

Effects of physiologic levels of glucagon and growth hormone on human carbohydrate and lipid metabolism. Studies involving administration of exogenous hormone during suppression of endogenous hormone secretion with somatostatin.

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Research Article

To study the individual effects of glucagon and growth hormone on human carbohydrate and lipid metabolism, endogenous secretion of both hormones was simultaneously suppressed with somatostatin and physiologic circulating levels of one or the other hormone were reproduced by exogenous infusion. The interaction of these hormones with insulin was evaluated by performing these studies in juvenile-onset, insulin-deficient diabetic subjects both during infusion of insulin and after its withdrawal. Infusion of glucagon (1 ng/kg-min) during suppression of its endogenous secretion with somatostatin produced circulating hormone levels of approximately 200 pg/ml. When glucagon was infused along with insulin, plasma glucose levels rose from 94 +/- 8 to 126 +/- 12 mg/100 ml over 1 h (P less than 0.01); growth hormone, beta-hydroxy-butyrate, alanine, FFA, and glycerol levels did not change. When insulin was withdrawn, plasma glucose, beta-hydroxybutyrate, FFA, and glycerol all rose to higher levels (P less than 0.01) than those observed under similar conditions when somatostatin alone had been infused to suppress glucagon secretion. Thus, under appropriate conditions, physiologic levels of glucagon can stimulate lipolysis and cause hyperketonemia and hyperglycemia in man; insulin antagonizes the lipolytic and ketogenic effects of glucagon more effectively than the hyperglycemic effect. Infusion of growth hormone (1 mug/kg-h) during suppression of its endogenous secretion with somatostatin produced circulating hormone levels of approximately 6 ng/ml. When growth [...]

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Effects of Physiologic Levels of Glucagon and Growth Hormone on Human Carbohydrate and Lipid Metabolism

STUDIES INVOLVING ADMINISTRATION OF EXOGENOUS HORMONE DURING SUPPRESSION OF ENDOGENOUS HORMONE SECRETION WITH SOMATOSTATIN

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ABSTRACT To study the individual effects of glucagon and growth hormone on human carbohydrate and lipid metabolism, endogenous secretion of both hormones was simultaneously suppressed with somatostatin and physiologic circulating levels of one or the other hormone were reproduced by exogenous infusion. The interaction of these hormones with insulin was evaluated by performing these studies in juvenile-onset, insulin-deficient diabetic subjects both during infusion of insulin and after its withdrawal.

Infusion of glucagon (1 ng/kg·min) during suppression of its endogenous secretion with somatostatin produced circulating hormone levels of approximately 200 pg/ml. When glucagon was infused along with insulin, plasma glucose levels rose from 94 ± 8 to 126 ± 12 mg/100 ml over 1 h ($P < 0.01$); growth hormone, β -hydroxybutyrate, alanine, FFA, and glycerol levels did not change. When insulin was withdrawn, plasma glucose, β -hydroxybutyrate, FFA, and glycerol all rose to higher levels ($P < 0.01$) than those observed under similar conditions when somatostatin alone had been infused to suppress glucagon secretion. Thus, under appropriate conditions, physiologic levels of glucagon can stimulate lipolysis and cause hyperketonemia and hyperglycemia in man; insulin antagonizes the lipolytic and ketogenic effects of glucagon more effectively than the hyperglycemic effect.

Infusion of growth hormone (1 μ g/kg·h) during suppression of its endogenous secretion with somatostatin

produced circulating hormone levels of approximately 6 ng/ml. When growth hormone was administered along with insulin, no effects were observed. After insulin was withdrawn, plasma β -hydroxybutyrate, glycerol, and FFA all rose to higher levels ($P < 0.01$) than those observed during infusion of somatostatin alone when growth hormone secretion was suppressed; no difference in plasma glucose, alanine, and glucagon levels was evident. Thus, under appropriate conditions, physiologic levels of growth hormone can augment lipolysis and ketonemia in man, but these actions are ordinarily not apparent in the presence of physiologic levels of insulin.

INTRODUCTION

The physiologic importance of glucagon and growth hormone in human carbohydrate and lipid homeostasis is poorly understood. Administration of pharmacologic amounts of glucagon can augment lipolysis (1-4), ketogenesis (1-4), and glucose production (1-5) in man, but these effects are difficult to interpret because such quantities of glucagon may promote growth hormone (6) and catecholamine (7) release. Moreover, similar results have not been consistently observed in studies using physiologic concentrations of glucagon (3, 8, 9). Evidence for the participation of growth hormone in human lipid and carbohydrate metabolism is based largely on results obtained after administration of pharmacologic quantities of growth hormone and on observations in hypophysectomized individuals. Growth hormone, when administered in pharmacologic doses, reportedly diminishes glucose utilization (10-15) and promotes lipolysis (10, 16) and ketosis (10, 15, 16) in man, but similar

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TABLE I
Clinical Characteristics of Diabetic Subjects

Subject	Age	Sex	Ideal body weight*	Duration of diabetes	Daily insulin requirement
	yr		%	yr	U
G. H.	29	M	99	21	60
R. O.	26	M	99	14	50
J. A.	25	M	92	8	45
R. T.	30	M	88	8	60
R. A.	30	M	97	27	70
J. G.	22	M	100	8	50
D. S.	19	F	108	12	45
J. R.	24	M	94	9	50

* Based on Metropolitan Life Insurance Co. tables.

effects have not been reported with physiologic quantities. Moreover, although hypophysectomy diminishes lipolysis, ketosis, and insulin requirements in diabetic subjects (10), these metabolic effects may not reflect growth hormone deprivation alone (17) because mobilization of FFA and ketosis can occur in growth hormone-deficient man (18, 19).

Recently, a new approach to the study of glucagon and growth hormone physiology has been made possible by the discovery of somatostatin. This hypothalamic peptide (20) inhibits the secretion of human glucagon (9, 21–23), insulin (23–26), and growth hormone (24, 27, 28) but has no intrinsic effect on glucose (22, 29, 30) or lipid (31, 32) metabolism. Infusion of somatostatin lowers plasma glucose, glucagon, and growth hormone levels in normal man (20, 28) and in insulin-dependent diabetics (21). Since similar decrements in plasma glucose levels also occur in hypophysectomized diabetic and normal subjects who lack growth hormone (21, 22), these studies have provided direct evidence that endogenous glucagon participates in normal glucose homeostasis and contributes to diabetic hyperglycemia in man. More recently, somatostatin has been shown to diminish markedly the rises in plasma FFA, glycerol, and β -hydroxybutyrate levels observed after acute withdrawal of insulin from ketosis-prone, insulin-dependent diabetics (33). These results were interpreted to indicate that endogenous glucagon secretion influences lipolysis and ketogenesis in man; however, because similar effects are seen after hypophysectomy in diabetics (10), the suppression of growth hormone secretion by somatostatin could not be excluded as a possible explanation.

The present studies were undertaken to characterize further the roles of glucagon and growth hormone in human carbohydrate and lipid metabolism by evaluating the contributions of these hormones to the metabolic derangements observed after acute withdrawal of insulin

from ketosis-prone, insulin-dependent diabetic subjects. To assess the contribution of each hormone individually, endogenous secretion of both was suppressed with somatostatin, and one or the other was infused at doses chosen to approximate circulating levels found spontaneously after acute insulin withdrawal (33, 34).

METHODS

Subjects

Informed consent was obtained from eight patients with juvenile-onset, insulin-dependent diabetes mellitus. (Their pertinent clinical characteristics are shown in Table I). All had volunteered previously as research subjects, and none were acutely ill at the time of the present studies.

Experimental protocol

After admission to a metabolic ward, subjects were maintained for at least 36 h on a 2,200-Cal American Diabetes Association diet and s.c. regular U-100 insulin (10–15 U every 8 h; from Eli Lilly Co., Indianapolis, Ind.). In order to ensure abrupt insulin withdrawal, patients were maintained solely on i.v. regular insulin for 14–16 h beginning the afternoon of the day before testing. This consisted of 5–10 U as a bolus before dinner followed by an infusion (20 U dissolved in 60 ml of 0.9% saline solution containing 0.6 ml of the subject's plasma). Plasma glucose levels were monitored periodically, and the rate of infusion was adjusted to maintain normoglycemia. This resulted in an average infusion rate of 1 U/h. After an overnight fast, a 0.9% saline infusion was begun between 6 and 8 a.m. in the other arm. After a 30-min equilibration period, appropriate base-line blood specimens were obtained at the saline infusion site and the insulin infusions were stopped.

Four experimental protocols were used:

Saline. The metabolic consequences of acute insulin deficiency were observed for 8 h, during which a 0.9% saline solution was infused (100 ml/h) after cessation of the insulin infusion.

Somatostatin. Instead of the saline used in the above protocol, synthetic linear somatostatin (kindly provided by Dr. Roger Guillemin of The Salk Institute, San Diego, Calif., and prepared as previously described [33]) was infused for 6 h at a rate of 500 μ g/h after cessation of the insulin infusion. A 2-h infusion of saline solution followed.

Glucagon and somatostatin. 1 h before stopping the insulin infusion, a constant infusion of glucagon (1 ng/kg·min; from Eli Lilly Co.) was begun and continued for a total of 7 h. This dose was chosen because a previous report (9) indicated that it would produce circulating glucagon levels (150–250 pg/ml) similar to those observed after acute withdrawal of insulin (33, 34). Somatostatin was infused as described above for 8 h via a different syringe upon stopping the insulin infusion.

Growth hormone and somatostatin. 1 h before stopping the insulin infusion, an infusion of human growth hormone (kindly provided by Dr. C. H. Li of the Hormone Research Laboratory, University of California, San Francisco, Calif.), dissolved in 0.9% saline (1 μ g/ml) containing 1% human serum albumin, was begun and continued for 7 h. The infusion rate (1 μ g/kg·h) was chosen to provide exogenous growth hormone at approximately two to three times the production rate of endogenous growth hormone previously reported in man (35, 36). Somatostatin was infused as

described above for 8 h via a separate syringe upon stopping the insulin infusion.

Analytical procedures

Glucose, β -hydroxybutyrate, glucagon, growth hormone, FFA, glycerol, and alanine levels were determined by previously described methods (33, 34).

Statistical analysis

Paired two-tailed Student's *t* tests were used for statistical evaluation.

RESULTS

Effect of glucagon infusion on plasma β -hydroxybutyrate, glucose, FFA, glycerol, and alanine levels (Figs. 1 and 2, Table II). After overnight infusion of insulin, mean (\pm SEM) fasting levels of plasma β -hydroxybutyrate, glucose, glucagon (Fig. 1), FFA, glycerol, and alanine (Fig. 2) were normal in each study. In control experiments when saline solution alone was infused, plasma β -hydroxybutyrate, glucose, and glucagon rose progressively after stopping insulin to 1.15 ± 0.2 mM, 278 ± 18 mg/100 ml, and 156 ± 12 pg/ml, respectively, over 6 h. Plasma FFA and glycerol rose to 1.10 ± 0.07 mM and 77 ± 12 μ M, respectively, while alanine levels fell slightly. As previously reported (33), no change in growth hormone levels was observed (data not shown).

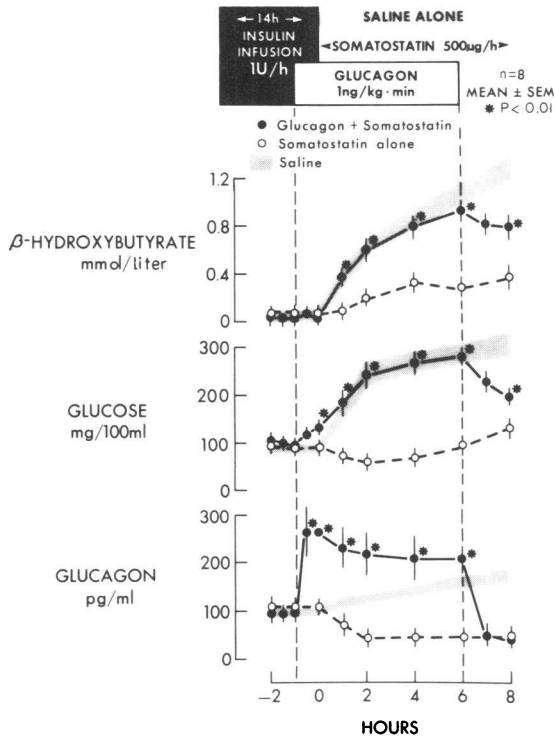


FIGURE 1 Effect of glucagon infusion on plasma β -hydroxybutyrate, glucose, and glucagon levels after acute withdrawal of insulin from insulin-dependent diabetic subjects.

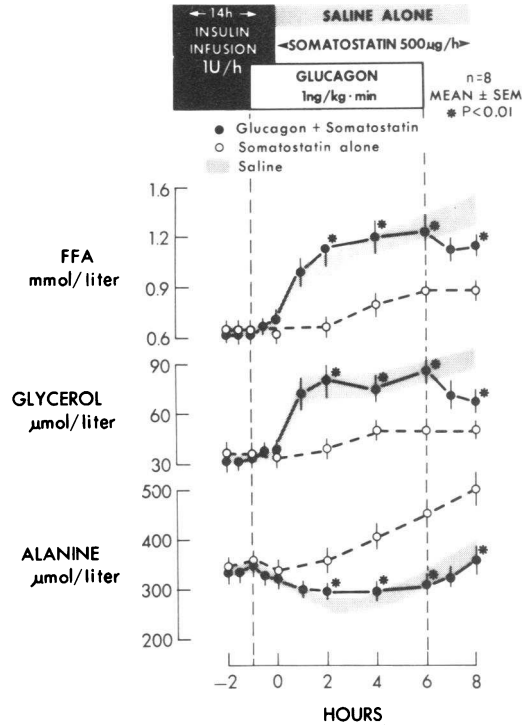


FIGURE 2 Effect of glucagon infusion on plasma FFA, glycerol, and alanine levels after acute withdrawal of insulin from insulin-dependent diabetic subjects.

In experiments in which somatostatin alone was infused after stopping insulin, plasma β -hydroxybutyrate rose to 0.21 ± 0.04 mM, which was significantly lower than the level observed in control experiments ($P < 0.001$), and plasma glucose did not rise at all above baseline values. Glucagon levels were suppressed approximately 50% to 45–55 pg/ml ($P < 0.001$); growth hormone levels were suppressed from a mean basal value of 4.3 ± 0.9 ng/ml to levels averaging 1.5–2 ng/ml. Plasma FFA and glycerol rose to 0.75 ± 0.05 mM and 41 ± 3 μ M, respectively.

Thus, as previously reported (33, 34), somatostatin prevented or markedly diminished expression of the metabolic consequences of acute insulin deficiency. To determine whether this might have been due to suppression of endogenous glucagon secretion, exogenous glucagon was infused along with somatostatin after stopping insulin. Glucagon infusions were begun 1 h before substituting somatostatin for insulin in order to evaluate the effects of hyperglucagonemia in the presence of insulin and to determine whether exogenous glucagon might acutely inhibit endogenous glucagon secretion.

The infusion rate of glucagon chosen (1 ng/kg·min) elevated circulating glucagon levels to 273 ± 51 pg/ml within 30 min. An apparent steady state was achieved because levels were similar (276 ± 57 pg/ml) 30 min

TABLE II
Changes in Circulating Levels of Glucagon, Glucose, β -Hydroxybutyrate, FFA, Glycerol, Alanine, and Growth Hormone during Infusion of Exogenous Glucagon and Somatostatin in Individual Diabetic Subjects after Acute Insulin Withdrawal

Subject	Plasma* glucagon	Δ † glucagon	Δ ‡ glucose	Δ § β -hydroxy- butyrate	Δ § FFA	Δ § glycerol	Δ alanine	Serum* growth hormone
	pg/ml	pg/ml	mg/100 ml	mM	μ M	μ M	μ M	ng/ml
G. H.	207	+37	+132	+0.43	+705	+46	-30	1.4
R. O.	163	+98	+173	+0.89	+761	+46	-80	1.9
J. A.	293	+207	+145	+0.69	+760	+41	-155	1.0
R. T.	159	+100	+177	+0.50	+850	+52	-66	1.6
R. A.	106	+43	+180	+0.44	+650	+54	-45	1.1
J. G.	258	+198	+129	+1.92	+810	+77	-66	2.0
D. S.	349	+280	+255	+1.50	+710	+58	-73	1.0
J. R.	167	+130	+198	+0.73	+600	+120	-50	2.4

* Average of 2-, 4-, and 6-h levels.

† Average of 2-, 4-, and 6-h levels minus average of basal levels before glucagon infusion.

‡ Maximum level minus average of basal levels before glucagon infusion.

|| Nadir minus average of basal levels before infusion of glucagon.

later. During this period plasma glucose rose from 94 ± 8 to 126 ± 12 mg/100 ml ($P < 0.01$), but no changes were observed in plasma β -hydroxybutyrate, FFA, glycerol, alanine, or growth hormone. Thus, elevation of circulating glucagon to levels similar to those reported in the portal vein of nondiabetic subjects and in the peripheral plasma of poorly controlled diabetic subjects resulted in hyperglycemia despite concomitant infusion of insulin, which, according to the studies of Grey et al. (37), should have produced circulating insulin levels of 25–35 μ U/ml. These findings indicate that glucagon can be hyperglycemic without being lipolytic or ketogenic, depending on the availability of insulin (see below).

After stopping insulin, plasma β -hydroxybutyrate and glucose rose progressively to mean levels of 0.83 ± 0.04 mM and 269 ± 10 mg/100 ml, respectively, at hour 6 dur-

ing infusion of glucagon plus somatostatin. These values were similar to those observed in control experiments (when only saline solution was infused after stopping insulin) and significantly ($P < 0.01$) greater than those observed when somatostatin alone was infused after stopping insulin. Similarly, the rises in plasma FFA and glycerol observed during this period approximated those found in control experiments and significantly ($P < 0.01$) exceeded those during infusion of somatostatin alone. Plasma alanine levels declined as in control experiments, in contrast to the progressive rise observed during infusion of somatostatin alone.

Glucagon levels fell after initiation of the somatostatin infusion to 236 ± 38 pg/ml at 1 h and averaged 213 ± 29 pg/ml during hours 2–6 (Table II). Individual rises in plasma glucagon above basal levels were correlated with

TABLE III
Changes in Circulating Levels of Growth Hormone, Glucose, β -Hydroxybutyrate, FFA, Glycerol, Alanine, and Glucagon during Infusion of Exogenous Growth Hormone and Somatostatin in Individual Diabetic Subjects after Acute Insulin Withdrawal

Subject	Serum* growth hormone	Δ † growth hormone	Δ ‡ glucose	Δ § β -hydroxy- butyrate	Δ § FFA	Δ § glycerol	Δ § alanine	Plasma* glucagon
	ng/ml	ng/ml	mg/100 ml	mM	μ M	μ M	μ M	pg/ml
G. H.	5.5	+1.8	-9	+0.88	+1,029	+71	+21	49
R. H.	7.0	+2.1	+7	+1.61	+1,041	+66	+24	54
R. O.	5.2	+2.2	-12	+0.81	+731	+41	+16	48
R. T.	6.2	+1.6	-6	+0.57	+654	+52	+13	37
N. S.	5.1	+2.1	+5	+1.63	+1,010	+84	+28	51

* Average of 2-, 4-, and 6-h levels.

† Average of 2-, 4-, and 6-h levels minus average of basal levels before growth hormone infusion.

‡ Maximum level minus average of basal levels before growth hormone infusion.

rises in plasma β -hydroxybutyrate ($r = 0.74$; $P < 0.02$) but not with changes in glucose, FFA, glycerol, and alanine levels (Table II).

Although mean circulating levels of glucagon observed during infusion of glucagon were slightly higher than those observed during control experiments, this resulted primarily from values in three of the eight subjects (Table II). In the remaining five subjects, levels during hours 2–6 (160 ± 16 pg/ml) were similar to those in control experiments (149 ± 11 pg/ml). Thus, infusion of exogenous glucagon to levels approximating those found in control experiments along with somatostatin was able to reverse completely the effects of somatostatin and reproduce the metabolic changes observed after insulin withdrawal in the control studies.

Effect of growth hormone infusion on plasma β -hydroxybutyrate, glucose, FFA, glycerol, and alanine levels (Table III, Figs. 3 and 4). After overnight infusion of insulin, mean (\pm SEM) plasma β -hydroxybutyrate, glucose, growth hormone (Fig. 3), FFA, glycerol, and alanine (Fig. 4) levels were normal. Changes observed after withdrawal of insulin in control experiments in which saline solution was subsequently infused and also in experiments in which somatostatin was subsequently infused were similar to analogous studies described in the previous section. To evaluate the contribution of the sup-

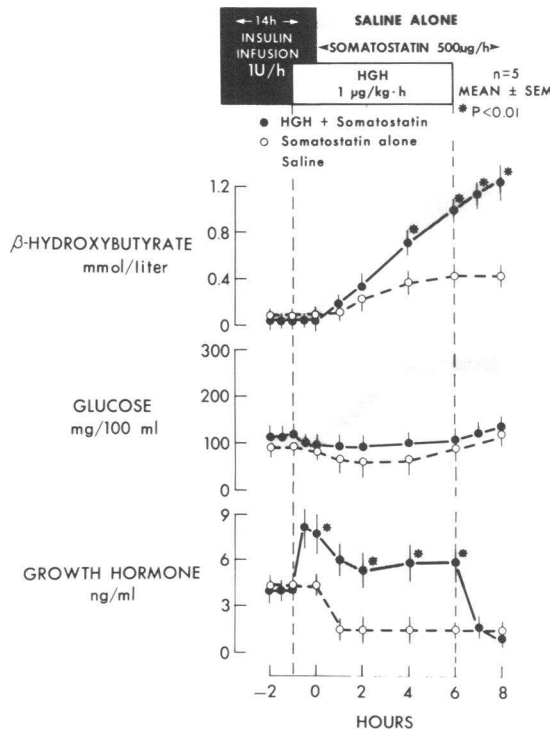


FIGURE 3 Effect of growth hormone infusion on plasma β -hydroxybutyrate, glucose, and serum growth hormone levels after acute withdrawal of insulin from insulin-dependent diabetic subjects.

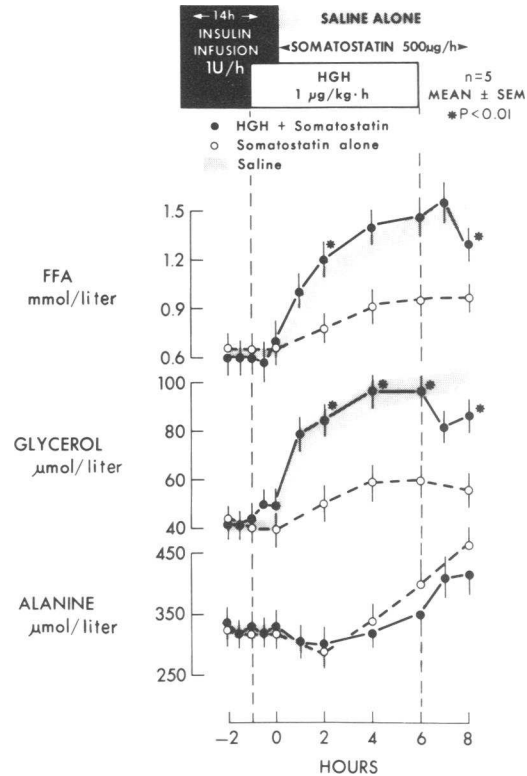


FIGURE 4 Effect of growth hormone infusion on plasma FFA, glycerol, and alanine levels after acute withdrawal of insulin from insulin-dependent diabetic subjects.

pression of endogenous growth hormone secretion by somatostatin, exogenous growth hormone was infused along with somatostatin after stopping insulin. Growth hormone infusions were begun 1 h before substituting somatostatin for insulin in order to determine the effects of elevation of growth hormone levels in the presence of insulin and also to evaluate whether exogenous growth hormone might inhibit endogenous growth hormone secretion.

The infusion rate of growth hormone chosen ($1 \mu\text{g}/\text{kg}\cdot\text{h}$) elevated circulating growth hormone levels to 8.0 ± 1.2 ng/ml after 30 min, and an apparent steady state was achieved since levels were similar (7.8 ± 1.1 ng/ml) 30 min later. After initiation of the somatostatin infusion, growth hormone levels fell to 6.0 ± 0.9 ng/ml at 1 h and averaged 5.8 ± 0.5 ng/ml during the 6-h experiment, thus approximating levels observed during control studies. During the interval when insulin was being concomitantly infused, no changes were observed in plasma β -hydroxybutyrate, glucose, glucagon, FFA, glycerol, or alanine levels. After stopping insulin, plasma β -hydroxybutyrate, FFA, and glycerol levels rose progressively during the 6-h infusion of somatostatin to levels that approximated those found in control studies when saline was infused after stopping insulin. These levels

were significantly ($P < 0.01$) greater than those observed when somatostatin alone was infused after stopping insulin. In contrast, plasma glucose and alanine levels were no different during infusion of growth hormone and somatostatin from those found during infusion of somatostatin alone. Glucagon levels were suppressed by somatostatin to levels averaging 35–55 pg/ml (Table III). These results indicate that, in the absence of insulin, physiologic levels of growth hormone accelerate lipolysis and ketosis in man.

DISCUSSION

Somatostatin has recently been shown to forestall the development of hyperglycemia and hyperketonemia in juvenile-onset, ketosis-prone diabetics after acute withdrawal from insulin (33). Since this agent inhibits both glucagon (20–23) and growth hormone secretion (26–28) in man but has no intrinsic effect on carbohydrate (29–31) and lipid (31, 32) metabolism, suppression of either glucagon or growth hormone secretion (or both) could have accounted for these results. The present studies were undertaken to determine the relative contributions of each of these hormones and, in so doing, to evaluate their roles in human carbohydrate and lipid metabolism.

Infusion of exogenous glucagon and growth hormone at respective rates of 1 ng/kg·min and 1 μg/kg·h for 1 h in the absence of somatostatin produced stable circulating levels within the physiologic range for each hormone (i.e., < 300 pg/ml for glucagon and < 10 ng/ml for growth hormone). Shortly after initiation of the somatostatin infusion, levels of both hormones declined despite their being infused at a constant rate. Presumably this occurred because somatostatin suppressed endogenous secretion of each hormone, indicating that acute administration of exogenous glucagon or growth hormone had not suppressed its own endogenous secretion.

Infusion of exogenous glucagon in the presence of somatostatin completely reversed somatostatin's effects, causing changes in plasma glucose, β-hydroxybutyrate, FFA, glycerol, and alanine similar to those observed in control experiments after the withdrawal of insulin. This occurred while growth hormone levels were still suppressed by somatostatin. Accordingly, the modification of the metabolic consequences of insulin deprivation observed during somatostatin infusion could have been accounted for exclusively by its suppression of endogenous glucagon secretion.

This conclusion, however, is valid only insofar as the levels of glucagon used in the present study were comparable to those in the control experiments. The following considerations indicate that this was indeed the case. First of all, although slightly higher mean levels of glucagon were observed during infusion of glucagon, these

could be accounted for by levels found in three of the eight subjects studied—the other five subjects having similar or lower levels of glucagon than those found in control experiments. Secondly, the metabolic effects of somatostatin were reversed with circulating glucagon levels as low as 110 pg/ml in one subject and with a mean level less than 170 pg/ml in five of the eight subjects studied. Most likely, these levels were less than portal vein values occurring in the control studies because, in the latter circumstance, peripheral glucagon levels averaged 140 pg/ml during the 6 h after insulin withdrawal (38, 39). For these reasons, it seems reasonable to conclude that the effects of somatostatin could be reversed with levels of glucagon comparable to those observed in the control experiments. Accordingly, the present results indicate that endogenous glucagon, under appropriate conditions, can promote hyperglycemia, lipolysis, and hyperketonemia in man. Indeed, since much higher levels of glucagon than those observed in the present study occur spontaneously in human diabetic ketoacidosis (40), it seems very likely that these actions of glucagon contribute to the metabolic disturbances of this condition.

Effects of glucagon on human carbohydrate and lipid metabolism. The hyperglycemia observed during infusion of glucagon in the present studies could have been due to either glycogenolysis or gluconeogenesis or both because glucagon can affect both of these processes (41) and hepatic glycogen would not have been depleted in overnight-fasted individuals (42). Changes in alanine levels suggest that gluconeogenesis was at least partly involved. Plasma levels of this major gluconeogenic precursor (43) fell during infusion of exogenous glucagon plus somatostatin, whereas, when endogenous glucagon secretion was suppressed by infusing somatostatin alone, plasma alanine levels rose and hyperglycemia did not occur. These results suggest that hepatic alanine uptake and conversion to glucose were stimulated during infusion of glucagon and were diminished when circulating glucagon levels were lowered with somatostatin. This interpretation is supported by recent studies in which suppression of glucagon secretion in the dog with somatostatin resulted in decreased hepatic glucose output (44–47) and concomitant diminished conversion of alanine to glucose (46).

With respect to lipid metabolism, in the present study physiologic quantities of glucagon infused along with somatostatin resulted in rises in plasma FFA, glycerol, and β-hydroxybutyrate levels which were two- to threefold greater than those observed during infusion of somatostatin alone when endogenous glucagon was suppressed. These observations indicate that physiologic concentrations of glucagon can, under certain conditions, stimulate lipolysis in man. Glucagon has been previously

demonstrated to augment lipolysis (1, 48) and ketogenesis (48) in man, but it cannot be concluded with certainty from these and the present data that physiologic concentrations of glucagon enhance ketone body production by a direct hepatic effect in addition to that resulting from enhanced lipolysis because elevation of circulating FFA could have in itself led to the modest increase in ketosis observed. Nevertheless, several *in vitro* studies have shown that glucagon can enhance hepatic ketone body production directly (41, 49). In the rat *in vivo*, McGarry and co-workers (50) have demonstrated that physiologic quantities of glucagon can convert the fed liver to a ketogenic mode. Possibly, a similar key action of glucagon in the human liver could explain, in part, the lack of ketoacidosis after withdrawal of insulin from ketosis-prone diabetics during suppression of glucagon secretion (33).

Other studies using physiologic quantities of glucagon have not consistently found lipolytic and ketogenic actions of this hormone in man (5, 51). A possible explanation for this discrepancy is that glucagon may stimulate sufficient insulin secretion (52) to counteract its effect on lipolysis and limit substrate available for ketogenesis. This point is illustrated in the present studies by the fact that concomitant infusion of glucagon and insulin resulted in hyperglycemia without causing significant changes in plasma FFA and β -hydroxybutyrate levels. Only when exogenous insulin was discontinued and any possible residual insulin secretion was suppressed by somatostatin did accelerated lipolysis occur and the ketogenic potential of glucagon become manifest.

Effects of growth hormone on human carbohydrate and lipid metabolism. Infusion of growth hormone along with somatostatin in the present studies had no effect on plasma glucose and alanine levels but did result in significantly ($P < 0.01$) greater rises in plasma FFA, glycerol, and β -hydroxybutyrate levels than were observed with somatostatin alone; these rises approximated those found during control experiments after withdrawal of insulin. Previous studies using pharmacologic doses of exogenous growth hormone have demonstrated that growth hormone can augment lipolysis and cause hyperketonemia in man (10, 12, 13, 15, 16), but to our knowledge the present studies represent the first demonstration that these effects occur with physiologic levels of growth hormone.

No rise in plasma FFA and β -hydroxybutyrate levels was observed during infusion of growth hormone in the present studies until after discontinuation of insulin infusions, i.e., 2 h after initiation of growth hormone administration. Whether this was due to initial antagonism by infused insulin (16) or to slow activation of lipolysis by growth hormone (53) is unclear. Rabinowitz et al. (13), examining the effects of growth hormone on hu-

man forearm metabolism, observed stimulation of lipolysis within 30 min, but this has not been confirmed (14). Others using large doses of growth hormone have not found rises in plasma FFA levels until 2 h after growth hormone administration (10, 16), but such large doses have an early insulin-like action (10, 54) that could explain this delayed effect. In the present study, using physiologic levels of growth hormone, no early insulin-like effect on either glucose or lipid metabolism was found, suggesting that this phenomenon represents a pharmacologic action of growth hormone.

Although these present studies indicate that physiologic levels of growth hormone are lipolytic and can lead to ketosis in man under appropriate conditions, no conclusion can be drawn as to whether growth hormone at such concentrations directly affects hepatic ketogenesis. Indeed, since *in vitro* experiments using perfused livers have failed to demonstrate augmentation of ketone body production by growth hormone (55, 56), it seems most likely that the ketosis observed was the result of the enhanced lipolysis induced by growth hormone providing additional substrate for ketogenesis.

The failure of growth hormone to alter plasma glucose levels both during infusion of insulin and after its termination suggests that its ability to diminish glucose utilization (10–14) is easily overcome by insulin and is not apparently a major factor in the hyperglycemia occurring with insulin deficiency. This conclusion does not exclude an important role for growth hormone in the carbohydrate intolerance of acromegaly where prolonged exposure to high circulating levels of growth hormone may result in marked insulin resistance (57).

Regarding the respective roles of glucagon and growth hormone in human carbohydrate and lipid metabolism, the present studies indicate that glucagon is of more importance than growth hormone in glucose homeostasis because, during suppression of endogenous secretion of both hormones, infusion of glucagon but not growth hormone resulted in hyperglycemia. However, physiologic levels of both hormones appear to influence lipolysis and ketogenesis to a similar degree. Their contribution to the regulation of carbohydrate and lipid metabolism in man is underscored by the fact that, despite severe insulin lack, there was minimal spontaneous lipolysis and accumulation of glucose and ketone bodies when endogenous glucagon and growth hormone secretion were both suppressed with somatostatin. These observations indicate that the metabolic activity of human liver and adipose tissue may depend predominantly on their hormonal milieu.

The present data support the concept that physiologic levels of growth hormone and glucagon modulate carbohydrate and lipid metabolism in man but that these actions are usually minimized when insulin is available;

when insulin deficiency of sufficient degree occurs, the effects of glucagon and growth hormone normally counterbalanced by insulin become exaggerated, resulting in hyperglycemia, elevated plasma FFA levels, hyperketonemia, and, ultimately, diabetic ketoacidosis. Previously, glucagon had been considered to play a negligible role relative to insulin lack in the metabolic derangements of diabetes mellitus. To a great extent this was due to the fact that total pancreatectomy—a procedure thought to cause combined glucagon and insulin deficiency—produced fulminant diabetes. However, the recent demonstration in several laboratories of persistent circulating glucagon after complete pancreatectomy (58–60) and the apparent biologic equivalence of such extrapancreatic glucagon with pancreatic glucagon (61) provide a reasonable explanation for this phenomenon, consistent with the concept of an essential role of glucagon (pancreatic or extrapancreatic) in the pathogenesis of diabetes mellitus (33, 62).

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REFERENCES

- Liljenquist, J. E., J. D. Bomboy, S. B. Lewis, B. C. Sinclair-Smith, P. W. Felts, W. W. Lacy, O. B. Crofford, and G. W. Liddle. 1974. Effects of glucagon on lipolysis and ketogenesis in normal and diabetic men. *J. Clin. Invest.* **53**: 190–197.
- Salter, J. M., C. Ezrin, J. C. Laidlaw, and A. G. Gornall. 1960. Metabolic effects of glucagon in human subjects. *Metab. Clin. Exp.* **9**: 753–768.
- Schade, D. S., and R. P. Eaton. 1975. Modulation of fatty acid metabolism by glucagon in man. I. Effects in normal subjects. *Diabetes.* **24**: 502–509.
- Schade, D. S., and R. P. Eaton. 1975. Modulation of fatty acid metabolism by glucagon in man. II. Effects in insulin-deficient diabetics. *Diabetes.* **24**: 510–515.
- Marliss, E. B., T. T. Aoki, R. H. Unger, J. S. Soeldner, and G. F. Cahill, Jr. 1970. Glucagon levels and metabolic effects in fasting man. *J. Clin. Invest.* **49**: 2256–2270.
- Mitchell, M. L., P. Suvunrungsi, and C. T. Sawin. 1971. Effect of propranolol on the response of serum growth hormone to glucagon. *J. Clin. Endocrinol. Metab.* **32**: 470–475.
- Sarcione, E. J., N. Back, J. E. Sokal, B. Mehlman, and E. Knoblock. 1963. Elevation of plasma epinephrine levels produced by glucagon in vivo. *Endocrinology.* **72**: 523–526.
- Sherwin, R., M. Fisher, R. Hendler, and P. Felig. 1975. Failure of physiologic hyperglucagonemia to produce glucose intolerance or altered substrate levels in normal man. In Program of the 57th Annual Meeting of The Endocrine Society, New York, June 18–20, 1975. 85. (Abstr.)
- Alford, F. P., S. R. Bloom, J. D. N. Nabarro, R. Hall, G. M. Besser, D. H. Coy, A. J. Kastin, and A. V. Schally. 1974. Glucagon control of fasting glucose in man. *Lancet.* **2**: 974–977.
- Pearson, O. H., J. M. Dominguez, E. Greenberg, A. Pазianos, and B. S. Ray. 1960. Diabetogenic and hypoglycemic effects of human growth hormone. *Trans. Assoc. Am. Physicians Phila.* **73**: 217–226.
- Frohman, L. A., M. H. MacGillivray, and T. Aceto, Jr. 1967. Acute effects of human growth hormone on insulin secretion and glucose utilization in normal and growth hormone deficient subjects. *J. Clin. Endocrinol. Metab.* **27**: 561–567.
- Cheng, J. S., and N. Kalant. 1970. Effects of insulin and growth hormone on the flux rates of plasma glucose and plasma free fatty acids in man. *J. Clin. Endocrinol. Metab.* **31**: 647–653.
- Rabinowitz, D., G. A. Klassen, and K. L. Zierler. 1965. Effect of human growth hormone on muscle and adipose tissue metabolism in the forearm of man. *J. Clin. Invest.* **44**: 51–61.
- Fineberg, S. E., and T. J. Merimee. 1974. Acute metabolic effects of human growth hormone. *Diabetes.* **23**: 499–504.
- Felig, P., E. B. Marliss, and G. F. Cahill, Jr. 1971. Metabolic response to human growth hormone during prolonged starvation. *J. Clin. Invest.* **50**: 411–421.
- Raben, M. S., and C. H. Hollenberg. 1959. Effect of growth hormone on plasma free fatty acids. *J. Clin. Invest.* **38**: 484–488.
- Harlan, W. R., J. Laszlo, M. D. Bogdonoff, and E. H. Estes, Jr. 1963. Alterations in free fatty acid metabolism in endocrine disorders. I. Effect of thyroid hormone. *J. Clin. Endocrinol. Metab.* **23**: 33–40.
- DiRaimondo, V. C., and J. M. Earll. 1968. Remarkable sensitivity to insulin in a patient with hypopituitarism and diabetic ketoacidosis. *Diabetes.* **17**: 147–151.
- Merimee, T. J., P. Felig, E. Marliss, S. E. Fineberg, and G. F. Cahill, Jr. 1971. Glucose and lipid homeostasis in the absence of human growth hormone. *J. Clin. Invest.* **50**: 574–582.
- Rivier, J., P. Brazeau, W. Vale, N. Ling, R. Burgus, C. Gilon, J. Yardley, and R. Guillemin. 1973. Synthèse totale par phase solide d'un tétradécapeptide ayant les propriétés chimiques et biologiques de la somatostatine. *C. R. Hebd. Seances. Acad. Sci. Ser. D Sci. Natl.* **276**: 2737–2740.
- Gerich, J. E., M. Lorenzi, V. Schneider, J. H. Karam, J. Rivier, R. Guillemin, and P. H. Forsham. 1974. Effects of somatostatin on plasma glucose and glucagon levels in human diabetes mellitus: pathophysiologic and therapeutic implications. *N. Engl. J. Med.* **291**: 544–547.
- Gerich, J. E., M. Lorenzi, S. Hane, G. Gustafson, R. Guillemin, and P. H. Forsham. 1975. Evidence for a physiologic role of pancreatic glucagon in human glucose homeostasis: studies with somatostatin. *Metab. Clin. Exp.* **24**: 175–182.
- Yen, S. S. C., T. M. Siler, and G. W. DeVane. 1974. Effect of somatostatin in patients with acromegaly: Suppression of growth hormone, prolactin, insulin and glucose levels. *N. Engl. J. Med.* **290**: 935–938.

24. Alberti, K. G. M. M., N. J. Christensen, S. E. Christensen, Aa. Prange Hansen, J. Iversen, K. Lundbaek, K. Seyer-Hansen, and H. Ørskov. 1973. Inhibition of insulin secretion by somatostatin. *Lancet*. 2: 1299-1301.
25. Gerich, J. E., M. Lorenzi, V. Schneider, and P. H. Forsham. 1974. Effect of somatostatin on plasma glucose and insulin responses to glucagon and tolbutamide in man. *J. Clin. Endocrinol. Metab.* 39: 1057-1060.
26. Prange Hansen, Aa., H. Ørskov, K. Seyer-Hansen, and K. Lundbæk. 1973. Some actions of growth hormone release inhibiting factor. *Br. Med. J.* 3: 523-524.
27. Gerich, J. E., M. Lorenzi, V. Schneider, C. W. Kwan, J. H. Karam, R. Guillemin, and P. H. Forsham. 1974. Inhibition of pancreatic glucagon responses to arginine by somatostatin in normal man and in insulin-dependent diabetics. *Diabetes*. 23: 876-880.
28. Mortimer, C. H., W. M. G. Tunbridge, D. Carr, L. Yeomans, T. Lind, D. H. Coy, S. R. Bloom, A. Kastin, C. N. Mallinson, G. M. Besser, A. V. Schally, and R. Hall. 1974. Effects of growth-hormone release-inhibiting hormone on circulating glucagon, insulin, and growth hormone in normal, diabetic, acromegalic, and hypopituitary patients. *Lancet*. 1: 697-701.
29. Haas, R., E. Clausen, C. Woods, M. Lorenzi, D. Bier, S. Hane, and J. E. Gerich. 1975. Effect of somatostatin, insulin, and glucagon on glucose uptake and alanine release by the isolated perfused rat hindlimb. *Clin. Res.* 23: 110A. (Abstr.)
30. Chideckel, E. W., J. Palmer, D. J. Koerker, J. Ensinnck, M. B. Davidson, and C. J. Goodner. 1975. Somatostatin blockade of acute and chronic stimuli of the endocrine pancreas and the consequences of this blockade on glucose homeostasis. *J. Clin. Invest.* 55: 754-762.
31. Gerich, J. E., D. Bier, R. Haas, C. Wood, R. Byrne, and J. C. Penhos. 1975. In vitro and in vivo effects of somatostatin on glucose, alanine, and ketone body metabolism in the rat. In Program of the 57th Annual Meeting of The Endocrine Society, New York, June 18-20, 1975. 128. (Abstr.)
32. Lorenzi, M., J. H. Karam, V. Schneider, G. Gustafson, S. Horita, and J. E. Gerich. 1975. Effect of somatostatin on plasma glucose, free fatty acid, and glucagon responses to epinephrine in human diabetes. *Clin. Res.* 23: 112A. (Abstr.)
33. Gerich, J. E., M. Lorenzi, D. M. Bier, V. Schneider, E. Tsalikian, J. H. Karam, and P. H. Forsham. 1975. Prevention of human diabetic ketoacidosis by somatostatin. Evidence for an essential role of glucagon. *N. Engl. J. Med.* 292: 985-989.
34. Gerich, J. E., E. Tsalikian, M. Lorenzi, J. H. Karam, and D. M. Bier. 1975. Plasma glucagon and alanine responses to acute insulin deficiency in man. *J. Clin. Endocrinol. Metab.* 40: 526-529.
35. Sperling, M. A., F. Wollesen, and P. V. DeLamater. 1973. Daily production and metabolic clearance of growth hormone in juvenile diabetes mellitus. *Diabetologia*. 9: 380-383.
36. Kowarski, A., R. G. Thompson, C. J. Migeon, and R. M. Blizzard. 1971. Determination of integrated plasma concentrations and true secretion rates of human growth hormone. *J. Clin. Endocrinol. Metab.* 32: 356-360.
37. Grey, N. J., I. Karl, and D. M. Kipnis. 1975. Physiologic mechanisms in the development of starvation ketosis in man. *Diabetes*. 24: 10-16.
38. Blackard, W. G., N. C. Nelson, and S. S. Andrews. 1974. Portal and peripheral vein immunoreactive glucagon concentrations after arginine or glucose infusions. *Diabetes*. 23: 199-202.
39. Felig, P., R. Gusberg, R. Hendler, F. E. Gump, and J. M. Kinney. 1974. Concentrations of glucagon and the insulin: glucagon ratio in the portal and peripheral circulation. *Proc. Soc. Exp. Biol. Med.* 147: 88-90.
40. Müller, W. A., G. R. Faloona, and R. H. Unger. 1973. Hyperglucagonemia in diabetic ketoacidosis: its prevalence and significance. *Am. J. Med.* 54: 52-57.
41. Exton, J. H., and C. R. Park. 1972. Interaction of insulin and glucagon in the control of liver metabolism. *Handb. Physiol. Section 7. Endocrinology*. 1: 437-455.
42. Nilsson, L. H. 1973. Liver glycogen content in man in the postabsorptive state. *Scand. J. Clin. Lab. Invest.* 32: 317-323.
43. Felig, P. 1973. The glucose-alanine cycle. *Metab. Clin. Exp.* 22: 179-207.
44. Altszuler, N., B. Gottlieb, and J. Hampshire. 1975. Interaction of somatostatin, glucagon and insulin on hepatic glucose output in the normal dog. *Diabetes (Suppl. 2)*. 24: 407. (Abstr.)
45. Ross, G., and M. Vranic. 1975. Effects of somatostatin-induced decreases in immunoreactive insulin (IRI) and glucagon (IRG) on glucose turnover. *Diabetes (Suppl. 2)*. 24: 408. (Abstr.)
46. Chiasson, J. L., A. S. Jennings, A. D. Cherrington, J. E. Liljenquist, and W. W. Lacy. 1975. The fine regulation of basal gluconeogenesis in vivo. *Diabetes (Suppl. 2)*. 24: 407. (Abstr.)
47. Jennings, A. S., A. D. Cherrington, J. L. Chiasson, J. E. Liljenquist, and W. W. Lacy. 1975. The fine regulation of basal hepatic glucose production. *Clin. Res.* 23: 323A. (Abstr.)
48. Samols, E., J. M. Tyler, V. Marks, and P. Mialhe. 1969. The physiological role of glucagon in different species. *Excerpta Med. Int. Congr. Ser. No.* 184: 206-219.
49. Fritz, I. B., and L. P. K. Lee. 1972. Fat mobilization and ketogenesis. *Handb. Physiol. Section 7. Endocrinology*. 1: 579-596.
50. McGarry, J. D., P. H. Wright, and D. W. Foster. 1975. Hormonal control of ketogenesis. Rapid activation of hepatic ketogenic capacity in fed rats by anti-insulin serum and glucagon. *J. Clin. Invest.* 55: 1202-1209.
51. Lefebvre, P. 1972. Glucagon and lipid metabolism. In *Glucagon: Molecular Physiology, Clinical and Therapeutic Implications*. P. Lefebvre and R. H. Unger, editors. Pergamon Press, Inc., Elmsford, N. Y. 109-121.
52. Samols, E., G. Marri, and V. Marks. 1966. Interrelationship of glucagon, insulin and glucose: the insulinogenic effect of glucagon. *Diabetes*. 15: 855-866.
53. Fain, J. N., V. P. Kovacev, and R. O. Scow. 1965. Effect of growth hormone and dexamethasone on lipolysis and metabolism in isolated fat cells of the rat. *J. Biol. Chem.* 240: 3522-3529.
54. Merimee, T. J., and D. Rabin. 1973. A survey of growth hormone secretion and action. *Metab. Clin. Exp.* 22: 1235-1251.
55. Penhos, J. C., C. H. Wu, A. Lemberg, J. Daunas, B. Brodoff, and R. Levine. 1966. The effect of growth hormone on the metabolism of lipids and on urea formation by the perfused rat liver. *Metab. Clin. Exp.* 15: 1109-1119.
56. Chernick, S. S., C. M. Clark, Jr., R. J. Gardiner, and R. O. Scow. 1972. Role of lipolytic and glucocorticoid hormones in the development of diabetic ketosis. *Diabetes*. 21: 946-954.

57. Davidoff, F. 1968. The disturbances of carbohydrate metabolism in acromegaly—a perspective view, 1927–1967. *Proc. Rudolf Virchow Med. Soc. City N. Y.* 26 (Suppl.): 83–115.
58. Vranic, M., S. Pek, and R. Kawamori. 1974. Increased “glucagon immunoreactivity” in plasma of totally depancreatized dogs. *Diabetes.* 23: 905–912.
59. Matsuyama, T., and P. P. Foà. 1974. Plasma glucose, insulin, pancreatic, and enteroglucagon levels in normal and depancreatized dogs. *Proc. Soc. Exp. Biol. Med.* 147: 97–102.
60. Dobbs, R., H. Sakurai, H. Sasaki, G. Faloona, I. Valverde, D. Baetens, L. Orci, and R. Unger. 1975. Glucagon: role in the hyperglycemia of diabetes mellitus. *Science (Wash. D. C.)*. 187: 544–547.
61. Sasaki, H., B. Rubalcava, D. Baetens, E. Blazquez, C. B. Srikant, L. Orci, and R. H. Unger. 1975. Identification of glucagon in the gastrointestinal tract. *J. Clin. Invest.* 56: 135–145.
62. Unger, R. H., and L. Orci. 1975. The essential role of glucagon in the pathogenesis of diabetes mellitus. *Lancet.* 1: 14–16.