Cholinergic Blockade in Reactive Hypoglycemia

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SUMMARY

The effects of cholinergic blockade on the plasma glucose and insulin responses during oral and intravenous glucose administration were studied. Propantheline (30 mg.) was given by mouth 45 minutes before standard glucose tolerance testing to produce symptomatic cholinergic blockade. In 10 normal subjects a flattening of the over-all plasma glucose response to oral glucose was observed compared with the control test, whereas insulin secretion was not different. In seven patients with repeated episodes of symptomatic reactive hypoglycemia, cholinergic blockade eliminated both symptomatic and chemical hypoglycemia in each, raising the mean nadir glucose from 44 ± 4 mg./dl. to 84 ± 8 mg./dl. ($p<0.01$) and significantly reducing insulin secretion. In contrast, following intravenous glucose challenge, cholinergic blockade produced no significant difference in the rate of glucose utilization or insulin secretion in either group.

These results are compatible with the hypothesis that excessive vagal stimulation may contribute to the hypoglycemia seen in patients with reactive hypoglycemia but suggest that the predominant effect is on the gastrointestinal tract rather than on pancreatic islets directly. These studies confirm that anticholinergic drugs may be useful adjuvants in treating these patients. DIABETES *26*:121-27, February, 1977.

The ability of vagal stimulation to increase pancreatic insulin release has long been suspected and was recently confirmed in a variety of experimental models. Pancreatic islets in various species have an abundant, although variable, autonomic nerve supply,[1] and neural elements have been demonstrated within islets to contain cholinesterase by light[2] and electron microscopy.[3] Both stimulation of the vagus nerve and in-vivo administration of cholinergic drugs elicit insulin secretion in dogs,[4-6] baboons,[7] and man.[8] This insulin-secretory response is blocked by concomitant administration of atropine. In addition, various cholinergic agents added directly to isolated rat islets have been shown to stimulate insulin release, documenting a direct pharmacologic effect on pancreatic β-cells.[9,10]

There is also much evidence that insulin secretion from pancreatic islets is modulated by insulin and/or glucose receptors within the hypothalamus via the vagus nerve.[11] For instance, stimulation of the ventral lateral hypothalamus increases insulin secretion, and this is blocked by vagotomy. Destruction of this area leads to decreased insulin secretion.[12] Intracisternal insulin administration produces insulin secretion that is blocked by vagotomy.[13] Several studies have indicated that simply presenting animals or man with food-associated stimuli (sight or smell) may cause insulin release.[14,15]

The physiologic role of the cholinergic nervous system in modulating glucose-stimulated insulin release in man is unknown. A reduction of glucose tolerance has been reported after both vagotomy[16] and ingestion of atropine.[17] Some aspects of disturbed autonomic function have long been suspected as a possible factor

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in the etiology of reactive hypoglycemia.[18,19] Excluding patients with early diabetes and previous gastric surgery, there are a large number of patients with so-called functional or idiopathic reactive hypoglycemia who have been noted to have increased incidence of peptic ulcers, gastric hypermotility, etc.,[20,21] with a single report that vagotomy cured this syndrome,[22] and reports of use of anticholinergic drugs in two patients.[23,24] Psychotherapy has been reported to alleviate this condition in the absence of dietary therapy.[25]

Because of the limited data on this subject, these studies were designed to measure the effect of cholinergic blockade on glucose-stimulated insulin release in normal subjects and patients with reactive hypoglycemia. In addition, an attempt was made to evoke reactive hypoglycemia in normal subjects by giving a cholinergic stimulus at the time of oral glucose challenge. The results presented are compatible with the hypothesis that excessive vagal activity may be an important concomitant of idiopathic hypoglycemia and demonstrate the potential effectiveness of anticholinergic therapy in this syndrome.

METHODS

All subjects were studied on the Washington University Medical School Clinical Research Center. The research protocol was approved by the Human Experimentation Committee of Washington University, and informed consent was obtained from each subject. At least 250 gm. of carbohydrate was ingested for three days prior to admission. Normal subjects (five males, five females) were within 15 per cent of ideal body weight by standard insurance tables (Metropolitan Life Insurance Company), were taking no medications, and had no family history of diabetes or hypoglycemia. The patients with reactive hypoglycemia had all been referred for diagnosis of postprandial symptoms suggestive of hypoglycemia. The presenting symptoms of each are shown in table 1. The diagnosis of reactive hypoglycemia was made by observing patients during at least one previous oral glucose tolerance test who had symptoms of hypoglycemia and a concomitant plasma glucose of 50 mg./dl. or less. The symptoms occurring during the test reproduced the symptoms of which the patient complained during usual life. These patients therefore met the requirements for diagnosis of reactive hypoglycemia recommended recently.[26] The diagnosis of idiopathic reactive hypoglycemia was arbitrarily made by exclusion, since none of the patients had had gastric surgery and all had normal intravenous glucose tolerance tests and acute-phase insulin release (see table 3) and no fasting hypoglycemia. None of the patients were obese (i.e., all were within 15 per cent ideal body weight).

After a 10-12-hour overnight fast an intravenous infusion with normal saline was started in an antecu-

TABLE 1

Clinical summary of patients with reactive hypoglycemia

Case	Age	Sex	Presenting symptoms and duration	Diagnostic OGTT Nadir glucose + symptoms of hypoglycemia		Other clinical findings
1	46	F	"Black-out spells"—1 yr.	32 mg./dl. 38 & 49 mg./dl. 33,46,29 mg./dl.	— 1972 — 1974 — 1975	Tolbutamide tolerance and 72-hour fast normal.
2	53	F	Nervousness, fatigue, mental clouding after eating—20 years	49 mg./dl. Peak insulin 1,000 U./ml. Normal fasting insulins	— 1971	Tolbutamide tolerance and 72-hour fast normal, "pharyngeal epilepsy" and "weak spells."
3	46	F	Nervousness, palpitations—1 year	44 & 45 mg./dl. 25 mg./dl.	— 1971 — 1972	Idiopathic seizure disorder previously treated with Dilantin.
4	54	F	Episodic palpitations, sweating, nervousness, fatigue, anxiety—10 yr.	50 mg./dl. 45 mg./dl. 50 & 50 mg./dl.	— 1971 — 1972 — 1975	Depression treated with antidepressant medications—5 yr.
5	24	F	Nervousness, sweating, hunger, anxiety 2-3 hours after eating—0.5 years	36 mg./dl. 50 mg./dl.	— 1971 — 1972	Family history of diabetes; depression treated with electroshock—1969.
6	54	F	Fatigue, nervousness, palpitations, insomnia—1 year	25 mg./dl. 38 mg./dl.	— 1970 — 1971	Family history of diabetes; depression treated with tranquilizers and antidepressants—5 yr.
7	38	M	Bizarre mental complaints—27 years	44 mg./dl.	— 1973	Family history of diabetes; under psychiatric care for disorder—3 years.

bital vein to facilitate blood sampling. The oral glucose tolerance was determined with 100 gm. glucose, and blood was obtained at frequent intervals and centrifuged at 4°C. for 10 minutes, and plasma was stored at −20°C. until assayed. For the cholinergic blockade studies, propantheline (30 mg.) was given orally 45 minutes before glucose administration. Intravenous glucose tolerance testing was performed by administering 25 gm. of glucose as a 50 per cent (w/v) solution intravenously over two minutes with samples of blood removed at 0, 2, 5, 10, 20, 30, 40, 50, and 60 minutes. All plasma glucose levels were determined by a glucose oxidase method adapted to an AutoAnalyzer[27] and plasma insulin by a radioimmunoassay using human insulin standards.[28] The rate of glucose utilization (Kg, defined as $0.693/t½$) was determined on the 10-60-minute glucose samples as previously described.[29]

The glucose tolerance tests with cholinergic stimulus were performed by administering 2.5 mg. bethanecol subcutaneously immediately preceding ingestion of the glucose. Statistical analysis of the data was performed by either the Wilcoxon rank sign test[30] or analysis of variance (AOV) for nonparametric data.[31]

TABLE 2

Effects of cholinergic blockade during an OGTT on glucose and insulin responses

	Control test (x ± S.E.M.)		Plus cholinergic blockade (x ± S.E.M.)
Normals (n = 10)			
Peak plasma glucose (mg./dl.)	159 ± 8	p <0.05	137 ± 5
Nadir plasma glucose (mg./dl.)	73 ± 5	p <0.05	89 ± 4
Total insulin ($\mu U. \cdot ml.^{-1} \cdot min.$)	10,500 ± 1,820	N.S.	8,867 ± 1,386
Reactive hypoglycemics (n = 7)			
Peak plasma glucose (mg./dl.)	189 ± 8	N.S.	164 ± 13
Nadir plasma glucose (mg./dl.)	44 ± 4	p <0.01	84 ± 8
Total insulin 4,569 ($\mu U. \cdot min. \cdot ml.^{-1}$/	34,056 ± 17,067	p <0.01	11,311 ± 4,569

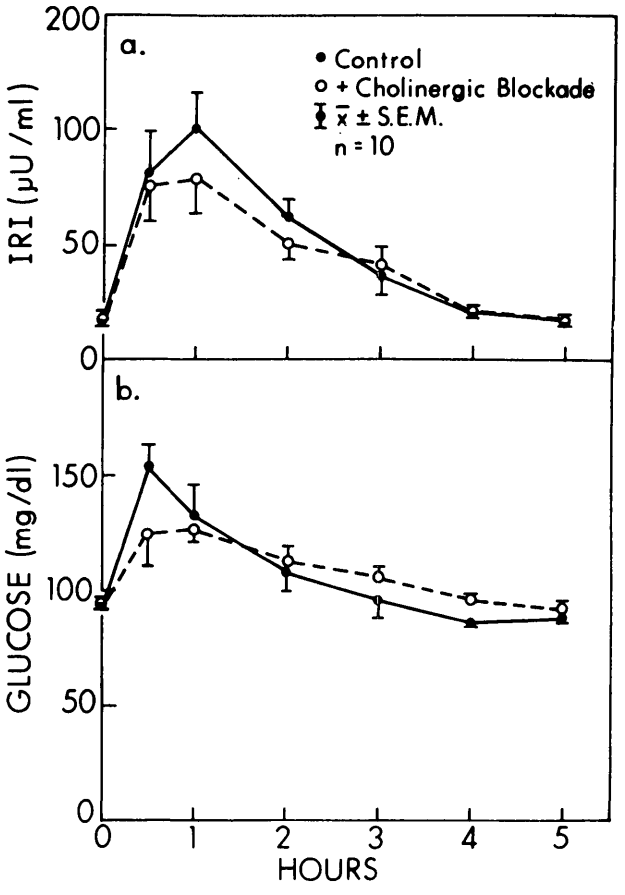

FIG. 1. Plasma glucose and insulin responses to oral glucose ingestion ± cholinergic blockade in normal subjects.

RESULTS

A. *Effects of Cholinergic Blockade During Oral Glucose Administration*

1. *Normal subjects.* Cholinergic blockade was documented by the presence of dry mouth and increased pulse rate in all subjects and of blurred vision in some. The plasma glucose response curve showed an over-all flattening with propantheline when compared to the control tests (figure 1). Plasma glucose at 30 minutes was 155 ± 8 mg./dl. vs. 124 ± 13 ($p<0.05$), and at 240 minutes was 86 ± 3 mg./dl. vs. 97 ± 6 mg./dl. ($p<0.05$) for the control vs. cholinergic blockade tests, respectively. Since peak and nadir plasma glucose responses occur at different times in each individual, these values are recorded in table 2. Cholinergic blockade significantly reduced the peak plasma glucose and increased the nadir glucose response. The insulin-secretory response to oral glucose in the normal subjects was not significantly affected by cholinergic blockade whether each time point or the total amount secreted was compared (AOV, $p>0.05$).

2. *Patients with reactive hypoglycemia.* Cholinergic

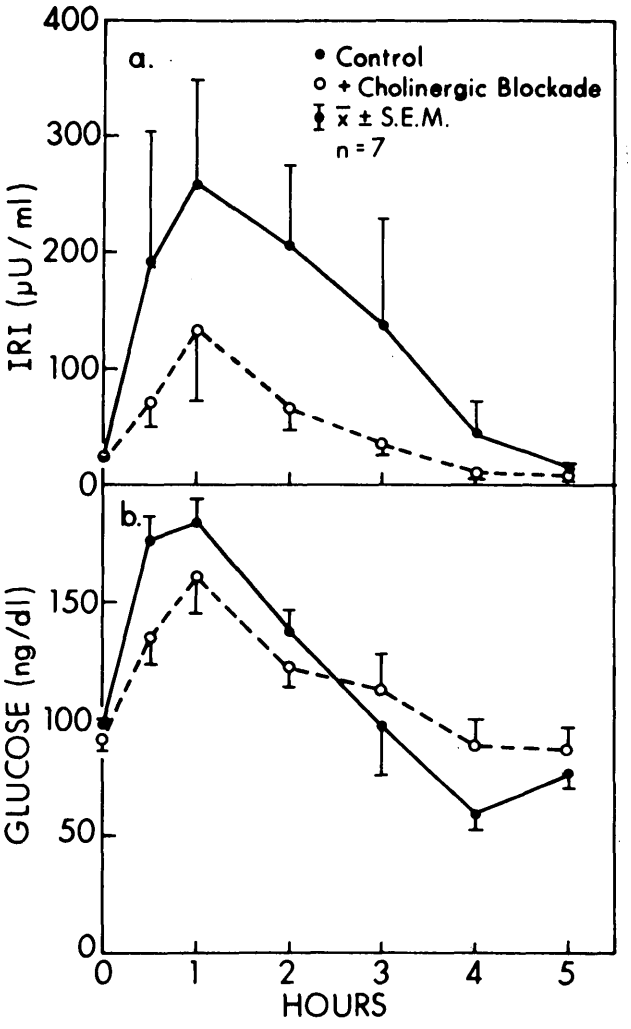

FIG. 2. Plasma glucose and insulin response to oral glucose± cholinergic blockade in patients with reactive hypoglycemia.

blockade produced similar symptoms to those observed in normal subjects and was associated with a dramatic flattening of the plasma glucose response (figure 2). The nadir plasma glucose was significantly raised, and no hypoglycemia or hypoglycemic symptoms were observed (table 2). Insulin secretion was significantly reduced in this group (AOV, $p < 0.01$).

B. *Cholinergic Blockade During Intravenous Glucose*

Standard intravenous glucose tolerance tests were performed with and without cholinergic blockade. The results are shown in table 3. The rate of glucose utilization (Kg) was not reduced, and the acute insulin response was unchanged in both normal subjects and patients with reactive hypoglycemia.

C. *Effect of Cholinergic Stimulation*

If excessive cholinergic stimulation is a concomitant of reactive hypoglycemia, it might be possible to reproduce this disorder in normal subjects given oral glucose and cholinergic stimulation. Each normal volunteer was therefore given bethanecol, an acetylcholine-like drug with long-acting effects, in a dose previously shown to stimulate insulin release in dogs and man.[8] The drug was given subcutaneously immediately preceding ingestion of the glucose, and a systemic cholinergic response was documented in each subject by the presence of tearing, salivation, pulse rate slowing, and an urge to urinate and defecate. Despite this cholinergic stimulus, there was no significant effect on either the plasma glucose or insulin responses following oral glucose administration (figure 3). The nadir glucose was not altered, nor was hypoglycemia produced in any subject.

DISCUSSION

The diagnosis of reactive hypoglycemia may be difficult.[32] Several authors have recently emphasized in editorials[33,34] that between 23 and 48 per cent of normal subjects during oral glucose tolerance tests have been noted to have whole blood glucose values below 50 mg./dl. (equivalent plasma glucose about 56 mg./dl.) without hypoglycemic symptoms. Jung et al.[35] reported that 17 per cent of normal women had whole blood glucoses of 59 mg./dl. or less (plasma glucose about 65 mg./dl.) during a five-hour oral glucose tolerance but gave no information on the incidence of symptoms during the test or during usual life. Fariss[36] determined two-hour plasma glucoses in 4,928 Air Force recruits and found values below 50 mg./dl. in 8.4 per cent. Again no data on symptoms were obtained. Luyckx and Lefebvre[37] performed 663 oral glucose tolerance tests and found plasma glucoses of less than 50 mg./dl. in 45 (7.2 per cent). Of the 45

TABLE 3

Effects of cholinergic blockade during an intravenous glucose tolerance test on plasma glucose and insulin responses

	Rate of glucose utilization (%·min.$^{-1}$)	Peak insulin (μU./ml.)
Normals (n = 10)		
Control	1.94 ± 0.21	97 ± 14
Plus cholinergic blockade	2.10 ± 0.21	105 ± 14
Reactive hypoglycemics (n = 7)		
Control	1.56 ± 0.16	82 ± 22
Plus cholinergic blockade	1.82 ± 0.13	101 ± 13

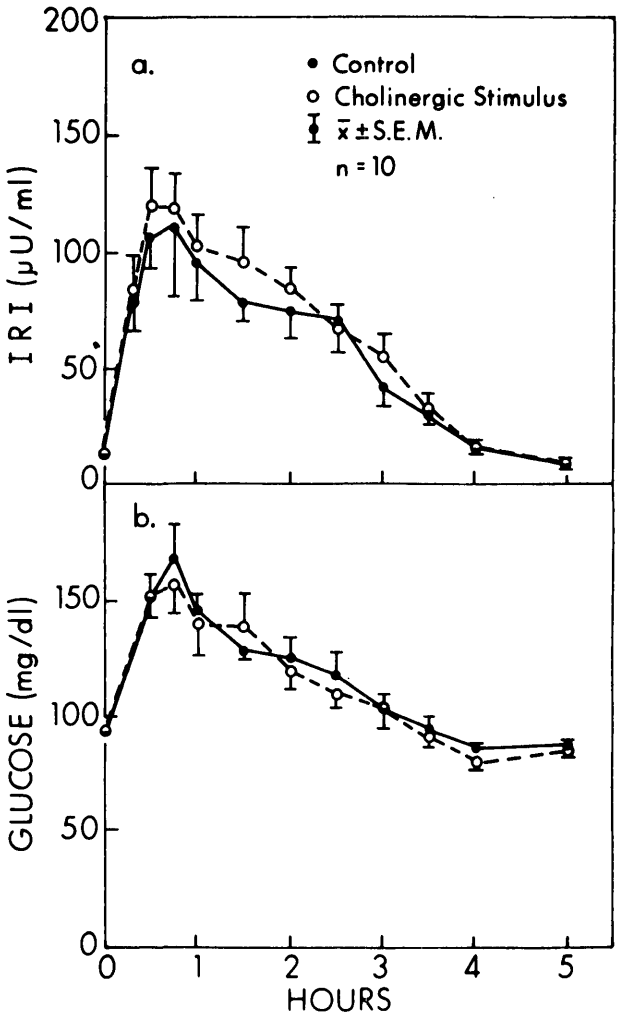

FIG. 3. Plasma glucose and insulin responses following oral glucose ± cholinergic stimulation with bethanecol (2.5 mg. subcutaneously) in normal subjects.

patients with biochemical hypoglycemia, 30 reported hypoglycemic symptoms during usual life. Permutt[32] reported glucose tolerance tests in 44 normal adults during which eight had lowest plasma glucose below 55 mg./dl. but none below 50 mg./dl. In another study in which normals were made hypoglycemic by three days of CHO restriction followed by an oral GTT, five of six normals with plasma glucoses of less than 50 mg./dl. had signs and symptoms of hypoglycemia, including perspiration, anxiety, feelings of hunger, tachycardia, and mental dullness.[38] The above data suggest that a diagnosis of reactive hypoglycemia can be made with reasonable confidence in a patient who complains of symptoms suggestive of hypoglycemia following meals and who during an oral GTT has a plasma glucose of less than 50 mg./dl., at which time symptoms occur reproducing those noted in usual life. The seven patients reported in the present study were diagnosed by this means. Each had been referred for study because of recurrent postprandial symptoms suggestive of hypoglycemia, and each had at least one previous oral GTT that confirmed the diagnosis (table 1).

The relationship between diabetes and idiopathic reactive hypoglycemia is unknown. A delay in peak insulin secretion following oral glucose challenge has been reported in two studies.[37,39] Whether the patients reported here have reactive hypoglycemia secondary to early diabetes is unknown. Three of seven patients had a positive family history for diabetes. The mean two-hour plasma glucose during the control oral GTT was 137 ± 8 for the hypoglycemic group, as against 112 ± 7 mg./dl. for the normal subjects ($p<0.05$, figures 1 and 2). In addition, the rate of glucose utilization during the intravenous GTT was significantly greater in the normal subjects (table 3). Yet the rate of glucose utilization for the hypoglycemic group was within normal limits,[40] and none had values in the diabetic range. Insulin secretion was not delayed following oral glucose (compare figures 1 and 2), and the acute insulin response to intravenous glucose challenge was not different from that of the normal subjects. Serial glucose tolerance testing over a more prolonged period[32] may be necessary to determine whether some of these patients have diabetes.

These studies demonstrate that cholinergic blockade in human beings affects the response to an oral glucose challenge but not to an intravenous one. Although the islets of Langerhans are supplied with parasympathetic nerve fibers,[1-3] cholinergic factors may augment insulin release through indirect effects on the gut. The importance of the gut in glucose-stimulated insulin release has been well documented,[41] and a growing number of gut factors have been shown to potentiate or modulate glucose-stimulated insulin release. For example, cholinergic tone affects the rate of gastrin production, gastric acid secretion, gastric emptying, secretin release, and over-all gut motility.[42] All of these factors may be modulating factors in pancreatic insulin responses following oral glucose challenge. In man, the effects of cholinergic agents on insulin secretion are limited to a study in which methacholine, a cholinergic agent with a half life longer than acetylcholine, was given intramuscularly, and a significant rise in plasma insulin over basal levels observed.[8] This effect was reproducibly blocked by atropine. The authors were careful

to point out that the methacholine stimulation may not be directly on the β-cells of the islets but indirectly, "by possible mobilization of a gastrointestinal insulin releasing hormone." In fact, the only two reports of use of anticholinergic drugs in patients with reactive hypoglycemia suggest effects of the drug on the gut. Veverbrants et al.[23] showed that anticholinergic agents blocked hypoglycemia in a patient with hypoglycemia secondary to rapid gastric emptying. O'Brien et al.[24] inhibited insulin release and blocked reactive hypoglycemia in a patient with Zollinger-Ellison syndrome and markedly elevated plasma gastrin levels.

Since Harris[43] originally described spontaneous hypoglycemia produced by excessive secretion of endogenous insulin, the concept of functional hypoglycemia secondary to neurogenic influences has received greater acceptance.[18,19] Patients with reactive hypoglycemia have been described as emotionally labile persons who complain of mild manifestations of hypoglycemia as well as symptoms of autonomic imbalance, such as weakness, faintness, nervousness, palpitations, and perspiration.[18,19,21,44] Anthony et al.[45] found that patients with reactive hypoglycemia tend to manifest abnormally high Minnesota Multiphasic Personality Inventory scales for hysteria and hypersomatization as part of their personality profile. Ford et al.[46] noted also the high prevalence of psychiatric disorders and reactive hypoglycemia. Since reflex secretion of insulin after a carbohydrate-free meal can be elicited by a variety of conditioning procedures,[14,15] it has been speculated that patients with reactive hypoglycemia may have learned to secrete insulin inappropriately.[11] Therefore, four patients in this study were told they were going to get a repeat glucose tolerance but got a sweetened solution with saccharine. No change in insulin secretion above baseline was observed.* All of the patients in the present study considered themselves to be generally nervous and anxious, and all had been placed on tranquilizers by their physicians at some time prior to these studies (table 1). Tranquilizers had little effect on relief of symptoms of hypoglycemia in these particular patients. Although anticholinergic drugs depressed insulin secretion in these patients (figure 2, table 2), the presence of excessive vagal tone in these patients has not been quantitated.

We could not elicit reactive hypoglycemia in normal subjects with cholinergic stimulation during an oral glucose tolerance test. Alternative explanations for these results are that (1) excessive cholinergic stimulation alone is not sufficient to produce reactive hypoglycemia or (2) excessive cholinergic stimulation may have to be more prolonged before the response can be induced.

Although the use of anticholinergic drugs in reactive hypoglycemia is mentioned in current texts of endocrinology[44] and manuals of medical therapy,[47] this is the first detailed study of effects of these drugs on carbohydrate tolerance. The overwhelming majority of patients with reactive hypoglycemia respond to diet therapy,[21,44] but in those who fail, various drugs have been used. An especially effective drug is phenformin,[29] but because of potential harmful cardiovascular side effects and its association with lactic acidosis, there is concern over use of this drug at the present time.[48] A relatively high dose of probanthine (30 mg.) was chosen for this study since the glucose challenge was 100 gm. For ordinary meals, use of anticholinergic drugs in doses small enough to give tolerable side effects (probanthine, 7.5 mg.) may be effective in controlling the symptoms of hypoglycemia in carefully selected patients.

*Permutt et al., unpublished observations.

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