Effect of Adrenergic Agents on Postgastrectomy Hypoglycemia

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SUMMARY

Reactive hypoglycemia was documented in ten postgastrectomy patients by a control oral glucose tolerance test (OGTT). Nine patients experienced nausea, flushing, and fatigue during the first hour of the test. Neuroglycopenic or adrenergic symptoms of hypoglycemia occurred in eight patients two to five hours after oral glucose. The oral administration of phenylephrine elixir, 15 mg., thirty minutes before a repeat OGTT, significantly raised the lowest plasma glucose from 37.5 ± 2.8 mg./dl. to 45.2 ± 3.8 mg./dl. ($p < 0.05$) but did not affect the occurrence of either the early or the late symptoms. In contrast, propranolol, 10 mg., raised the lowest plasma glucose from 37.5 ± 2.8 mg./dl. to 57 ± 5.2 mg./dl. ($p < 0.02$) and prevented the occurrence of early and late symptoms. Neither peak nor total plasma insulin levels were affected by either drug. The rate of glucose utilization, as determined by intravenous glucose tolerance tests, did not significantly change after the oral administration of either drug. It is concluded that propranolol ameliorated the symptoms and chemical hypoglycemia after oral glucose and merits more detailed study as a long-term therapy for this disorder. DIABETES *24*:1005-10, November, 1975.

Postgastrectomy hypoglycemia is generally considered to be a benign disorder,[1,2] although cases have been reported relating neuropsychiatric dysfunction to this disorder.[3-8] Little is known about the efficacy or suitability of present recommended therapies, low-carbohydrate diets, or anticholinergic drugs. Alternative therapies, utilizing agents that inhibit insulin secretion in normal subjects or animals, have been suggested.[9] These drugs include alpha-adrenergic stimulants, such as phenylephrine,[10] and propranolol, which induces beta-adrenergic blockade.[11]

We have studied the effects of phenylephrine and propranolol on the symptoms and on plasma glucose and insulin concentrations following oral glucose in ten patients with postgastrectomy hypoglycemia.

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METHODS AND MATERIALS

Patients known to have undergone vagotomy and pyloroplasty or a Billroth II resection more than five years before the study were invited to participate. Their names were obtained from the Barnes Hospital Surgical Registry or from physician referrals. Patients with a history of malignancy, glaucoma, or significant cardiac or pulmonary disease were excluded. After informed consent was obtained, the patients were admitted to the Clinical Research Center of Washington University and a history and physical examination were performed. Blood samples were obtained for serum vitamin B_{12} levels and a complete blood count, and a five-hour oral glucose tolerance test was administered with 100 gm. of glucose. All glucose tolerance tests were performed following an overnight fast, with the patients in the sitting position. Samples for measurement of plasma glucose and insulin were obtained every thirty minutes. Patients with reactive hypoglycemia, defined as having a plasma glucose of 50 mg./dl. or less, who agreed to continue in the study were then given an intravenous glucose tolerance test with 25 gm. of glucose administered as previously described.[12] Each patient had a repeat oral and a repeat intravenous test on subsequent days thirty minutes after oral administration of phenylephrine elixir, 15 mg., and a similar set of tests thirty minutes after oral administration of propranolol tablets, 10 mg. The sequence of tests varied from patient to patient. In some patients, an additional oral glucose tolerance test was performed with the prior oral administration of propranolol, 25 mg.

Oral administration was used in order to evaluate each agent as a therapy. Doses used represented standard therapeutic levels recommended by the manufacturers for use in treating other, nonemergent disorders. Conservative doses were selected in order to minimize possible untoward side effects.

Serum vitamin B_{12} levels were determined by the method of Raben and Robson.[13] Plasma glucose was measured on venous blood by the AutoAnalyzer,

Technicon, Ardsley, New York. Plasma insulin levels were measured according to the method of Morgan and Lazarow.[14]

RESULTS

Control oral glucose tolerance tests were performed on seventeen patients, and fifteen were found to have a plasma glucose of 50 mg./dl. or less during the test (table 1). In addition, sixteen had a peak glucose exceeding 170 mg./dl. Of the patients with reactive hypoglycemia, three refused further study and two suffered from presenile dementia, which transiently but severely worsened during testing, and were excluded. The remaining ten patients included five men and five women from twenty-nine to sixty-two years of age. A vagotomy and pyloroplasty had been performed on six patients and a Billroth II procedure on four, from five to twelve years earlier. Only one of the initial seventeen patients had a low serum B_{12} level, and she had no evidence of neuropsychiatric dysfunction or hypoglycemia. No patient was anemic at the time of study.

The mean plasma glucose and insulin levels found in the study group at each thirty-minute interval are shown in figure 1. The group had significantly elevated plasma glucose levels, compared with a group of ten normal controls, during the first ninety minutes. Plasma insulin was also elevated from sixty to 120 minutes compared with the controls'. At 150 and 180 minutes, significantly lower mean plasma glucose levels were observed compared with controls'. Neither phenylephrine nor propranolol preadministration significantly altered the mean plasma glucose or insulin levels of the study group at any time (figure 2).

In contrast, the lowest plasma glucose levels observed during each glucose tolerance test was significantly raised in most patients by both drugs (figures 3 and 4). Phenylephrine preadministration raised the lowest plasma glucose in seven patients, and the mean for the entire study group increased from 37.5 ± 2.8 mg./dl. to 45.2 ± 3.8 mg./dl. ($p < 0.05$) (figure 3). However, seven patients still had chemical hypoglycemia. Propranolol pretreatment raised the lowest plasma glucose in eight patients, and only three had chemical hypoglycemia (figure 4). The mean lowest plasma glucose for the entire group increased from 37.5 ± 2.8 mg./dl. to 57 ± 5.2 mg./dl. ($p < 0.02$). An additional oral glucose tolerance test, following propranolol, 25 mg., was given to four patients who had responded to propranolol, 10 mg. (figure 4). Again the lowest plasma glucose was increased in every patient, but the higher dose of propranolol was not demonstrably more effective than the lower. Total observed plasma insulin levels were not significantly

TABLE 1

Characteristics of Patients in Study

Sex	Age	Year and type of surgery	Other medical problems	Serum B_{12} ($n > 200$ $\mu\mu$g./ml.)	Peak* glucose (mg./dl.)	Lowest* glucose (mg./dl.)
Study Patients						
M	60	1969 V and P†	postprandial "wooziness"	970	263	43
F	54	1967 Billroth II	irritability	480	380	46
M	29	1967 V and P	congenitally dislocated hips	330	221	23
M	44	1968 V and P	none	330	203	40
M	62	1965 Billroth II	mild emphysema	210	206	42
F	49	1969 V and P	nervousness, irritability	490	177	50
F	44	1965 V and P	none	430	255	38
F	49	1967 V and P	dysarthria, memory lapses	410	205	27
F	59	1962 Billroth II	osteopenia, memory lapses	250	531	36
M	32	1967 Billroth II	alcoholism, peripheral neuropathy	300	266	39
Patients Not Completing Study						
M	53	1957 Billroth II	presenile dementia	330	275	47
M	65	1964 Billroth II	presenile dementia	700	250	50
F	62	1966 V and P	mild emphysema	440	272	45
M	55	1963 Billroth II	none	230	250	72
M	37	1967 V and P	none	190	177	33
F	35	1969 V and P	none	290	127	56

*Peak glucose and lowest glucose indicate plasma glucose levels measured during the control oral glucose tolerance test.
†V and P indicate vagotomy and pyloroplasty.

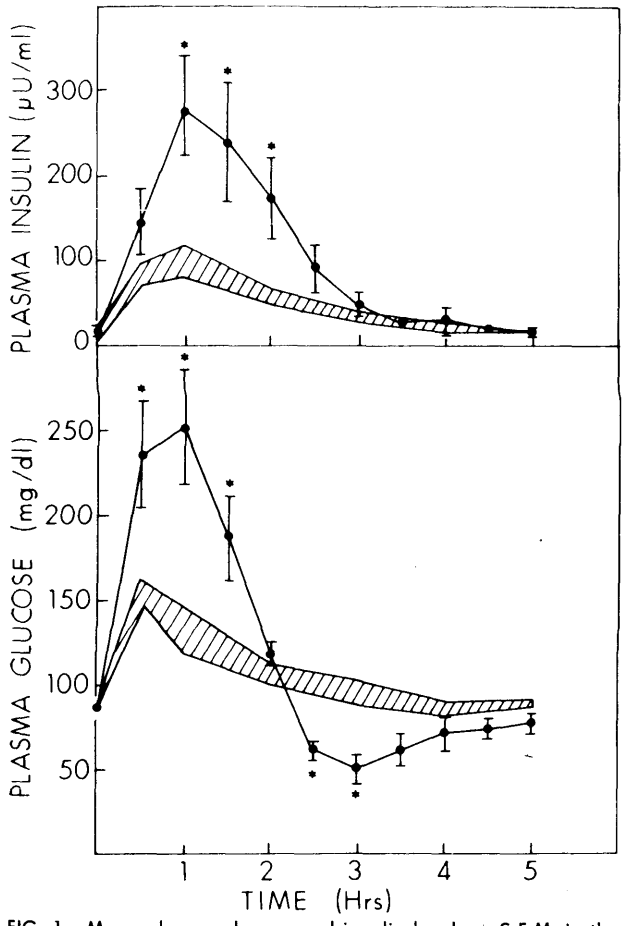

FIG. 1. Mean plasma glucose and insulin levels ± S.E.M. in the ten study patients (closed circles) and in ten normal volunteers (shaded area) following 100 gm. of oral glucose. Asterisk indicates a significant difference between the two groups ($p < 0.05$).

affected by either drug. Mean peak glucose and the rate of decline in plasma glucose, from peak glucose, was not changed by phenylephrine or propranolol (data not shown). However, propranolol did significantly reduce the total decrease in plasma glucose from peak to lowest glucose, from 233 ± 35 mg./dl. to 191 ± 27.

Both early and late symptoms occurred in the study group following oral glucose (table 2). With no pretreatment, nine of the ten patients experienced nausea, flushing, and fatigue during the first hour after glucose loading. However, only two patients had abdominal bloating or diarrhea. Preadministration of phenylephrine did not affect the occurrence of these symptoms. In contrast, only one patient had these symptoms after propranolol pretreatment. Neuroglycopenic symptoms (headache, lethargy, irritability) and adrenergic symptoms (nervousness, hunger, and tachycardia) occurred two to five hours after oral glucose and corresponded to periods of chemical hypoglycemia. The neuroglycopenic systems were noted in six patients with no pretreatment and with phenylephrine but in no patient after propranolol. Similarly, five patients experienced adrenergic symptoms during the control test and after phenylephrine preadministration, but no patient had such symptoms following propranolol pretreatment.

The rate of glucose utilization, as measured by intravenous glucose tolerance testing, was not affected by pretreatment with either drug (figure 5). Two patients had clearly abnormal rates of glucose utilization and two others had an abnormal test on one occasion. Observed plasma insulin levels during these tests were also unaffected by phenylephrine or propranolol.

DISCUSSION

Reactive hypoglycemia occurs in 5 to 50 per cent of patients following gastrectomy,[15-18] but little is known about its long-term course and the efficacy or suitability of presently recommended therapies. Re-

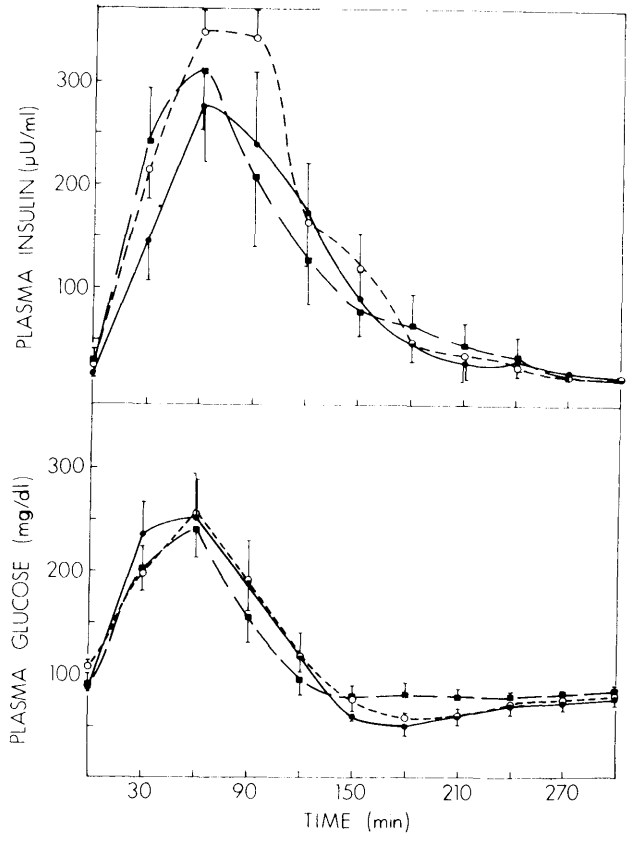

FIG. 2. Mean plasma glucose and insulin levels ± S.E.M. in the ten study patients following 100 gm. of oral glucose and no pretreatment (closed circles), pretreatment with phenylephrine elixir, 15 mg. (open circles), and pretreatment with propranolol, 10 mg. (squares).

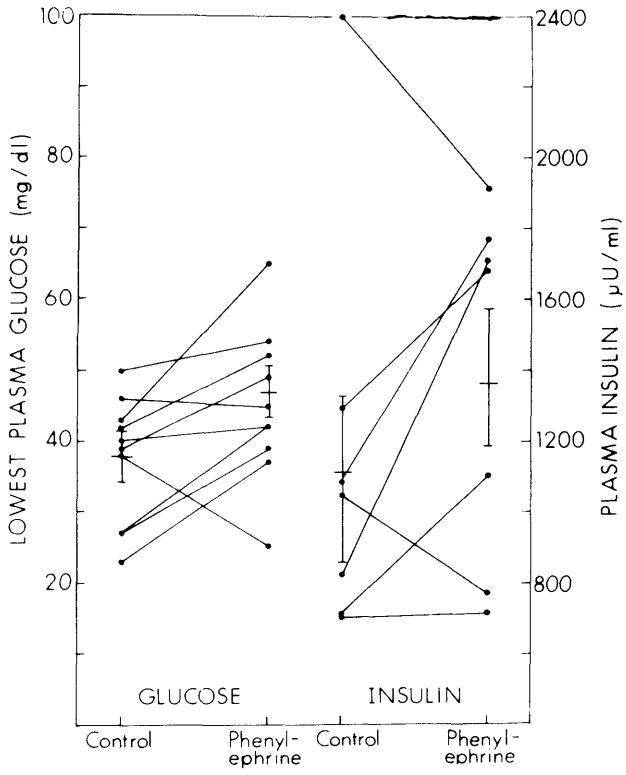

FIG. 3. Lowest plasma glucose and total plasma insulin levels observed in the study patients during the control oral glucose tolerance test and the oral glucose tolerance test after prior administration of phenylephrine elixir, 15 mg.

cent case reports relating neuropsychiatric dysfunction to postgastrectomy hypoglycemia suggest that the consequences of the disorder can be significant.[3-8] Low-carbohydrate diets, which are commonly prescribed as treatment,[1,2] are unpalatable to many patients, and adherence to them is often poor. Pharmacologic therapy of reactive hypoglycemia, including anticholinergic drugs,[19] chlorpropamide,[4] or phenformin,[7,20] has not been evaluated adequately in postgastrectomy hypoglycemia.

Alternative therapies, utilizing agents that inhibit insulin secretion in normal subjects, have been suggested.[9] The rationale for this type of treatment is that in patients with postgastrectomy hypoglycemia a hyperinsulinemia occurs following oral glucose.[21-23] This hyperinsulinemia is due to a rapid absorption of glucose[15,21,23] and a hypersecretion of enteric hormones that stimulate insulin release.[24-26] In a previous report, twenty-six of ninety-one patients with postgastrectomy hypoglycemia had an early hyperglycemia after glucose ingestion.[15] Plasma enteroglucagon levels have been found to be elevated in these patients following oral glucose.[24,25]

It is well accepted that adrenergic agents exert significant effects on insulin secretion. Alpha-adrenergic stimulants have been shown to inhibit basal and glucose-mediated insulin release in normal men,[10,26-29] baboons,[30] and isolated islet cells.[31] Propranolol, which produces beta-adrenergic blockade, inhibits basal, glucose-stimulated, diazoxide-stimulated, and tolbutamide-stimulated insulin release in man, baboons, dogs, mice, and isolated islet cells.[11,29,32-36] The effect of these drugs in postgastrectomy hypoglycemia has not been studied previously. Propranolol has been reported to prevent hypoglycemic episodes in a patient with insulinoma by lowering plasma insulin levels.[37]

The postgastrectomy patients reported in the current study had a higher incidence of early hyperglycemia and reactive hypoglycemia than noted in previous studies. A surprising number were also found to have symptoms of flushing, nausea, and fatigue, which correspond to the vasomotor symptoms of "early dumping,"[38] during the first hour after oral glucose loading. The occurrence of reactive hypoglycemia and symptoms of "early dumping" in the same patients is said to be rare.[9]

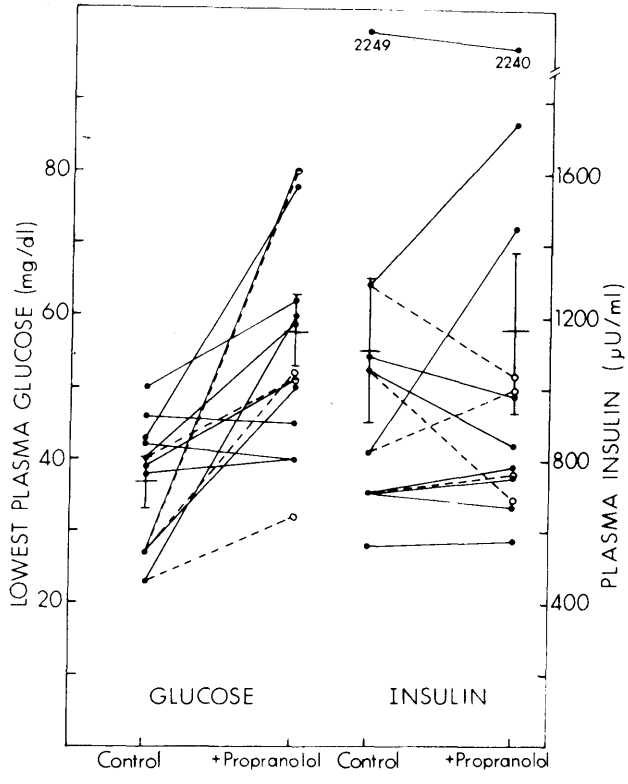

FIG. 4. Lowest plasma glucose and total plasma insulin levels observed in the study patients during the control oral glucose tolerance test and the test after prior administration of propranolol, 10 mg. (closed circles) or 25 mg. (open circles).

TABLE 2

Symptoms during oral glucose tolerance tests

	Early symptoms (0-1½ hr.)			Late symptoms (2-5 hr.)					
		Nausea, flushing, fatigue			Neuroglycopenic symptoms			Adrenergic symptoms	
Pt. No.	C	Ph	P	C	Ph	P	C	Ph	P
4	+*	+	–	+	+	–	–	–	–
5	+	+	+	+	+	–	+	+	–
6	+	+	–	–	–	–	+	++	–
8	+	–	–	+	+	–	+	+	–
9	–	–	–	–	–	–	–	–	–
13	+	+	–	+	+	–	–	–	–
14	+	–	–	–	–	–	+	+	–
15	+	+	–	+	+	–	–	–	–
16	+*	+*	–	+	+	–	+	+	–
17	+	+	–	–	–	–	–	–	–

*Patient also had abdominal bloating or diarrhea.
C-Control OGTT; Ph-Phenylephrine; P-Propranolol. .

Both phenylephrine and propranolol significantly raised the lowest plasma glucose in these patients after oral glucose without affecting insulin secretion. Neither drug reduced the early hyperglycemia or decreased the rate of fall in plasma glucose from peak glucose to lowest glucose. Propranolol was more effective than phenylephrine in raising the lowest plasma glucose, and, unlike phenylephrine, abolished the associated symptoms of hypoglycemia. Propranolol also relieved the early symptoms of flushing, nausea, and fatigue, in contrast to phenylephrine.

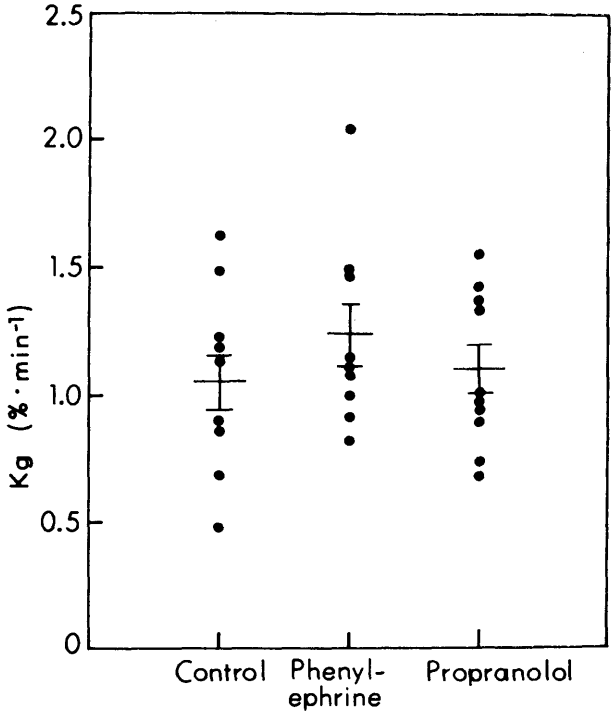

FIG. 5. Rates of glucose utilization with no pretreatment, pretreatment with phenylephrine elixir, 15 mg., or pretreatment with propranolol, 10 mg., following 25 gm. of glucose given intravenously.

Since the mechanism by which propranolol improves the chemical hypoglycemia and abolishes its symptoms clearly does not entail insulin secretion, its mode of action may depend on its effects on the secretion or action of gut hormones, pancreatic glucagon, or endogenous catecholamines. At present, there is no available data on the effect of propranolol on enteric hormone release. Adrenergic stimulants can increase pancreatic glucagon secretion,[39] which does not increase during periods of hypoglycemia in these patients.[25] The effects of propranolol are unclear.[40,41] Similarly, no data are available on the effect of propranolol on the formation or action of plasma bradykinin, which has been found to be elevated in association with the vasomotor symptoms of "early dumping," possibly from enteric hormonal stimulation.[37] Further studies are required to clarify the action of propranolol and its efficacy and suitability as a long-term therapy.

ACKNOWLEDGMENT

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REFERENCES

[1]Conn, J. W., and Seltzer, H. S.: Spontaneous hypoglycemia. Am. J. Med. *19*:460-78, 1955.

[2]Berger, H.: Hypoglycemia: A perspective. Postgrad. Med. 57:81-85, 1975.

[3]Belding, W. L., and Freedman, D. A.: Postprandial hypoglycemia presenting as a neurologic problem. Neurology *10*:613-18, 1960.

[4]Pankey, G. A.: Postgastrectomy hypoglycemia: Report of a patient treated with chlorpropamide. Diabetes *12*:82-83, 1963.

[5]Burton, R. A., and Raskin, N. H.: Alimentary (postgastrectomy) hypoglycemia: A remediable cause of recurrent seizures. Arch. Neurol. *23*:14-17, 1970.

[6]Bacon, P. A., and Myles, A. B.: Hypoglycemic coma after partial gastrectomy. Postgrad. Med. J. *47*:134-36, 1971.

[7]Hall, W. H., and Sanders, L. L.: Hypoglycemic convulsions after vagotomy and pyloroplasty. South. Med. J. *66*:502-04, 1973.

[8]Hafken, L., Leichter, S., and Reich, T.: Organic brain dysfunction as a possible consequence of postgastrectomy hypoglycemia. Am. J. Psychiat. In press.

[9]Ensinck, J. W., and Williams, R. H.: Disorders causing hypoglycemia. *In* Textbook of Endocrinology. Williams, R. H., Ed. Philadelphia, W. B. Saunders, 1974, p. 642.

[10]Robertson, R. P., and Porte, D.: Adrenergic modulation of basal insulin secretion in man. Diabetes *22*:1-8, 1973.

[11]Cerasi, E., Luft, R., and Efendic, S.: Effect of adrenergic blocking agents on insulin response to glucose infusion in man. Acta Endocrinol. *69*:335-46, 1972.

[12]Permutt, M. A., Kelley, J., Bernstein, R., Alpers, D. H., Siegel, B. A., and Kipnis, D. M.: Alimentary hypoglycemia in the absence of gastrointestinal surgery. N. Engl. J. Med. *1288*:1206-10, 1973.

[13]Raben, J. L., and Robson, M. B.: Experience with a commercial kit for the radioisotopic assay of vitamin B_{12} in serum: The Phadebas B_{12} test. J. Clin. Path. *27*:59-65, 1974.

[14]Morgan, C. R., and Lazarow, A.: Immunoassay of insulin:two antibody system: Plasma insulin levels of normal, subdiabetic and diabetic rats. Diabetes *12*:115-26, 1963.

[15]Evensen, O. K.: Alimentary hypoglycemia after stomach operations and influence of gastric emptying on glucose tolerance curve. Acta Med. Scand. (Suppl.) *127*:1-388, 1941-42.

[16]Smith, W., Fraser, R., Staynes, K., and Willcox, J. M.: The causes of postprandial attacks of palpitation and weakness after gastric operation. Q. J. Med. *22*:381-404, 1953.

[17]Huntington, F. K., and Sessions, J. T.: The postgastrectomy syndrome. Disease-A-Month, pp. 1-32, 1963.

[18]Sullivan, M., and Boshell, B.: Aetiological factors and therapeutic approach to the dumping syndrome. Br. Med. J. *1*:414-16, 1964.

[19]Salans, L. B.: Reactive Hypoglycemia. *In* Current Therapy, Conn, H. F., Ed. Philadelphia, W. B. Saunders, 1975, pp. 400-01.

[20]Grodsky, G. M., Karam, J. H., Pavlatos, F. C., et al.: Reduction by phenformin of excessive insulin levels after glucose loading in obese and diabetic subjects. Metabolism *12*:278-86, 1963.

[21]Roth, D. A., and Meade, R. C.: Hyperinsulinism-hypoglycemia in the postgastrectomy patient. Diabetes *14*:526-28, 1965.

[22]Cameron, A. J., Ellis, J. P., McGill, J. I., and LeQuesne, L.: Insulin response to carbohydrate ingestion after gastric surgery with special reference to hypoglycemia. Gut *10*:825-30, 1969.

[23]Holdsworth, C. D., Turner, D., and McIntyre, N.: Pathophysiology of postgastrectomy hypoglycemia. Br. Med. J. *4*:257-59, 1969.

[24]Rehfield, J. F., and Heding, L. G.: Increased release of gut glucagon in reactive hypoglycemia. Br. Med. J. *2*:706-07, 1970.

[25]Rehfield, J. F., Heding, L. G., and Holst, J. J.: Increased gut glucagon release as a pathogenic factor in reactive hypoglycemia? Lancet *1*:116-18, 1973.

[26]Porte, D., Graber, A. L., Kuzuya, T., and Williams, R. H.: The effect of epinephrine on immunoreactive insulin levels in man. J. Clin. Invest. *45*:228-36, 1965.

[27]Porte, D.: A receptor mechanism for the inhibition of insulin release by epinephrine in man. J. Clin. Invest. *46*:86-94, 1967.

[28]Cerasi, E., Luft, R., and Efendic, S.: Antagonism between glucose and epinephrine regarding insulin secretion. Acta Med. Scand. *190*:411-17, 1971.

[29]Imura, H., Kato, Y., Ikeda, M., et al.: Effect of adrenergic-blocking or -stimulating agents on plasma growth hormone, immunoreactive insulin, and blood free fatty acid levels in man. J. Clin. Invest. *50*:1069-79, 1971.

[30]Cryer, P., Coran, A. G., Sode, J., et al.: Lethal Escherichia coli septicemia in the baboon: Alpha-adrenergic inhibition of insulin secretion and its relationship to the duration of survival. J. Lab. Clin. Med. *79*:622-38, 1972.

[31]Vance, J. E., Buchanan, K. D., and Williams, R. H.: Glucagon and insulin release. Diabetes *20*:78-82, 1971.

[32]Bressler, R., and Cordon, M. V.: The effect of β-adrenergic receptor blocking agents on drug-induced insulin secretion. Adv. Metab. Dis. *1* (Suppl. 1):87-94, 1970.

[33]Loubatieres, A., Mariani, M. M., Sorel, G., and Savi, L.: The action of β-adrenergic blocking and stimulating agents on insulin secretion. Diabetologia 7:127-32, 1971.

[34]Massara, F., Strumia, E., Camanni, F., and Motinatti, G.: Depressed tolbutamide-induced insulin response in subjects treated with propranolol. Diabetologia 7:287-89, 1971.

[35]Anderson, J. H., Jr., Byrd, G. W., and Blackard, W. G.: Hyperresponsiveness to tolbutamide of dogs pretreated with diazoxide. Metabolism *20*:1023-30, 1971.

[36]Goodner, C. J., Koerker, D. J., Werrbach, J. H., et al.: Adrenergic regulation of lipolysis and insulin secretion in the fasted baboon. Am. J. Physiol. *224*:534-39, 1973.

[37]Blum, I., Doron, M., Laron, Z., and Atsmon, A.: Prevention of hypoglycemic attacks by propranolol in a patient suffering from insulinoma. Diabetes *24*:535-37, 1975.

[38]Wong, P. Y., Talamo, R. C., Babior, B. M., et al.: Kallikrein-kinin system in postgastrectomy dumping syndrome. Ann. Intern. Med. *80*:577-81, 1974.

[39]Leichter, S. B., Pagliara, A. S., Greider, M. H., et al.: Uncontrolled diabetes mellitus and hyperglucagonemia associated with an islet cell carcinoma. Am. J. Med. *58*:285-93, 1975.

[40]Gerich, J. E., Karam, J. K., and Forsham, P. H.: Reciprocal adrenergic control of pancreatic alpha- and beta-cell function in man. Diabetes *21* (Suppl. 1):332, 1973.

[41]Iversen, J.: Adrenergic receptors for the secretion of immunoreactive glucagon and insulin from the isolated perfused canine pancreas. Diabetologia 7:485, 1971.