Special Article

Glucoregulatory Hormones in Health and Disease

A Teleologic Model

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SUMMARY

A teleologic model, based upon currently available knowledge of the glucoregulatory hormones, insulin, glucagon and growth hormone, has been presented in an effort to simplify understanding of their physiologic importance. The approach employed in this conceptual "repackaging" stresses in evolutionary terms the contribution of these hormones to the solution of critical problems of energy storage and supply, which, in their absence, would block phylogenetic progress.

Clinical disorders of glucoregulatory hormone secretion, both real and theoretical, are classified and briefly discussed. DIABETES *15*:500-06, July, 1966.

It is the purpose of this communication to assemble available information concerning the actions of the glucoregulatory peptide hormones, insulin, glucagon, and growth hormone, into a simplified teleologic model, in the hope of providing a more integrated perspective of the roles these hormones play in the regulation of blood glucose homeostasis both in health and in disease. The approach employed is that of evolutionary teleology rather than short-term physiology. It will be argued that the advent of the glucoregulatory peptide hormones in the course of phylogenetic development constituted an adaptive event of such great importance that evolutionary development, as we understand it, would otherwise have been insurmountably blocked.

To support this view, it must be assumed that the state of energy balance which prevails at the most primitive levels of the phylogenetic scale is extremely precarious, i.e., that the major expenditure of energy which such organisms generate is spent for energy-gathering purposes. Whatever slim "sliver" of positivity remains on their "energy balance sheet" must be invested in reproductive activities. In other words, such primitive creatures, in a very real sense, live to eat and eat to live, with just a little time off for reproductive activities. They are, therefore, prisoners of their energy requirements and lack the freedom to determine the direction of their activities, since deviation from their energy-gathering activities would lead quickly to starvation. Consequently, it may be argued that, even if these organisms were endowed with superior mental equipment such as the human brain, they would be unable to exploit it fully unless they solved the problem of energy balance, compressing their energy-gathering into discrete meal times. Moreover, a definite survival advantage would accrue from the ability to withstand prolonged starvation, not only in the basal state or during hibernation, but also during periods of increased energy consumption. Only in this way would it be possible, in time of famine, to outrun and capture scarce prey, to outrun or to outfight a rival for scarce food, or to migrate long distances from barren to fertile land areas.

EVOLUTIONARY PROBLEMS AND THEIR SOLUTIONS

Two closely interrelated problems blocking evolutionary development will be considered: First, the problem of precarious state of energy balance, and second, the problem of "brainlessness," i.e., the absence of a brain.

The obvious solution to the first problem would be the development of an energy storage depot. The fat cell is an ideal storage depot because of its almost unlimited capacity to expand according to need, and because of its ability to take up glucose and reshuffle the carbon atoms into readily storable triglycerides, from which the free fatty acids can be released instantaneously in easily transportable form for delivery to all portions of the body as a source of energy. It would seem, therefore, that the over-all problem of energy balance thus was solved in a simple and most ingenious fashion.

The second problem, that of "brainlessness," was solved by the development of a brain; however, the organ which evolved is an apparent example of "teleologic illogic," containing within it the seeds of its own de-

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struction in the form of dependence upon a single substrate, glucose. Consequently, the energy stores of the fat depot are worthless as a cerebral energy source. A possible explanation for this seemingly un-Darwinian circumstance is that other major sources of energy, such as free fatty acids and amino acids or their metabolites, in some way interfere with normal function of nervous tissue, leaving no choice but glucose. In any case, cerebral glucose dependence requires a special glucose producing system capable of maintaining a steady flow of glucose to the brain whenever exogenous glucose is unavailable. Ideally such a system would have the ability to provide both instantaneous flow of glucose toward the brain for emergency needs, and sustained glucose production for more extended glucose need. The problem of instantaneous glucose need was solved by storing glucose molecules in intact form as long-branched glycogen chains, and evolving the glycogenolytic enzymes necessary for their prompt release. However, the spatial limitations of the liver cell preclude storage of enough glucose to satisfy prolonged needs and consequently a system of gluconeogenic enzymes for the synthesis of new glucose from nonglucose precursors was required.

Although these systems provide the raw machinery necessary to store and release the energy needed both for glucose-independent and glucose-dependent tissues, the needs of the organism would be satisfied only when storage and release of energy are carefully coordinated with energy abundance and energy need. Inappropriate storage of glucose by fat or liver cells in time of glucose need would compete with, rather than aid, the energy needs of the brain. A system of controls was obviously required.

Control of glucose storage was accomplished by encasing the cells of fat, muscle, and certain other tissues for which glucose is not an obligatory substrate, in a lipoid membrane which, under basal conditions, is highly impermeable to glucose, and by developing a hormone of glucose storage, insulin, released in time of glucose abundance,[1] which would enhance glucose entry into these cells,[2] and promote glucose retention by liver cells.[3]

Whereas a single hormone, insulin, sufficed to control the problem of glucose abundance, the more life-threatening problem of glucose lack required an entire battery of glucoregulatory hormones. The glycogenolytic hormones include epinephrine which, in addition, suppresses insulin secretion,[4] and glucagon. The hormones of gluconeogenesis include glucagon[5] and ACTH via the corticosteroids. Thus, hepatic glucose production is activated for immediate and sustained activity by hormones which presumably are secreted in response to glucose need.

Despite this elaborate control of glucose production, the hepatic glucose-producing system is remotely situated from the brain, and glucose produced by the liver must travel through tissues which are capable of competing with the brain for its vital substrate. Even though, in the absence of insulin, the glucose-impermeable membrane theoretically excludes the glucose, during exercise muscle cells are capable of utilizing glucose even in the absence of insulin.[6] Consequently, a hormone of exercise is required to "guard" glucose against predatory usurpation by exercising muscle. It seems improbable that a bird could migrate thousands of miles without access to exogenous glucose and yet retain exquisite navigational skill, indicating perfect cerebral function, if substantial quantities of glucose were used by wing muscles. Growth hormone may be the hormone of exercise designed to prevent glucose wastage for muscle energy either by a direct action on cellular glucose metabolism, or via its adipokinetic effect, which mobilizes free fatty acids as an alternative and competitive substrate, or both.

Thus, the complicated machinery of energy storage and glucose production is carefully regulated by hormonal interplay to answer the needs of the organism. These problems and their solutions are summarized in table 1.

MEASUREMENTS OF THE GLUCOREGULATORY HORMONES

The availability of radioimmunoassays[7-9] for the peptide hormones considered in the foregoing teleologic model makes it possible to test its validity by direct measurement.

Studies employing the radioimmunoassay for insulin confirm a direct and almost parallel relationship between blood glucose concentration and insulin secretion[10] and will not be reviewed further. The development of a radioimmunoassay for glucagon in 1959[8] made possible studies designed to prove that glucagon was a hormone and to elucidate its role in the regulation of blood glucose homeostasis[11,12]; similarly, in 1963, Roth, Glick, Yalow and Berson established by radioimmunoassay the role of growth hormone in glucoregulation.[13] Since experimental support for the roles of glucagon and growth hormone has been reviewed previously,[14,15] it will be but briefly summarized here.

All experiments described were designed to determine

TABLE 1

Evolutionary problems and the contribution of glucoregulatory hormones to their solution

Problems	Solution	Specific device	Secondary problems	Solution	Specific device
I. Precarious energy balance	Energy storage depot	Fat cell which stores glucose and releases FFA	Appropriate regulation of storage activity of fat cell	Glucose impermeable cell membrane made permeable only during hyperglycemia by a hormone of glucose abundance	Insulin
II. "Brainlessness"	Brain	A glucose-dependent encephalon			
III. Glucose dependence of brain	Glucose-producing system	Liver cell	1. Appropriate regulation of glucose production	Hormones	
		which:		which:	
	a. for immediate glucose needs	*a.* releases stored glucose (glycogenolytic enzyme system)	*a.* for immediate needs	*a.* stimulate glycogenolysis	*a.* Epinephrine glucagon
	b. for sustained glucose needs	*b.* manufactures new glucose (gluconeogenic enzyme system)	*b.* for sustained needs	*b.* stimulate gluconeogenesis	*b.* Glucagon ACTH-cortisol
			2. Prevention of wasteful glucose utilization by exercising muscle	Hormone of exercise to block peripheral glucose utilization and provide other substrate (FFA)	Growth hormone

the impact of glucose need upon glucagon and growth hormone secretion. In dogs, glucose need resulting from profound insulin-induced hypoglycemia was accompanied by a progressive rise in glucagon secretion, which, at the end of 180 min., reached a level more than three times the baseline level.[11] Similarly, insulin hypoglycemia in normal humans resulted in a striking rise in plasma growth hormone secretion.[13]

Another form of glucose need has been induced in dogs by phloridzin administration,[11] which, by impairing tubular reabsorption of glucose, produces a renal "glucose leak." Animals made chronically hypoglycemic by this technic had a mean glucagon concentration of over 1,000 μμg/ml., in contrast to a mean of 500 μμg/ml. in the normoglycemic control group, a highly significant difference.

After 48 hrs. of starvation, glucagon concentration in the peripheral venous plasma of five male volunteers rose in every individual, and at the end of 72 hrs., the mean glucagon concentration was approximately three times the prestarvation average.[12] A modest rise in growth hormone concentration also occurred,[13] but this was small compared to the growth hormone response to hypoglycemia.

TABLE 2

Effect of glucose need upon glucoregulatory hormone secretion

Cause of glucose need	Insulin	Glucagon	Growth hormone
Insulin hypoglycemia	—	↑	↑
Phloridzin	↓	↑	*
Exercise	*	*	↑
Starvation	↓	↑	↑

* = Not measured

Exercise caused a dramatic rise in the growth hormone level[21]; glucagon concentration has not been studied in exercise. The effects of these various forms of glucose need upon the secretion of glucoregulatory hormones are summarized in table 2.

In the case of glucagon, rapid termination of glucose

need by intravenous glucose loading results in return of the elevated levels of glucagon to normal.[11] Glucose loading has a similar effect upon elevations of growth hormone.[13]

From this, it would seem that the secretion of glucagon and growth hormone increases in glucose need and returns to normal when glucose need ends. These findings would fit in well with the postulated functions of the hormones, namely, maximization of hepatic glucose production by glucagon, and the minimization of peripheral glucose utilization by growth hormone.

However, recent work suggests that glucagon may play a significant role during glucose abundance as well as during glucose need. The demonstration by Samols[16] and Crockford[17] that glucagon stimulates insulin release was followed by the observations of Lawrence[18] and Samols[19] that large doses of orally administered glucose evoke a rise in plasma glucagon levels; these findings are not in keeping with the role of glucagon as a hormone of glucopenia alone and suggest that it may play an additional role in time of glucose abundance. Current work in our laboratory suggests that pancreozymin elicits the release of both glucagon and insulin from the pancreas, as does the ingestion of a large meal. On this basis, it is tempting to suggest that food results in the release of either glucagon from the small intestine or of a hormone which stimulates the release of pancreatic glucagon which in turn potentiates the stimulatory action of hyperglycemia upon insulin release.

The teleology of the simultaneous emergence of glucagon and insulin during glucose feeding is somewhat perplexing. If it is assumed that, in a setting of glucose abundance, the action of glucagon is primarily glycogenolytic, the net effect of this bihormonal secretion upon the distribution of glucose storage would be to limit hepatic glycogen while favoring deposition of muscle glycogen. A possible survival advantage of this arrangement is suggested by the studies of Saltine[20] which indicate that the ability to perform exhausting muscular work is reduced when muscle glycogen stores are depleted; by increasing the ratio of muscle to liver glycogen, this function of glucagon might extend the limits of physical endurance.

ABNORMALITIES OF GLUCOREGULATORY HORMONE SECRETION

If the foregoing hormonal interrelationships are important for normal regulation of blood glucose homeostasis, abnormal glucoregulatory hormone secretion could cause or be caused by disturbances in blood glucose homeostasis. Table 3 gives a list of the possible disorders of glucoregulatory hormone secretion, both real and postulated.

Syndromes in which hormone secretion is excessive will be separated into primary and secondary categories; syndromes in which hormonal secretion is deficient will

TABLE 3

Disorders of glucoregulatory hormone secretion

	Insulin	Glucagon	Growth hormone
Hypersecretion	*Primary* Malignant insulinoma Benign insulinoma Aminogenic hypoglycemia	*Primary* Malignant glucagonoma ? Benign glucagonoma ? Hyperglucagonism ? Paraendocrine tumor	*Primary* Eosinophilic tumors with acromegaly or gigantism
	Secondary Obesity Acromegaly Minimal diabetes (not always)	*Secondary* Hypoglycemia ? Starvation ? Exercise	*Secondary* Exercise Hypoglycemia Starvation Severe diabetic ketoacidosis Surgical stress ? Addison's disease
Hyposecretion	*Partial* Moderately to markedly severe diabetes, ketoacidosis-resistant type Tumor-induced hypoglycemia (non-islet cell)	*Partial* ? Idiopathic infantile hypoglycemia	*Partial* ? Moderate growth retardation Obesity ? Hypercorticoidism
	Complete Ketoacidosis-prone diabetes Complete destruction or removal of pancreas	*Complete* ? Insulin-sensitive, ketoacidosis-prone diabetes	*Complete* Panhypopituitarism Isolated growth hormone deficiency

be classified as either partial or complete.

1. INSULIN

Primary excess: Benign and malignant beta cell tumors, and perhaps the syndromes of aminogenic hypoglycemia, can be classified as examples of primary hyperinsulinemia.

Secondary excess: In obesity, plasma insulin is elevated both in the fasting state and after glucose;[22] such elevations are, presumably, examples of secondary hyperinsulinemia, since they disappear when obesity is corrected, and may represent a compensatory beta cell response to some type of peripheral insulin resistance, perhaps caused by higher tissue fatty acid levels.

Even in the absence of obesity, insulin levels are increased in some, but not all, mild ketoacidosis-resistant diabetics.[10] However, in nonobese prediabetics (persons with a normal glucose tolerance test who have two diabetic parents) plasma insulin levels in the fasting state and after glucose do not differ from those of controls.[23]

Deficiency: As ketoacidosis-resistant diabetes becomes more severe, a decline in insulin secretion relative to blood glucose concentration becomes increasingly apparent, and in established ketoacidosis-prone diabetes a complete primary insulin deficiency exists.[24]

A secondary inhibition in insulin secretion is observed, even after glucose or tolbutamide, in tumor-induced hypoglycemia[25] presumably caused by a circulating insulin-like material.

2. GLUCAGON

Primary excess: The first proven instance of a disorder of glucagon secretion was recently established.[26] A forty-two-year-old white female was recently shown by McGavran et al. to have a carcinoma with all of the histochemical and ultrastructural characteristics of alpha cells. The primary tumor contained enormous tissue concentrations of extractable glucagon, 14 μg/gm. of wet weight, which is more than in the tail of a human pancreas. The patient's fasting plasma glucagon level ranged from 17-56 mμg/ml.; normal levels for this laboratory are less than 2 mμg/ml. The patient's hyperglycemic and hyperinsulinemic response to usual test doses of glucagon was markedly attenuated. Extracts of her tumor had both the hyperglycemic and hyperinsulinemic activity of identical quantities of commercial glucagon when injected into a test animal.

Deficiency: The possibility that certain hypoglycemic syndromes are a consequence of glucagon deficiency has long been entertained. Certain forms of idiopathic infantile hypoglycemia have been particularly suspect. Plasma glucagon has been measured in only one case of McQuarrie's syndrome, a patient of Dr. Maria New. At a time when the blood glucose level was 22 mg. per 100 ml., this child had a glucagon level of 370 $\mu\mu$g./ml., a low normal value. Although this result could be interpreted as an inadequate response to hypoglycemic provocation, the presence of substantial quantities of circulating glucagon excludes absolute glucagon deficiency as the cause of this child's hypoglycemia.

Although Grollman has recently reported the apparent absence of alpha cells in patients with hypoglycemia, glucagon deficiency was not verified by glucagon assay.[27]

Deficiency of glucagon has been suggested as a possible cause of the insulin sensitivity which often occurs in the brittle ketoacidosis-prone diabetic. Nine pancreases collected from such patients were extracted and assayed for glucagon. Four of the pancreases were virtually devoid of glucagon, while the other five had levels within the normal range. However, the absence of extractable glucagon has, on occasion, been noted in pancreas from nondiabetic patients, and the significance of the findings is consequently uninterpretable.

3. GROWTH HORMONE

Primary excess: Acromegaly and gigantism due to eosinophilic tumors of the hypophysis are well-known causes of primary growth hormone excess.

Secondary excess: In addition to the physiologic causes of secondary growth hormone hypersecretion, exercise, starvation, and hypoglycemia, inappropriate secondary growth hormone secretion of considerable magnitude despite hyperglycemia has recently been noted in some cases of severe diabetic ketoacidosis.[28] It is possible that insulin lack results in exclusion of glucose from the insulin-dependent pituitary cell and that "intracellular hypoglycemia" stimulates growth hormone secretion in a manner similar to 2-deoxyglucose administration;[21] however, there are other equally plausible alternative explanations for these findings.

Secondary hypersomatotropinemia has also been observed in many patients during and just after surgery,[29] even in the presence of sustained hyperglycemia. In table 4 a group of patients exhibit elevations in plasma growth hormone levels despite hyperglycemia induced by the continuous infusion of 5 per cent glucose; thus, during surgical stress, the "negative feedback" effect of hyperglycemia is inoperative, and a marked increase in growth hormone secretion is noted. In teleologic terms, surgically induced hypersomatotropinemia may be part of a general increase in counter-regulatory hormone secretion designed to elevate arterial glucose concen-

TABLE 4

Growth hormone levels during continuous glucose infusion before and after surgery

Patient		Preoperative	Hours postoperative 1	2	3	Procedure
R.B.	BS	152	164	138	126	Iliac endarterectomy
	HGH	0.6	11.8	16.0	7.6	
C.C.	BS	170	150	164	196	Iliac endarterectomy
	HGH	0.5	7.1	3.4	11.7	
L.H.	BS	138	240	150	162	Resection of omental
	HGH	0	31.0	24.8	1.8	phlegmon
J.H.	BS	120	186	150	117	Resection of floor
	HGH	0	23.6	14.6	11.4	of mouth
N.S.*	BS	173	663	332	288	Renal endarterectomy
	HGH	1.0	5.2	16.3	8.6	
R.T.*	BS	234	444	374	220	Portocaval shunt with
	HGH	13.5	84.0	73.0	62.5	near-exsanguination

*Diabetic

tration to levels which will maintain the rate of cerebral glucose delivery despite a decline in cerebral blood flow.

Preliminary evidence, as yet inconclusive, suggests that prediabetes may be associated with a type of growth hormone hypersecretion. A recent study of prediabetic subjects revealed an exaggeration of the normal rebound of plasma growth hormone between three to five hours after glucose ingestion. However tantalizing these findings, considerable extension of the study is required before this apparent growth hormone hyperresponsiveness can be accepted.

In view of the demonstration of a suppressive effect of steroids upon growth hormone secretion,[30] one might predict that Addison's disease would be associated with secondary hypersomatotropinemia.

Complete deficiency: Complete growth hormone deficiency may exist as a consequence of anterior pituitary disease, either as an isolated hormonal defect or as a part of polyhormonal pituitary deficiency.

Partial deficiency: Diseases of the pituitary gland may, of course, lead to partial growth hormone deficiency. Recently, unexplained hypofunction has been recognized in obesity, in which a sluggish response of growth hormone secretion to such stimuli as starvation and exercise occurs.[31] It is reasonable to wonder if the combination of hyperinsulinemia and hyposomatotropinemia which characterizes obesity, i.e., an excess of a "storage" hormone and a deficit of an "antistorage" hormone, reduces the effectiveness of weight reduction regimens and thus encourages the persistence of obesity.

One would predict that Cushing's disease is associated with reduced levels of plasma growth hormone, secondary to the suppressive effect of the high levels of cortisol.

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REFERENCE

[1] Grafe, E., and Meythaler, F.: Beitrag zur Kenntnis der Insulinproduction. Naunyn-Schmeideberg's Arch. Exp. Path. Pharmak. *125*:181, 1927.

[2] Levine, R., and Goldstein, M. S.: On the mechanism of the action of insulin. Recent Progr. Hormone Res. *11*:343, 1955.

[3] Madison, L. L., Combes, B., Strickland, W., Unger, R. H., and Adams, R.: Evidence for a direct effect of insulin on hepatic glucose output. Metabolism *8*:469, 1959.

[4] Porte, D., Jr., Graber, A., Kuzaya, T., and Williams, R. H.: Epinephrine inhibition of insulin release. J. Clin. Invest. *45*: 228, 1966.

[5] Izzo, J. L., and Glasser, S. R.: Comparative effects of glucagon, hydrocortisone, and epinephrine on protein metabolism of the fasting rat. Endocrinology *68*:189, 1961.

[6] Sanders, C. A., Levinson, G. E., Abelman, W. H., and Freinkel, N.: Effect of exercise on the peripheral utilization of glucose in man. New Eng. J. Med. *271*:220, 1964.

[7] Berson, S. A., and Yalow, R. S.: Isotopic tracers in the study of diabetes. Advanced Biol. Med. Phys. *6*:349, 1958.

[8] Unger, R. H., Eisentraut, A. M., McCall, M. S., Keller, S., Lanz, H. C., and Madison, L. L.: Glucagon antibodies and their use for an immunoassay for glucagon. Proc. Soc. Exp. Biol. Med. *102*:621, 1959.

[9] Utiger, R. D., Parker, M. L., and Daughaday, W. H.: Studies on human growth hormone. I. A radioimmunoassay for human growth hormone. J. Clin. Invest. *41*:254, 1962.

[10] Yalow, R. S., and Berson, S. A.: Immunoassay of endogenous plasma insulin in man. J. Clin. Invest. *39*:1157, 1960.

[11] Unger, R. H., Eisentraut, A. M., McCall, M. S., and Madison, L. L.: Measurements of endogenous glucagon in plasma and the influence of blood glucose concentration upon its secretion. J. Clin. Invest. *41*:682, 1962.

[12] Unger, R. H., Eisentraut, A. M., and Madison, L. L.: The effect of total starvation upon the levels of circulating glucagon and insulin in man. J. Clin. Invest. *42*:1031, 1963.

[13] Roth, J., Glick, S. M., Yalow, R. S., and Berson, S. A.: Hypoglycemia: A potent stimulus to secretion of growth hormone. Science *140*:987, 1963.

[14] Unger, R. H., and Eisentraut, A. M.: Studies of the physiologic role of glucagon. Diabetes *13*:563, 1964.

[15] Roth, J., Glick, S. M., Yalow, R. S., and Berson, S. A.: The influence of blood glucose on the plasma concentration of growth hormone. Diabetes *13*:355, 1964.

[16] Samols, E., Mari, G., and Marks, V.: Promotion of insulin by glucagon. Lancet *7409*:415, 1965.

[17] Crockford, P. M., Porte, D., Wood, F. C., and Williams, R. H.: Effect of glucagon on serum insulin, plasma glucose, and FFA in man. Metabolism *15*:114, 1966.

[18] Lawrence, A.: Radioimmunoassayable glucagon levels in man: Effects of starvation, hypoglycemia, and glucose administration. Proc. National Acad. Sci. *55*:2, 1966.

[19] Samols, E., Tyler, J., Mari, G. and Marks, V.: Stimulation of glucagon secretion by oral glucose. Lancet *7425*:1257, 1965.

[20] Saltine, B.: Unpublished observations.

[21] Roth, J., Glick, S. M., Yalow, R. S., and Berson, S. A.: Secretion of human growth hormone: Physiologic and experimental modification. Metabolism *12*:577, 1963.

[22] Karam, J. H., Grodsky, G. M., and Forsham, P. H.: Excessive insulin response to glucose in obese subjects as measured by immunochemical assay. Diabetes *12*:197, 1963.

[23] Unger, R. H., Siperstein, M. D., and Madison, L. L.: Insulin levels in prediabetes. To be published.

[24] Berson, S. A., and Yalow, R. S.: Immunoassay of plasma insulin. Immunoassay of hormones. Ciba Foundation Colloquia on Endocrinology *14*:182, 1962.

[25] Samols, L.: Hypoglycemia in neoplasia. Postgrad. Med. J. *39*:634, 1963.

[26] McGavran, M. H., Unger, R. H., Recant, Lillian, Polk, H. C., Kilo, Charles, and Levin M. E.: Glucagonoma: The identification of a glucagon-secreting-alpha-cell-carcinoma of the pancreas. New Eng. J. Med. *274*:1408, 1966.

[27] Grollman, A., McCaleb, W. E., and White, F. N.: Glucagon deficiency as a cause of hypoglycemia. Metabolism *13*: 686, 1964.

[28] Unger, R. H.: High growth hormone levels in diabetic ketoacidosis. JAMA *191*:945, 1964.

[29] Schalch, D. S.: The effect of physical stress and exercise in the human on growth hormone and insulin secretion. Clin. Res. *13*:334 (Abstract), 1965.

[30] Frantz, Andrew G., and Rabkin, Mitchell T.: Human growth hormone—Clinical measurements, response to hypoglycemia and suppression of corticosteroids. New Eng. J. Med. *271*:1375, 1964.

[31] Beck, P., Koumans, J. H., Winterling, C. A., Stein, F., Daughaday, W. H., and Kipnis, D. M.: Studies of insulin and growth hormone secretion in human obesity. J. Lab. Clin. Med. *64*:654, 1964.