics	Hyperglycemic Non-Diabetics
Fasting Glucagon	108	114 N.S.	118 N.S.	57 $p<0.01$
Arginine Infusion	↑239	↑371 $p<0.01$	↑362 $p<0.01$	↑137 $p<0.01$
Carbohydrate Meal	↓45	↓ 0 $p<0.01$	↓ 0 $p<0.01$	--- ---
Protein Meal	↑121	↑124 N.S.	↑129 N.S.	↑ 0 $p<0.01$

CONCLUSION: Diabetics are relatively hyperglucagonemic at all times—in the fasting state and after carbohydrate or protein meals. This must exaggerate the metabolic consequences of insulin lack and contribute substantially to the net metabolic disorder and influence the control of the diabetes in an unfavorable way (63, 64).

Case #2: [redacted] a 37-year old [redacted] m. was admitted to [redacted] in diabetic ketoacidosis. admission lab work revealed a glucose of 520, serum acetone large at 1:4 dilution, a pH of 7.05.

His insulin was 0 μU/ml and his glucagon was 640 $\mu\mu$g/ml, about 6 X normal despite severe hyperglycemia.

After 400 U of insulin in 4-1/2 hours his glucose and glucagon returned to normal.

A. Summary of Findings in Diabetic Ketoacidosis (63).

1. Most patients with severe diabetic ketoacidosis have severe hyperglucagonemia, sometimes >1000 $\mu\mu$g/ml, despite marked hyperglycemia. Mild cases have only slight elevations.

2. With insulin therapy hyperglucagonemia recedes together with hyperglycemia and ketoacidosis.

3. Marco has tested extracts of ketoacidotic plasma in the rat liver perfusion bioassay and has found glycogenolytic activity commensurate with the immunoassayable glucagon present, indicating the glucagon is biologically active (66).

4. It would be surprising if the excess of active glucagon failed to increase the glucose abnormality, the ketonemia, and the amount of insulin required to reverse them.

MECHANISM OF THE ALPHA CELL ABNORMALITY IN DIABETES:

1. The disorder appears to be a non-suppressibility of the diabetic alpha cell to hyperglycemia, resulting in unnecessary and undesirable release of glucagon under circumstances, which should suppress its release.

2. Since glucose lack stimulates glucagon secretion, could it be that in diabetes, despite extracellular hyperglycemia, the alpha cell lacks glucose (or its critical product) intracellularly because of insulin deficiency and is thereby deceived into inappropriate secretion of glucagon? Is insulin lack the cause of the hyperglucagonemia?

Evidence for the Insulin Lack Theory

a. Severe alloxan diabetes in dogs results in extreme fasting hyperglucagonemia (>14,000 $\mu\mu$g/ml) rapidly corrected by insulin infusion (50).

b. Acute insulin deficiency induced by mannoheptulose infusion results in prompt hyperglucagonemia, which recedes promptly when mannoheptulose is stopped and insulin secretion resumes.

c. Human diabetic ketoacidosis is characterized by hyperglucagonemia reversed by insulin.

CONCLUSION: Clearly, insulin lack can cause hyperglucagonism, presumably by excluding glucose from the alpha cells and creating a deficiency of energy required to inhibit its secretion.

NOTE: However, there are certain puzzling facts that suggest that simple insulin lack does not explain the hyperglucagonemia of human diabetes.

1. Many of the adult diabetics who were hyperglucagonemic had insulin levels as high as some non-diabetics who exhibited a normal glucagon response.

2. The return to normal of the elevated glucagon values of many ketoacidotics in response to insulin therapy seems markedly delayed as compared to the rapid fall of glucagon when insulin is given to alloxan diabetic dogs with extreme hyperglucagonemia.

3. When adult diabetics who do not suppress normally during a carbohydrate meal are given such a meal, plus an insulin infusion, thereby producing insulin levels many times normal, glucagon still is not suppressed normally by the hyperglycemia.

4. In fact, if one infuses insulin and glucose (1U/g) in such diabetics, glucagon remains unsuppressed for up to 120 minutes, but does decline ultimately (67).

CONCLUSIONS: Diabetic alpha cells require exposure to larger quantities of insulin for longer periods of time before they can be suppressed by hyperglycemia.

X. WHAT THESE DATA SUGGEST ABOUT THE PATHOGENESIS OF DIABETES:

A. They rule out the possibility that diabetes is a consequence of primary occlusive disease of the capillaries of the islets of Langerhans.

In juvenile diabetes of 30 years duration, i.e. with beta cells presumably "dead" for 30 years, alpha cells respond as vigorously to arginine as do those of brand new juvenile diabetics. Clearly islet cell ischemia could not ischemically assault one cell type and spare the other. Even patients with terminal Kimmelsteil Wilson disease respond to arginine with a supernormal outpouring of glucagon.

B. They are compatible with the possibility that diabetes is a consequence of a diffusion barrier involving the capillaries of the islets of Langerhans.

A lack of energy stimulates alpha cell secretion and reduces beta cell secretion; a diffusion barrier to key nutrients, particularly glucose, would explain the abnormal behavior of both islet cells in diabetes. Or, a barrier to insulin, retarding its diffusion from islet capillaries into alpha cells, thereby reducing glucose entry, would explain the behavioe of alpha cells in diabetes. If thickened capillary basement membranes, retard the diffusion of insulin from the vascular compartment to tissues, the following puzzling aspects of diabetes would be explained: 1) the seemingly high fasting and post-glucose insulin levels noted in certain adult diabetics; 2) the delayed return of insulin to fasting values after glucose; and, 3) the apparent "resistance" to endogenous and exogenous insulin.

XIII. STUDIES OF THE DIFFUSION BARRIER HYPOTHESIS

A. Disappearance Time of Endogenous Insulin. After stopping an arginine infusion half-time of insulin disappearance appears to be >2X longer in adult diabetics with thickened membranes than in non-diabetics -- 30 minutes in diabetics versus 13 minutes in non-diabetics.

B. Glucagon Response to Arginine and Post-Arginine Disappearance Time of Endogenous Insulin in Prediabetics (Offspring of conjugal diabetics with normal GTT)

Only 5 prediabetics have been studies thus far; 3 of the 5, 4 of whom were known to have thickened MCBM, had an exaggerated glucagon response to arginine. If further studies should show an exaggerated glucagon response to arginine coupled with a delayed insulin disappearance time, strong support for the capillary diffusion barrier would be provided.

Patient	Age (yrs)	MCBM (Å)	Maximal Glucagon ↑ (μμg/ml)	Disappearance T 1/2 of Endogenous Insulin (minutes)
[redacted]	1.5	---	↑300	
[redacted]	37	1717	↑430	> 10
[redacted]	56	1481	↑390	> 30
[redacted]	55	1629	↑170	> 10
[redacted]	33	1660	↑135	> 10

XII. OTHER DISORDERS OF GLUCAGON SECRETION

Case #3

A 47 year old [redacted] male alcoholic entered with a 3-day history of nausea, vomiting and diarrhea. Physical revealed only dehydration without evidence of distress. There was hepatomegaly and moderate epigastric tenderness. Laboratory revealed glucose levels of 310 and 390 mg%. Acetone was positive at 1:4 dilution. SAD were 4 plus and large. CO_2 was 12 mEq/l Amylase was 167 (normal <161). 25 U of regular insulin brought the glucose down to 76 mg% but it rose to 225 mg% over the next 12 hours. Another 10 U brought it to normal. The patient remained normoglycemic thereafter and had a normal oral GTT at the time of discharge. His diagnoses included

chronic alcoholism and gastritis, possible acute pancreatitis and transient hyperglycemia of unknown etiology with ketoacidosis secondary to transient hypoinsulinism or starvation or both.

His islet cell hormone patterns were as follows:

Hrs After Adm	Glucose (mg%)	Insulin (μU/ml)	Glucagon ($\mu\mu$g/ml)	Insulin Rx (U)
1	230	9	1460	25U
2	100	68	1400	
3	61	72	1560	
6 1/2	58	27	1720	
9 1/2	126	17	1560	

The diagnosis of this patient is not clear; the radiologist suggests an inflammatory mass in the head of the pancreas, but other evidence of acute pancreatitis is marginal. Still, the diagnosis is acceptable. The 13-fold elevation of glucagon and its persistance is perhaps the best single bit of laboratory evidence for this. Release of glucagon from injured alpha cells could explain transient hyperglycemia and hypocalcemia of pancreatitis. However, Dr. Marco found little glycogenolytic activity in the sample of plasma obtained on admission, raising doubt as to activity of the circulating immunoassayable glucagon, which might have been tryptic fragments of glucagon.

Case #4

A 36 year old [redacted] male [redacted] was first admitted to the [redacted]ital on [redacted]68 with a chief complaint of increasing fatigue and a 64 lb. weight loss (200→ 126 lbs) despite increased appetite and food intake. In addition, he had noted polyuria and polydipsea of over a gallon per day for several months, associated with frequent loose stools which were greasy and floated. He has a long history of heavy alcohol intake, but denies abdominal pain. No family history of diabetes.

Physical revealed a w.n., w.d. [redacted] male with normal fundi. Only positive physical findings were absent ankle jerks and a wrist drop on the left.

Laboratory findings: Urinalysis: 4+ glycosuria, small acetone; plasma glucose 360 mg% serum acetone small 1:1; serum amylase 88; urine amylase 94 units/24 hours; urine lipase 0.2 units/24 hours; serum carotene 211 mg%; fecal fat 58g/24 hours. KUB revealed extensive pancreatic calcification.

His hyperglycemia was not controlled on 3 g of Orinase and he was begun on 15 U of NPH (AM) and 10 U NPH (PM). An arginine infusion test revealed fasting insulin and glucagon virtually at zero and these failed to rise perceptibly during the infusion.

He was discharged without enzyme therapy and returned for readmission on 4-3-69 because of cellulitis of neck and upper chest. His plasma glucoses fluctuated between 74 and 196 mg% on 10-20 U of NPH daily. He was discharged without any medication.

He is the only known subject who failed to exhibit a rise in glucagon during an arginine infusion and is regarded, therefore, as the only known case of glucagon deficiency. This may have explained his sensitivity to insulin, but, accompanied as it was by an insulin deficiency, produced no other apparent symptoms.

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