Prevention of the Glucose Intolerance of Thiazide Diuretics by Maintenance of Body Potassium

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SUMMARY

The effect of thiazide diuretics on the glucose tolerance of seven normal men in whom potassium loss was prevented with supplementation was studied using the glucose clamp technique. An initial control 2-h hyperglycemic clamp was performed to create a square wave of hyperglycemia 125 mg/dl above basal. At 1 h, 40 g glucose/m^2 body surface area was ingested. Serial insulin (IRI) and gastric inhibitory polypeptide (GIP) levels were measured as well as the level of glucose infusion necessary to maintain the stable hyperglycemic level. After the initial study, subjects were placed on a 10-day course of 100 mg hydrochlorothiazide and 80 meq potassium per day. Subjects were monitored for dietary potassium intake, urinary potassium, and sodium losses, and the replacement of potassium adjusted accordingly. A repeat glucose clamp was done on day 10. When potassium losses were prevented, thiazides induced no alterations in glucose tolerance, beta-cell sensitivity to glucose, GIP-cell sensitivity to glucose, beta-cell sensitivity to GIP, or tissue sensitivity to insulin. Two control studies in which hypokalemia was allowed to ensue after hydrochlorothiazide ingestion revealed a diminution in glucose tolerance, a consequence of diminished pancreatic beta-cell response to glucose. We conclude that the thiazide effect on glucose tolerance is a consequence of the resultant hypokalemia that the diuretic may create. DIABETES 32:106–111, February 1983.

Since Wilkins first described chlorothiazide-induced glucose intolerance in 1959,[1] the literature has been replete with further reports and discussions of this phenomenon. Impairment of carbohydrate metabolism by the benzothiadizines has been found in both nondiabetic[2–11] and diabetic[8,12–16] subjects. However, the mechanism(s) by which the thiazides induce glucose intolerance remains subject to dispute. Decreased insulin secretion by the pancreas,[17–20] decreased tissue sensitivity to insulin,[9,21,22] increased insulin output, accelerating the development of insulin depletion in the prediabetic state,[6] and an effect on the enteropancreatic insulin axis[23] have all been implicated. Such physiologic alterations of carbohydrate economy may be a consequence of a direct effect of the benzothiadiazine molecule at any or all of the loci that participate in this economy or the consequence of potassium deficiency induced by the diuretic, as has been suggested by others.[23,24] This paper reports experiments designed to examine the effect of thiazides on the carbohydrate metabolism of normal men in whom potassium depletion was prevented. The studies seek to determine if glucose intolerance is demonstrable and to identify the locus of any observed alteration. We have used a negative feedback infusion protocol, which creates steady-state plasma glucose concentrations during experimental perturbation.[25] This "clamp technique" permits quantification of (1) glucose tolerance, (2) beta-cell sensitivity to hyperglycemia, (3) endocrine gut cell sensitivity to ingested glucose, (4) beta-cell sensitivity to gastric inhibitory polypeptide (GIP), and (5) tissue sensitivity to insulin.

MATERIALS AND METHODS

Subjects. Seven male volunteers (aged 19–28 yr) who had normal oral glucose tolerance tests were studied after an overnight fast.[25] All studies began between 0730 and 0800 h. A baseline glucose clamp study was performed after which participants were placed on hydrochlorothiazide (100 mg/day) and a potassium supplement (initially 10% KCl elixir-80 meq/day). Each subject was on the regimen for 10 days during which time sequential 24-h urines were collected for volume, sodium, and potassium measurements, and a die-

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tary diary was kept. The diary was reviewed by a dietitian who computed daily intake of potassium. Oral potassium supplementation was adjusted to maintain eukalemic balance. A second clamp study was done on day 10 of the protocol.

In two additional young, normal male volunteers, 2-h intravenous glucose clamp studies were performed before and at the completion of 10 days of the hydrochlorothiazide regimen without potassium supplementation.

Glucose clamp. The basic procedure of the glucose clamp technique has been described and validated previously.[26] Briefly, an antecubital intravenous catheter was inserted for infusion of a glucose solution. A second polyethylene catheter was placed retrograde in a wrist or dorsal hand vein and the hand enclosed in an insulated, grounded chamber warmed to 69°C to arterialize the venous blood samples.[27] After allowing temperature equilibration, at least three control heparinized blood samples were obtained at 10-min intervals and immediately assayed for blood glucose. The blood samples were then quickly centrifuged at 4°C and the plasma further aliquoted and frozen for subsequent insulin and GIP assay. A priming infusion of 20% glucose was administered intravenously to raise the blood glucose 125 mg/dl above the subject's basal level within a few minutes. Samples for blood glucose, plasma immunoreactive gastric inhibitory polypeptide (IR-GIP), and plasma immunoreactive insulin (IRI) were obtained every 2 min for 10 min and then every 5 min for the duration of the study. The blood glucose was maintained at the preselected level for 120 min by a servo-controlled negative feedback formula coupled to a variable speed infusion pump (Harvard Apparatus Co., Millis, Massachusetts). At 60 min, subjects ingested 40 g of glucose per m^2 body surface area within 5 min. The blood glucose concentration was maintained at a constant level after oral glucose by appropriate reductions in the intravenous glucose infusion to compensate for the enteric glucose absorption. For the hypokalemic thiazide control patients, the glucose infusion was adjusted for 120 min without the ingestion of an oral glucose load.

This glucose clamp technique permits definition of several aspects of glucose homeostasis. Glucose tolerance (M) can be defined by the clamp as the glucose infusion necessary to maintain the chosen constant blood glucose level after corrections are made for space and kinetics of glucose distribution and urinary loss of glucose.[26] Beta-cell sensitivity to glucose is reflected by the plasma immunoreactive insulin (IRI) response to the controlled hyperglycemic stimulus. The sensitivity of the gut to ingested glucose is measured by the plasma immunoreactive GIP (IR-GIP) response. Beta-cell sensitivity to GIP can be estimated by the increase of IRI per unit increase of IR-GIP. Tissue sensitivity to insulin is defined as the M/IRI ratio.

Assays. Blood glucose concentrations were measured by the Auto Analyzer (Technicon Instruments Corp., Tarrytown, New York) ferricyanide reduction procedure, modified to provide determinations of values in 4 min from the time of sampling. Plasma insulin was assayed in duplicate by a semiautomated double-antibody radioimmunoassay technique[28] adapted to the Micromedic (Micromedic Systems, Inc., Philadelphia, Pennsylvania). Coded samples for plasma IR-GIP were assayed by a standard technique.[29] Due to a technical problem, plasma IR-GIP from the post-thiazide studies was available on six of the seven clamped subjects.

Statistics. Each subject served as his own control. Results after thiazide and potassium administration were compared with baseline studies by Student's paired *t* analysis.

RESULTS

Potassium homeostasis. The entire study is predicated on the ability to maintain eukalemia by replacing diuretic-induced urine losses of potassium. The dietary K^+ supplementation was completely successful. Prethiazide serum K^+ concentration in the seven normal subjects was 3.85 ± 0.12 meq/L. After 10 days of the drug and replacement regimens, the serum K just before repeat clamp protocol was 3.85 ± 0.14 meq/L. Significant serum hypokalemia was produced in the two control subjects ingesting hydrochlorothiazide without potassium supplementation with changes from 4.2 to 3.2 meq/L in one and from 4.5 to 2.9 meq/L in the other.

Glucose tolerance (M). The basal blood glucose concentration averaged 92 ± 1 and 93 ± 1 mg/dl before and after thiazide treatment (Figure 1). Hyperglycemia was held stable throughout the experiment (before and after glucose ingestion). The mean blood glucose concentration for the entire study was maintained at 97 ± 1.7% and 97 ± 1.2% (SD) of the desired goal before and after the thiazide treatment. As can be seen, the glucose infusion curves both before and after glucose ingestion at 60 min were nearly identical. Despite the influx of glucose from the gut, the glucose infusion rate needed to maintain stable hyperglycemia increased almost twofold from the 30–60-min period to the 90–120-min period (from 7.8 to 14.3 mg/kg • min). Clearly, this was due to the remarkable increase in plasma insulin in the second hour of the study (Figure 2).

The amount of glucose metabolized (M) under conditions of controlled hyperglycemia is an index of "intolerance" to glucose in these clamp studies. The glucose infusion necessary to maintain the hyperglycemic plateau is corrected for changes in glucose content in the glucose space of the body and for urinary glucose losses during the test. Once hyperglycemia is attained, the "space correction" is quite small as are the urinary glucose losses at the level of hyperglycemia used in these studies. Endogenous glucose production provides only a small fraction of the glucose metabolized in this type of study since the hyperglycemia and resultant hyperinsulinemia reduce the basal hepatic glucose production of about 1.7 mg/kg min[30] by greater than 90%.[31] Thus, M is a reasonable measure of tolerance. In the 0–60-min time period (the initial phase of the clamp study in which only intravenous glucose is administered) the glucose infusion rate required to maintain hyperglycemia, M, was not significantly changed after thiazide treatment (Table 1). Thus, in these studies the well-described glucose intolerance following thiazide administration was prevented by the potassium supplementation regimen.

It is of interest that in the 60–120-min time period, even though a large additional glucose load was administered orally, it was necessary, following a brief decrease in the glucose infusion rate, to increase the infusion markedly (Figure 1). The M values in Table 1 underestimate the glucose metabolized since they do not include the glucose absorbed from the gut. The oral dose of 40 g/m^2 body surface area is

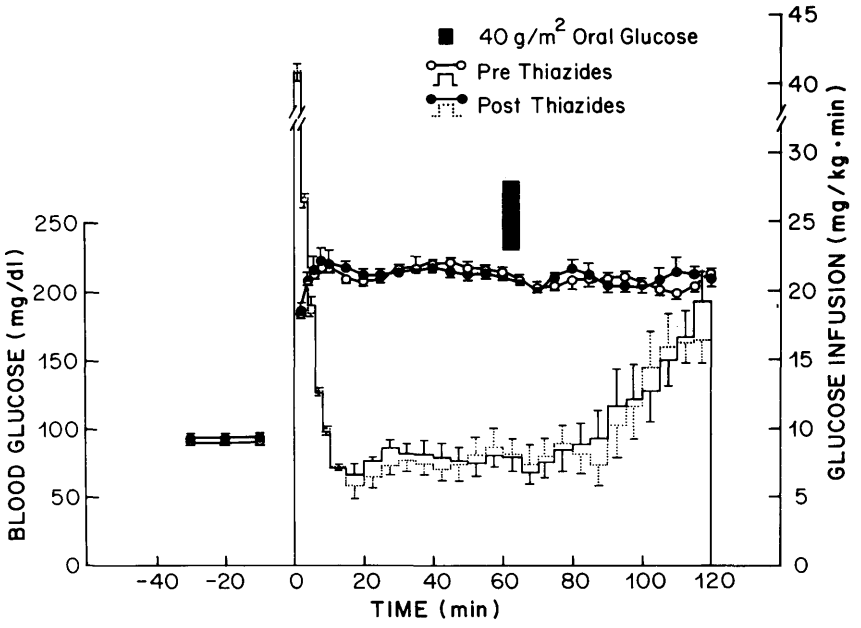

FIGURE 1. Glucose clamp studies before and after 10 days of thiazide administration. The line connecting the circles represents the blood glucose values during the study. The bar graph depicts the glucose infusion rate needed to maintain goal glucose. The point in the study at which the oral glucose load was ingested is marked by the heavy bar at 60 min. The means ± SEM are shown.

essentially equivalent to 1000 mg/kg body wt; it is probable that in the first hour after its ingestion, more than 50% of this dose is absorbed.[32] Thus, the mean glucose absorbed from the gut in this hour is approximately equal to the glucose infused, i.e., about 10 mg/kg • min. In any case, the high M values during the 60–120-min period were uninfluenced by thiazide administration in the face of normal body potassium.

Beta-cell sensitivity to glucose. Neither the pattern nor the level of insulin during the two glucose clamps varied (Figure 2). The 0–60-min plasma IRI, 40 ± 5 μU/ml after 10 days of potassium-supplemented thiazide administration, was not significantly different from the pretreatment value of 35 ± 3 μU/ml. Thus, drug administration alone had no effect on IRI levels in response to the glucose level.

GIP sensitivity to glucose. Oral, but not intravenous glucose, stimulates secretion of GIP by the gut.[33–37] The post-thiazide value for the IR-GIP during the intravenous phase (0–60 min) was not significantly different by paired analysis from the pretreatment level (Figure 2). The expected increase in IR-GIP in response to the glucose ingested at 60 min occurred in both baseline and post-thiazide studies, and the magnitude of the IR-GIP response during oral glucose absorption (60–120 min) was unaffected by potassium-supplemented thiazide treatment.

Beta-cell sensitivity to GIP. Andersen et al. have shown that the insulin response to the rise in IR-GIP provoked by oral glucose is a measure of beta-cell sensitivity to secreted GIP.[37] Sensitivity of the beta-cell to GIP can be computed as the ratio of insulin response to the GIP stimulus.[38] The response is taken as the ratio of actual insulin level achieved ($IRI_{90-120\ ACT}$) to the anticipated or predicted insulin level ($IRI_{90-120\ PRED}$) during the second hour of a hyperglycemic clamp had oral glucose not been administered. The latter can be predicted with accuracy from the insulin levels during the 30–60-min period[37]:

$$IRI_{90-120\ PRED} = 11 + 1.40\ (IRI_{30-60})$$

The stimulus is taken as the ratio of stimulated GIP level to the unstimulated level. Thus, sensitivity of the beta-cell to GIP is computed as:

$$\text{Sensitivity (S)} = \frac{IRI_{90-120\ ACT}/IRI_{90-120\ PRED}}{\text{IR-GIP}_{90-120}/\text{IR-GIP}_{0-60}}$$

In this study the baseline sensitivity of 1.67 ± 0.32 is not significantly different from 1.53 ± 0.12 obtained after thiazide treatment. One can conclude that thiazide administration in the absence of hypokalemia does not alter the enteropancreatic axis.

Tissue sensitivity to insulin. Glucose metabolized (M) in the first hour is determined from the glucose infusion rate, as discussed above. M in the second hour is the sum of glucose infused plus glucose absorbed from the gut. Since we have no independent measure of glucose absorption in these studies, tissue sensitivity before and after thiazides can be measured directly only during the first hour of the clamp study. Thus, we examined the M/I ratio for the 0–60-min period as affected by potassium-supplemented thiazide ingestion. As with the other measures of glucose economy, the treatment regimen had no effect on this variable of glucose homeostasis: M/I ratio of (15.9 ± 1.6) × 10^{-2} compared with (13.1 ± 0.5) × 10^{-2}. One can conclude that the reduction in tissue sensitivity to endogenous insulin reported after thiazide use was prevented by maintenance of normal body potassium.

Glucose tolerance in hypokalemic controls. Glucose metabolized (M) in the first hour and over the 2 h of clamped hyperglycemia fell importantly in each of the two control subjects. The M fell from 7.104 to 5.120 mg/kg • min for the 10–60-min period and from 8.273 to 6.53 mg/kg • min in the 10–120-min period in the first subject while falling from 8.477 to 6.078 during the first hour and from 10.552 to 9.147 mg/kg • min during the 2-h study in the second. This decline in

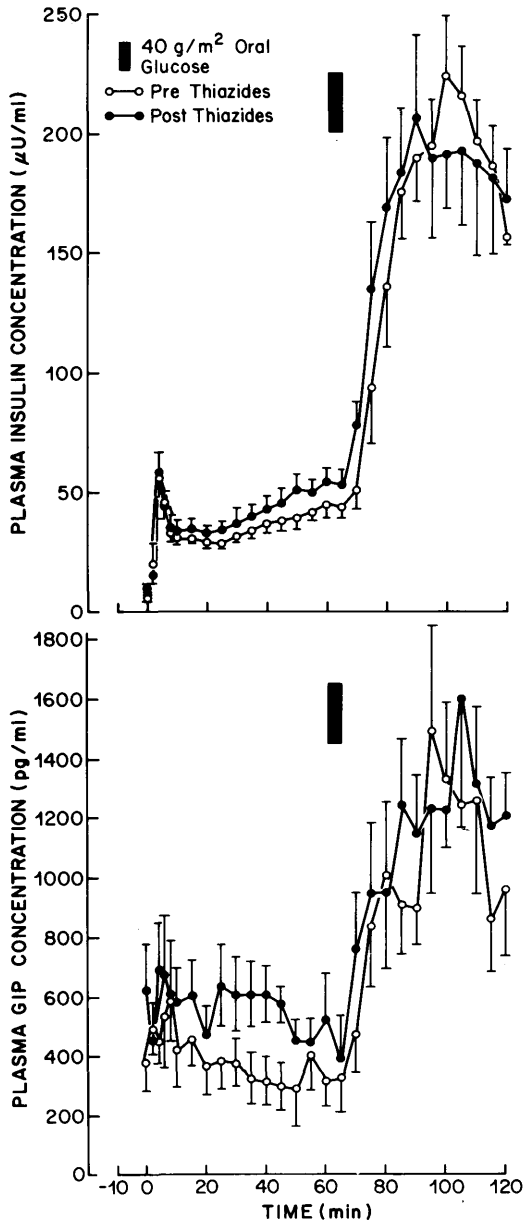

FIGURE 2. Mean insulin and GIP responses to steady-state hyperglycemia and an oral glucose load during the glucose clamp, pre- and post-thiazide administration. Data are presented as means ± SEM.

glucose "tolerance" can be completely explained by a fall in beta-cell response to glucose stimulus as the 10–60- and 10–120-min and peak IRI levels fell in each subject about 20% without a change in the M/I ratio.

DISCUSSION

There is no question that a variety of procedures, which have in common the depletion of potassium from the body, may induce glucose intolerance. These include thiazide administration,[10–15,21,23] primary and secondary aldosteronism,[39] and oral administration of potassium-binding resins.[24,40] However, Conn reported that glucose tolerance was normalized after potassium was replaced in patients with primary aldosteronism,[39] while Rapaport and Hurd[14] and Gorden[23] were able to correct the glucose intolerance induced by thiazides with potassium replenishment. Our studies using doses of thiazides and a duration of administration of the drug known to produce glucose intolerance[11–15] confirm these latter reports since we prevented potassium depletion and, in turn, prevented glucose intolerance.

The mechanism(s) by which thiazide diuretics produce glucose intolerance has been studied both in vitro and in vivo. There is evidence both for and against a primary role of (1) decreased beta-cell sensitivity to glucose and (2) decreased tissue sensitivity to insulin. Decreased beta-cell sensitivity has been implicated by the in vitro studies of Frerichs and Creutzfeld[20] with direct exposure of rat and pig pancreatic slices to thiazides and by Fuhrman[41] and Gardner et al.[42] with potassium-depleted tissue preparations. Rowe et al.,[40] using the glucose clamp technique in patients with resin-induced potassium depletion, reported a decreased M, decreased IRI response, and a normal M/IRI ratio. Those results suggested the presence of normal tissue sensitivity to insulin and decreased beta-cell sensitivity. However, earlier studies have proposed that decreased tissue sensitivity to insulin is the major mechanism for thiazide-induced glucose intolerance. Barnett and Whitney reported decreased glucose uptake by non-insulin-stimulated rat hemidiaphragms in the presence of thiazides.[22] Beardwood et al. suggested that the decreased glucose tolerance of their subjects on thiazides was due, at least in part, to decreased peripheral uptake of glucose.[21] Sagild et al., using a cation-exchange resin to deplete subjects of potassium, reported a significant decrease in glucose and tolbutamide response test performances, but a normal serum insulin response to these stimuli.[24]

The present studies were designed to evaluate possible direct pharmacologic effects of thiazides in intact man under conditions that prevent potassium depletion. The premise behind these studies came from the clinical observation of Gorden, who demonstrated that repletion of potassium after thiazide treatment reversed observed diminution of glucose tolerance.[23] The clamp technique was used since it permitted not merely a gross evaluation of the state of glucose disposition in man, but also allowed one to make some judgments as to the nature of any defined abnormalities. Glucose tolerance, beta-cell sensitivity to glucose, gut cell sensitivity to glucose, beta-cell sensitivity to GIP, and tissue sensitivity to insulin all remained unaltered by thiazide diuretics when potassium depletion was prevented. In two control studies in which normal subjects ingested thiazides without support of the serum potassium, the expected glucose intolerance was apparent by the clamp technique. The study, then, establishes that benzothiadiazine diuretics have no direct effect on any aspect of glucose homeostasis and implies that the clinical observations with respect to glucose intolerance in patients on such diuretics are a consequence of the propensity of the drug to induce potassium loss. The defect in thiazide-induced hypokalemia can be demonstrated by the control clamp studies to reside at the level of beta-cell responsiveness to glucose stimulus as has been shown for other models of hypokalemia.[23,24,40] The clinical lesson from such studies is that this major complication of thiazide administration may be avoided by assiduous attention to potassium balance.

TABLE 1
The effect of thiazide administration on metabolic variables during the hyperglycemic clamp measured before (0–60 min) and after (60–120 min) oral glucose administration

	Glucose tolerance M (mg/kg min)		β-Cell sensitivity to glucose IRI (μU/ml)		Gut cell sensitivity to glucose IR-GIP (pg/ml)		β-Cell sensitivity to GIP S*	Tissue sensitivity to insulin M/IRI $\times 10^{-2}$
	0–60 min	60–120 min	0–60 min	60–120 min	0–60 min	60–120 min	60–120 min	0–60 min
Pre-thiazide								
Mean	5.48	11.22	35	151	379	940	1.17	15.9
SE	0.55	1.69	3	12	87	166	0.23	1.6
Post-thiazide								
Mean	5.29	10.90	40	157	548	1072	1.10	13.1
SE	0.64	1.42	5	15	58	113	0.11	0.5
+(Pre–Post)								
Mean	0.19	0.32	−5	−6	−176	−105	0.01	2.8
SE	0.59	1.23	5	15	100	299	0.20	1.5
t	0.32	0.26	1.00	0.40	1.77	0.35	0.05	1.86
P	NS	NS	NS	NS	NS	NS	NS	NS

*See text for formula.

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REFERENCES

[1] Wilkins, R. W.: New drugs for the treatment of hypertension. Ann. Intern. Med. *50*:1, 1959.

[2] Ferguson, M. J.: Saluretic drugs and diabetes mellitus. Am. J. Cardiol. *7*:568, 1961.

[3] El-Ebrashy, M., El-Danasoury, M., and Higazi, A. M.: Hyperuricaemic and hyperglycaemic effects of thiazides in non-diabetic. J. Egypt Med. Assoc. *48*:467–78, 1965.

[4] Hauman, R. L., and Weller, J. M.: Hyperglycemic effect of chlorothiazide. Clin. Res. *9*:180A, 1961.

[5] Hollis, W. C.: Aggravation of diabetes mellitus during treatment with chlorothiazide. JAMA *176*:947–49, 1961.

[6] Khan, F., and Spergel, G.: Diabetogenic drugs. Lancet *1*:808, 1976.

[7] Lewis, P. J., Kohner, E. M., Petrie, A., and Dollery, C. T.: Deterioration of glucose tolerance in hypertensive patients on prolonged diuretic treatment. Lancet *1*:564–66, 1976.

[8] Shapiro, A. P., Benedek, T. G., and Small, J. L.: Effect of thiazides on carbohydrate metabolism in patients with hypertension. N. Engl. J. Med. *265*:1028–1033, 1961.

[9] Weller, J. N., and Borondy, P. E.: Effects of benzothiadiazine drugs on carbohydrate metabolism. Metabolism *14*:708–14, 1965.

[10] Wolff, F. W., Parmley, W. W., White, K., and Okun, R.: Drug induced diabetes. JAMA *185*:568–74, 1963.

[11] Zatuchni, J., and Kordasz, F.: The diabetogenic effect of thiazide diuretics. Am. J. Cardiol. *7*:565–67, 1961.

[12] Goldner, M. G., Zarowitz, H., and Akgun, S.: Hyperglycemia and glucosuria due to thiazide derivatives administered in diabetes mellitus. N. Engl. J. Med. *262*:403–405, 1960.

[13] Kansal, P. C., Buse, J., and Buse, M. G.: Thiazide diuretics and control of diabetes mellitus. South. Med. J. *62*:1374–79, 1969.

[14] Rapaport, M. I., and Hurd, H. F.: Thiazide-induced glucose intolerance treated with potassium. Arch. Intern. Med. *113*:405–408, 1964.

[15] Runyan, J. W.: Influence of thiazide diuretics on carbohydrate metabolism in patients with mild diabetes. N. Engl. J. Med. *267*:541–43, 1962.

[16] Wales, J. K., Viktoria, J. K., and Wolff, F. W.: The effect of hydrochlorothiazides in normal subjects receiving high carbohydrate diets. Am. J. Med. Sci. *254*:499–504, 1967.

[17] Selzer, H. S., and Allen, E. W.: Inhibition of insulin secretion in diazoxide diabetes. Diabetes *14*:439A, 1965.

[18] Fajans, S. S., Floyd, J. C., Knopf, R. F., Bull, J., Guntsche, E. M., and Conn, J. W.: Benzothiadiazine suppression of insulin release from normal and abnormal islet cell tissue in man. J. Clin. Invest. *45*:481–93, 1966.

[19] Hicks, B. H., Ward, J. D., Jarrett, R. J., Keen, H., and Wise, P.: A controlled study of clopamine, clorexolone, and hydrochlorothiazide in diabetes. Metabolism *22*:101–109, 1973.

[20] Frerichs, H., and Creutzfeldt, W.: Insulin release from pancreas of the rat, the rabbit, and miniature-pig in-vitro. Diabetologia *1*:80A, 1965.

[21] Beardwood, D. M., Alden, J. S., Graham, C. A., Beardwood, J. T., Jr., and Marble, A.: Evidence for a peripheral action of chlorothiazide in normal man. Metabolism *14*:561–67, 1965.

[22] Barnett, C. A., and Whitney, J. E.: The effect of diazoxide and chlorothiazide on glucose uptake in-vitro. Metabolism *15*:88–93, 1966.

[23] Gorden, P.: Glucose intolerance with hypokalemia. Diabetes *22*:544–51, 1973.

[24] Sagild, U., Andersen, V., and Andreasen, P. B.: Glucose tolerance and insulin responsiveness in experimental potassium depletion. Acta Med. Scand. *169*:243–51, 1961.

[25] Andres, R.: Aging and diabetes. Med. Clin. North Am. *55*:835–46, 1971.

[26] DeFronzo, R. A., Tobin, J. D., and Andres, R.: Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am. J. Physiol. *237*:E214–23, 1979.

[27] McGuire, E. A. H., Helderman, J. H., Tobin, J. D., Andres, R., and Berman, M.: Effects of arterial versus venous sampling on the analysis of glucose kinetics in man. J. Appl. Physiol. *41*:565–73, 1976.

[28] Morgan, C. R., and Lazarow, A.: Immunoassay of insulin: two; antibody system plasma insulin levels of normal, sub-diabetic, and diabetic rats. Diabetes *12*:115–26, 1963.

[29] Kuzio, M., Dryburgh, J. R., Malloy, J. M., and Brown, J. C.: Radioimmunoassay for gastric inhibitory polypeptide. Gastroenterology *66*:357–64, 1974.

[30] Insel, P. A., Liljenquist, J. E., Tobin, J. D., Sherwin, R. S., Watkins, P., Andres, R., and Berman, M.: Insulin control of glucose metabolism in man: a new kinetic analysis. J. Clin. Invest. *55*:1057–1064, 1975.

[31] DeFronzo, R. A., Alvestrand, A., Smith, D., Hendler, R., Hendler, E., and Wahren, J.: Insulin resistance in uremia. J. Clin. Invest. *67*:563–68, 1981.

[32] Radziuk, J., McDonald, J. T., Rubenstein, D., and Dupre, J.: Initial splanchnic extraction of ingested glucose in normal man. Metabolism *27*:657–69, 1978.

[33] Cataland, S., Crockett, S. E., Brown, J. C., and Mazzaferri, E. L.: Gastric inhibitory polypeptide (GIP) stimulation by oral glucose in man. J. Clin. Endocrinol. Metab. *39*:223–28, 1974.

[34] Thomas, F. B., Shook, D. F., O'Dorisio, T. M., Cataland, S., Mekjian, H. S., Caldwell, J. H., and Mazzaferri, E. L.: Localization of gastric inhibitory polypeptide release by intestinal glucose perfusion in man. Gastroenterology *72*:49–54, 1977.

[35] Ross, S. A., Brown, J. C., and Dupré, J.: Hyposecretion of gastric inhibitory polypeptide following glucose in diabetes mellitus. Diabetes *26*:525–29, 1977.

[36] Crockett, S. E., Mazzaferri, E. L., and Cataland, S.: Gastric inhibitory polypeptide (GIP) in maturity-onset diabetes mellitus. Diabetes *25*:931–35, 1976.

[37] Andersen, D. K., Elahi, D., Brown, J. C., Tobin, J. D., and Andres, R.:

Oral glucose augmentation of insulin secretion. Interactions of gastric inhibitory polypeptide with ambient glucose and insulin levels. J. Clin. Invest. *62*:152–61, 1978.

[38] Elahi, D., Andersen, D. K., Tobin, J. D., and Andres, R.: Discrepant performance on oral and intravenous glucose tolerance tests: the role of gastric inhibitory polypeptide. J. Clin. Endocrinol. Metab. *52*:1199–1203, 1981

[39] Conn, J. W.: Hypertension, the potassium ion and impaired carbohydrate tolerance. N. Engl. J. Med. 273:1135–43, 1965.

[40] Rowe, J. W., Tobin, J. D., Rosa, R. M., and Andres, R.: Effects of experimental potassium deficiency on glucose and insulin metabolism. Metabolism *29*:498–502, 1980.

[41] Fuhrman, F. A.: Glycogen, glucose tolerance and tissue metabolism in potassium deficient rats. Am. J. Physiol. *167*:314–20, 1951.

[42] Gardner, L. I., Talbot, N. B., Cook, C. D., Berman, H., and Uribe, C.: The effect of potassium deficiency on carbohydrate metabolism. J. Lab. Clin. Med. 35:592–602, 1950.