Effect of carbohydrate restriction and high carbohydrate diets on men with chemical diabetes[1]

James W. Anderson, M.D.

ABSTRACT The influence of low carbohydrate (CHO) diets, starvation, and high CHO diets on glucose tolerance tests (GTT) and plasma insulin responses of men with chemical diabetes was studied. The GTT and insulin responses of these seven lean diabetic men were unchanged when the carbohydrate content of the diet was reduced from 44 to 20% of calories. After a 48-hr fast a significant deterioration of the GTT was observed in these diabetic men but the percentage change was identical to that reported previously for normal men. Thus these studies indicate that changes in glucose metabolism with carbohydrate restriction in lean men with chemical diabetes are quite similar to those reported previously for normal men. The fasting plasma glucose values of seven lean and four obese men with chemical diabetes were significantly lower after one week on a 75% CHO diet than values on a 44% CHO diet. The 75% CHO diet also was accompanied by slight improvements in the oral and intravenous GTT and by slightly lower plasma insulin responses. The improvement in glucose metabolism on high CHO diets appears to result from increased insulin sensitivity. Serum triglyceride values were approximately 55% higher on the 75% CHO diet than values on the 44% CHO diet for the 11 men but these differences were not statistically significant. These studies support previous observations and suggest that high CHO diets may be beneficial in the management of certain diabetic patients. However, further studies are required to determine the long-term effects of high CHO diets containing natural foods on the glucose and lipid metabolism of diabetic patients. *Am. J. Clin. Nutr.* 30: 402-408, 1977.

Nondiabetic individuals have a remarkable capacity to maintain normal glucose homeostasis despite wide variations in the intake of carbohydrate or calories. We have previously demonstrated that the oral glucose tolerance tests (GTT) of normal men are essentially the same on isocaloric diets containing as low as 8% of calories as carbohydrate (1) to isocaloric diets containing as high as 80% of calories as carbohydrate (studies at 13 days, Reference 2). While starvation for 48 hr leads to impairment of glucose tolerance, normal men can consume as few as 500 cal for 10 days without alterations in their glucose tolerance (3). Thus these observations indicate that nondiabetic men can maintain normal glucose tolerance through a wide range of levels of carbohydrate intake. Normal men, however, are sensitive to increases in the fat content in the diet and regularly develop glucose intolerance on high fat diets (4, 5).

The response of diabetic patients to varying levels of carbohydrate intake under conditions where the fat content is not changed has not been systematically studied. Our previous observation (1) that patients with reactive hypoglycemia (some of whom were considered to have latent diabetes) are exquisitely sensitive to carbohydrate deprivation raised the question of whether mildly diabetic patients may show a deterioration of glucose tolerance on low carbohydrate diets. Additionally, a number of studies (6-10) have suggested that high levels of dietary carbohydrates may be beneficial for certain diabetics. The present study was designed to compare the glucose tolerance and insulin responses of men with chemical diabetes to carbohydrate restriction and high carbohydrate diets with the responses previously observed for normal individuals.

[1] From the Medical Service, Veterans Administration Hospital and Department of Medicine, University of Kentucky College of Medicine, Lexington, Kentucky.

Methods

Patients

Ten lean men (Table 1) who were within 15% of their ideal (desirable) body weight (11) and four obese men were studied. These men were considered to have chemical diabetes (12) on the basis of two abnormal oral GTT. Each man had plasma glucose values at 1 hr above 185 mg/dl and at 2 hr above 140 mg/dl on each of two GTT (See Reference 13). The known duration of glucose intolerance ranged from 1 to 16 months. All men were on weight-maintaining diets containing at least 200 g of carbohydrate per day for at least 1 week before the GTT. Three patients had received insulin or sulfonylurea agents previously. Patient 9 had been treated with tolazamide for 3 months but this had been discontinued 2 months prior to study. Patient 11 had received insulin for 6 months but had received none during the 3 months prior to study. Patient 13 had received tolbutamide 1 g per day for 3 months but this was discontinued prior to these studies. None of the other patients had received drug therapy for their diabetes. No patients had received thiazide diuretics or other drugs known to alter glucose tolerance during the 3 months prior to study.

Composition of diets

All studies were carried out on a metabolic ward and the caloric intake was individualized to maintain constant weight. All diets consisted of solid foods and were fed as three meals plus a snack; approximately $^2/_7$ of total calories were taken at 8:00 AM, 12:00 noon, and 5:30 PM and $^1/_7$ was taken at 9:00 PM. Except during the 48-hr fast which was done after the other studies were completed, the three diets (Table 2) were isocaloric. All men were on weight-maintaining diets containing at least 200 g of carbohydrate for at least 1 week before studies were initiated. The 44% carbohydrate (CHO) diet contained 55% of carbohydrates as oligosaccharides and 45% as polysaccharides. The 75% CHO diet contained 47% of carbohydrate as oligosaccharides and 53% as polysaccharides. GTT were performed at the end of 1 week on each of the three diets.

TABLE 1
Male patients. Weight is expressed as percentage of ideal body weight (10). Plasma glucose values represent the mean fasting value (0 hr) and values at 1 hr and 2 hr during the GTT

Patient	Age	Weight (ideal)	Plasma glucose		
			0 Hr	1 Hr	2 Hr
	yr	*%*		*mg/dl*	
1	38	103	106	242	148
2	53	100	93	202	154
3	21	100	123	212	192
4	50	98	105	221	180
5	25	89	90	193	152
6	59	86	96	310	206
7	56	109	131	224	270
8	59	107	102	186	169
9	68	107	119	210	251
10	48	114	114	193	148
11	50	126	102	194	184
12	65	139	123	198	188
13	63	128	143		
14	51	140	154		

TABLE 2
Composition of diets

Diet (CHO)	Composition, (% of cal)		
	Carbohydrate	Protein	Fat
44%	44	20	36
20%	20	44	36
75%	75	9	16

Measurements

Daily weights and fasting plasma glucose measurements were obtained. There were no significant changes in body weight in any of the men except during the 48 hr period of fasting. GTT were performed after an 11 hr fast by administering 100 g glucose orally over a 1 to 3 min period and blood was collected for plasma glucose and insulin measurements every 30 min over the next 3 hr. The glucose tolerance area (GTA) over 3 hr was calculated (1) and is expressed as mg-min/dl $\times 10^{-3}$. The total insulin area (TIA) over 3 hr also was calculated (1) and expressed as $\mu U-min/ml \times 10^{-3}$. Plasma glucose measurements and plasma insulin values, using the double antibody radioimmunoassay (14), were performed as previously described (1). Intravenous glucose tolerance tests were performed by injecting 25 g of glucose intravenously in less than 5 sec and the disappearance rate (K) of glucose was calculated (15). The paired t test was used for all statistical comparisons unless otherwise indicated.

Results

Influence of carbohydrate restriction

Although the 20% CHO diet contained an average of only 102 g of carbohydrate per day, the GTT of seven nonobese men (Figure 1A) was virtually identical to that observed on the 44% CHO diet containing an average of 225 g of carbohydrate. The fasting plasma glucose values were lower ($P < 0.02$) on the 20% CHO diet, but the GTA were virtually identical on these two diets (Table 3). The fasting plasma insulin values and the TIA were similar on these two diets. Thus carbohydrate restriction did not lead to an impairment of GTT in these men with chemical diabetes. These results are very similar to those we have reported previously (1) for normal men with similar degrees of carbohydrate restriction.

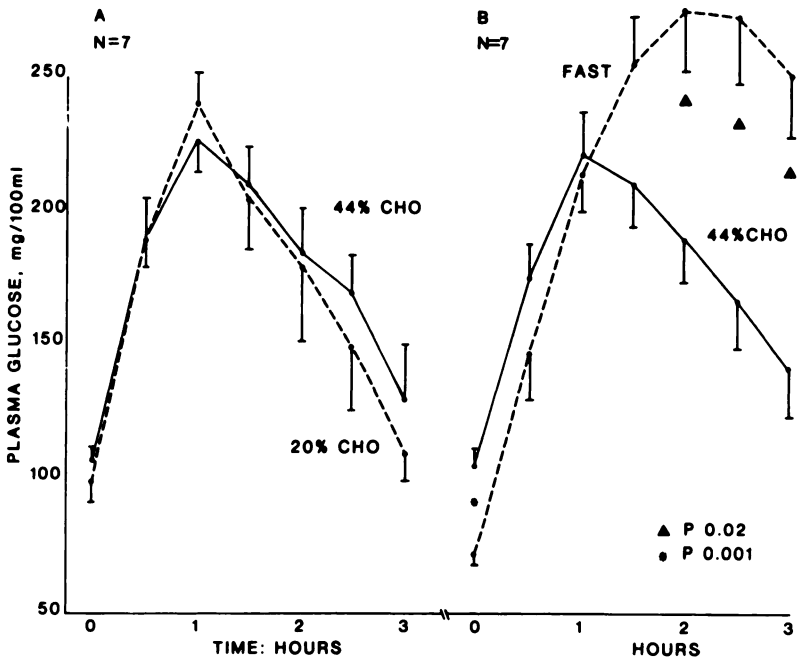

FIG. 1. Effect of low carbohydrate diet and 48-hr fast on GTT of seven lean diabetic men. Oral glucose was given a 0 time. Values represent means with SEM indicated by *brackets*.

TABLE 3
Glucose and insulin responses during GTT. Glucose values represent the mean ± SEM for seven nonobese men on each diet while insulin values for six nonobese men are presented

Diet	Patient	Fasting Plasma Glucose	GTA	Fasting Plasma Insulin	TIA
		mg/dl	*mg-min/dl* × 10^{-3}	*μU/ml*	*μU-min/dl* × 10^{-3}
44% CHO	1-7	106 ± 6	32.9 ± 2.1	14.2 ± 3.6	13.9 ± 3.9
20% CHO	1-7	98 ± 6[a]	32.2 ± 2.2	14.1 ± 5.0	13.1 ± 2.2
44% CHO	2-8	106 ± 6	32.6 ± 2.1	12.4 ± 3.1	13.2 ± 2.9
48-hr fast	2-8	73 ± 4[b]	39.7 ± 2.2[a]	7.7 ± 3.2[b]	15.4 ± 3.1
44% CHO	4-10	108 ± 5	33.6 ± 2.3	17.0 ± 4.3	15.3 ± 4.0
75% CHO	4-10	94 ± 4[a]	29.8 ± 1.4	13.1 ± 3.4	12.8 ± 3.4

[a] Value differs significantly from values on the 44% CHO diet ($P < 0.02$). [b] Value differs significantly from values on the 44% CHO diet ($P < 0.005$).

Influence of 48-hr fast

Starvation was accompanied by a significant reduction in fasting plasma glucose values and a significant deterioration of the GTT was observed in seven nonobese men (Fig. 1B). The GTA (Table 3) was 21% higher than that observed on a 44% CHO diet; this percentage change was virtually identical to that observed for normal men (1). Fasting plasma insulin values were significantly lower after the fast but the TIA was unchanged. Thus fasting these men with chemical diabetes was accompanied by changes in the GTT and insulin responses which were virtually identical to that observed for normal men (1).

Influence of high carbohydrate diet

After seven days on the 75% CHO diet, glucose values were lower at every point during the GTT for seven nonobese diabetic men (Fig. 2A). Fasting plasma glucose values (Table 4) and values at 30 min were significantly lower; the GTA was slightly improved (Table 3). Six of the seven men showed an improvement in the GTT but these changes in the GTA were not statistically significant.

Plasma insulin values were also lower at every time point during the GTT and the TIA was slightly lower in these nonobese men. In Figure 2B, only the mean values for plasma insulin concentration are given because of the wide range observed. Fasting insulin values on the 44% CHO diet ranged from 3.4 to 32.6 μU/ml and on the 75% CHO diet ranged from 3.2 to 22.4 μU/ml. Likewise, the TIA on the 44% CHO diet ranged from 5.8 to 31.7 μU-min/ml × 10^{-3} while ranging from 4.3 to 28.5 μU-min/ml × 10^{-3} on the 75% CHO diet. The TIA values were lower in four of the six men on the 75% CHO diet than values observed on the 44% CHO diet. Fasting plasma insulin values were lower in all six men on the 75% CHO diet than values observed on the 44% CHO diet. These observations suggest that the slight improvement in glucose tolerance

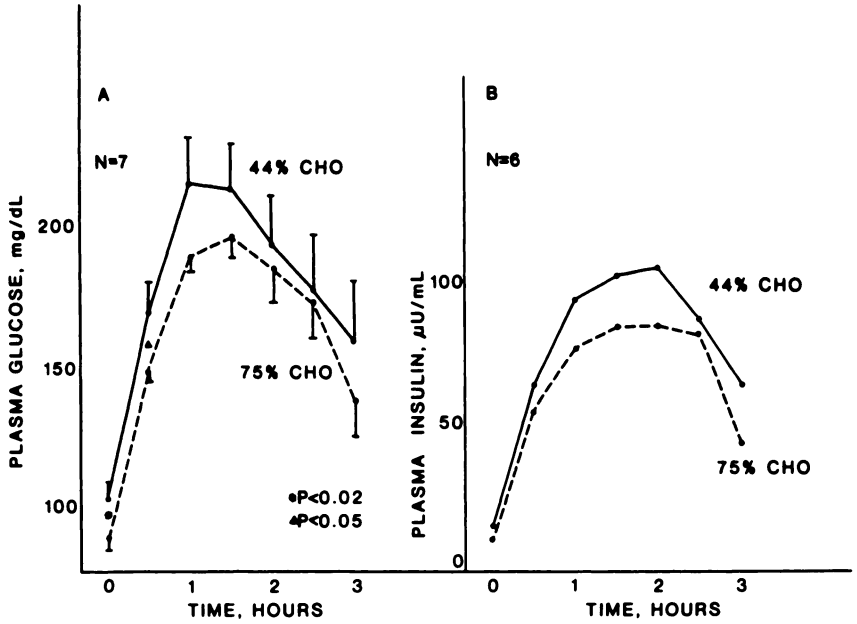

FIG. 2. Effect of high carbohydrate diet on GTT of seven lean diabetic men. A, glucose values with means and SEM indicated by *brackets*. B, mean plasma insulin responses of six men.

TABLE 4
Response to 75% CHO diet

Patient	Fasting Plasma Glucose		GTA		Fasting serum triglyceride	
	44% CHO diet	75% CHO diet	44% CHO diet	75% CHO diet	44% CHO diet	75% CHO diet
	mg/dl		*mg-min/dl* × 10^{-3}		*mg/dl*	
5	90	90	27.3	26.4	93	78
6	96	84	41.2	26.2	43	39
8	102	96	28.5	28.5	48	99
4	105	90	31.5	29.1	131	162
10	114	81	27.9	28.9	170	313
9	119	112	38.6	37.2	53	145
7	131	107	40.0	32.0	73	123
Mean ± SEM	108 ± 5	94 ± 4[a]	33.6 ± 2.3	29.8 ± 1.4	87 ± 18	137 ± 33
11	102	103	30.9	33.1	38	141
12	123	92	30.1	29.5	132	198
13	143	102			152	128
14	154	109			209	349
Mean ± SEM	131 ± 11	102 ± 4[b]			133 ± 36	204 ± 51

[a] Significant difference, $P < 0.02$ (paired t test). [b] Significant difference, $P < 0.05$ (mean t test).

is accompanied by a slight reduction in plasma insulin responses as previously reported (8).

Intravenous glucose tolerance tests were performed on six men and K values were higher in each man on the 75% CHO diet than on the 44% CHO diet. On the 44% CHO diet, K values ranged from 0.4 to 1.06%/min and averaged 0.75 ± 0.11 (mean ± SEM). On the 75% CHO diet, K values ranged from 0.54 to 1.77%/min and averaged 0.99 ± 0.18. These differences were not statistically significant.

The influence of the 75% CHO diet on the glucose metabolism of four obese men is presented in Table 4. The three men who had fasting hyperglycemia all had a distinct reduction in their fasting plasma glucose values that ranged from 31 to 45 mg/dl lower on the 75% CHO diet than on the 44% CHO diet. Of the 11 patients (lean and obese) studied, only patient 11 failed to show an improvement of either the fasting plasma glucose concentration or the GTA on the 75% CHO diet. He had a history of mild diabetic ketosis and had required 40 units of insulin to control his hyperglycemia for 2 months after this episode. His diabetes had improved, the insulin dose had been reduced and he had received no insulin for 3 months prior to study.

Changes in fasting serum triglyceride values are also presented in Table 4. Five of seven nonobese men and three of four obese men had higher fasting serum triglyceride values on the 75% CHO diet than on the 44% CHO diet; the mean increase in nonobese men was 57% and in obese men was 53% but these changes were not statistically significant.

Discussion

Men with chemical diabetes do not demonstrate an impairment of glucose tolerance when dietary carbohydrate is restricted to 20% of calories if the fat content of the diet is not increased. The response of these lean diabetic men is virtually identical to that reported previously for normal men (1). After a 48-hr fast, a significant deterioration in the GTT is observed in these diabetic men but the percentage increase in the GTA is similar to that observed in normal men (1). Thus these studies suggest that individuals with chemical diabetes are no more sensitive to carbohydrate restriction than are normal individuals.

On the other hand, the response of these men with chemical diabetes to a high carbohydrate diet appears to differ from that observed for normal men (2). Fasting plasma glucose values were significantly lower in seven nonobese and four obese men after 1 week on the 75% CHO diet than observed on the 44% CHO diet. Plasma glucose values at 30 min after oral glucose were also significantly lower in lean men on the 75% CHO diet than on the 44% CHO diet. The GTA was 11% lower on the high carbohydrate diet and was improved in five of the seven men. The disappearance rate (K) of intravenously administered glucose was higher in all six men studied. We have not studied the influence of high carbohydrate diets composed of natural foods on the glucose metabolism of normal men. Our own studies (2) and those of others (8) suggest that when high carbohydrate formula or liquid diets are fed for short periods there are no significant changes in glucose tolerance. Since all of the carbohydrate in these previous studies (2, 8) was provided as oligosaccharides, further studies are required to determine the influence of high carbohydrate diets containing natural foods on the glucose metabolism of nondiabetic individuals. Thus the present studies suggest that the glucose tolerance of individuals with chemical diabetes is improved slightly whereas the glucose tolerance of normal men (2, 8) may not be affected by short periods of high carbohydrate intake. It is noteworthy that the improvement in glucose tolerance on high CHO diets is not as dramatic in these men with chemical diabetes as we have observed (10) in overtly diabetic men. High CHO diets are accompanied by a marked reduction in fasting plasma glucose values and by significantly lower postprandial plasma glucose values (J. W. Anderson, unpublished observations) in overtly diabetic men with fasting hyperglycemia.

The response of diabetic and nondiabetic men to these high carbohydrate diets is very similar to that reported by Brunzell and col-

leagues (8). From their data (8) obtained from the National Auxiliary Publications Service, the glucose tolerance sum (GTS, Reference 2) of five diabetic and seven nondiabetic patients has been calculated. On the 45% CHO diet their diabetic patients had fasting plasma glucose values of 99 ± 6 mg/dl (mean ± SEM) and GTS of 1580 ± 160 mg/dl. On the 85% CHO diet these patients had fasting plasma glucose values of 90 ± 8 mg/dl ($P < 0.05$); the GTS of 1356 ± 127 mg/dl was 14% lower but not significantly different. In their nondiabetic patients the GTS on the 45% CHO diet (1127 ± 43 mg/dl) was identical to that observed on the 85% CHO diet (1130 ± 48). Thus the 85% CHO diet produced a lowering of fasting plasma glucose values and a slight decrease in GTS in diabetic patients but no significant alterations in the nondiabetic individuals (8).

In six diabetic men with fasting hyperglycemia (plasma glucose values above 110 mg/dl) that we studied (Table 4) the 75% CHO diet was associated with a uniform and significant ($P < 0.005$) reduction in fasting plasma glucose values (131 ± 6 versus 101 ± 5 mg/dl on the 44% CHO diet). These results differ from those reported subsequently by Brunzell and colleagues (9) in that their untreated patients had an increase in fasting plasma glucose values on the 85% CHO diet. Six of their patients with fasting plasma glucose values on the 45% CHO diet ranging from 130 to 158 mg/dl (mean 145 ± 5) had values of 156 ± 4 on the 85% CHO diet. These differences may be related to the obesity of all of their six subjects (150 ± 7% of ideal body weight) or to the fact that their diet was a formula diet containing either dextrose or dextrin and maltose (9).

The improvement in glucose tolerance associated with high carbohydrate diets appears related to increased insulin sensitivity. Fasting plasma insulin values and insulin responses are lower on high carbohydrate diets than on standard carbohydrate diets in both normal and diabetic individuals (Table 3 and References 2 and 8). The reason that diabetic patients show a significant improvement in glucose tolerance while normal individuals appear to show little change on these high carbohydrate diets is unclear. Preliminary studies in rats suggest that diabetic animals have a greater increase in glycolytic enzyme activities on high carbohydrate diets than do normal rats (16). Further studies are required to delineate these differences between diabetic and normal individuals.

One legitimate concern about the long-term use of high carbohydrate diets is that they may be accompanied by increases in fasting serum triglyceride values. When liquid or formula diets are fed to normal men (17, 18) or hypertriglyceridemic patients (17, 19), a significant rise in fasting triglyceride values is observed with regularity. This elevation of fasting triglyceride values appears to be transient (17, 19) and tends to return to base-line levels after 2 or 3 months. When solid diets containing large amounts of natural carbohydrates are fed, an increase in fasting triglyceride values has not been observed in several different studies (10, 20–23). In the present studies, solid diets were fed and fasting triglyceride values in 11 men averaged 55% higher on the 75% CHO diet than values on the 44% CHO diet. However, postprandial triglyceride values were significantly lower ($P < 0.02$) on the 75% CHO diet than on the 44% CHO diet (24).

The present studies suggest that high CHO diets may be of significant therapeutic benefit for certain diabetic patients. This suggestion is supported by several previous studies utilizing high carbohydrate diets for the long-term management of diabetic patients (6, 7, 10, 24). Further studies are required to delineate the optimal type and amount of carbohydrate for these diets and to determine which diabetic patients may be benefited by these diets. An increase in the content of dietary fiber (10, 25, 26) may prevent the increase in fasting plasma triglyceride values that we observed with the diets used in this study. In current studies we have modified the 75% CHO diet by lowering the oligosaccharide content and increasing the dietary fiber (10). After 2 weeks on this diet average fasting triglyceride values for 10 diabetic men are significantly lower than values on the 44% CHO diet (J.W. Anderson, unpublished data). These preliminary observations indicate that high CHO diets can be used in certain

diabetic patients without increasing fasting triglyceride values.

References

1. ANDERSON, J. W., AND R. H. HERMAN. Effects of carbohydrate restriction on glucose tolerance of normal men and reactive hypoglycemic patients. Am. J. Clin. Nutr. 28: 748, 1975.
2. ANDERSON, J. W., R. H. HERMAN AND D. ZAKIM. Effect of high glucose and high sucrose diets on glucose tolerance of normal men. Am. J. Clin. Nutr. 26: 600, 1973.
3. ANDERSON, J. W., and R. H. HERMAN. Effect of fasting, caloric restriction, and refeeding on glucose tolerance of normal men. Am. J. Clin. Nutr. 25: 41, 1972.
4. HIMSWORTH, H. P. The physiological activation of insulin. Clin. Sci. 1: 1, 1933.
5. HALES, C. N., AND P. J. RANDLE. Effects of low-carbohydrate diet and diabetes mellitus on plasma concentrations of glucose, nonesterified fatty acid, and insulin during oral glucose-tolerance tests. Lancet 1: 790, 1963.
6. SINGH, I. Low-fat diet and therapeutic doses of insulin in diabetes mellitus. Lancet 1: 422, 1955.
7. KEMPNER, W., R. L. PESCHEL AND C. SCHLAYER. Effect of rice diet on diabetes mellitus associated with vascular disease. Postgrad. Med. 24: 359, 1958.
8. BRUNZELL, J. D., R. L. LERNER, W. R. HAZZARD, et al. Improved glucose tolerance with high carbohydrate feeding in mild diabetes. New Engl. J. Med. 284: 521, 1971.
9. BRUNZELL, J. D., R. L. LERNER, D. PORTE, JR. et al. Effect of a fat free, high carbohydrate diet on diabetic subjects with fasting hyperglycemia. Diabetes 23: 138, 1974.
10. KIEHM, T. G., J. W. ANDERSON AND K. WARD. Beneficial effects of a high carbohydrate, high fiber diet on hyperglycemic diabetic men. Am. J. Clin. Nutr. 29: 895, 1976.
11. New weight standards for men and women. Metropolitan Life Insurance Co. Statist. Bull. 40: 1, 1959.
12. RIFKIN, H., AND H. ROSS. Classification and natural history of genetic diabetes mellitus. In: Diabetes Mellitus, (4th ed.). Edited by K. E. Sussman and R. J. S. Metz. New York: American Diabetes Assoc. 1975, p. 45.
13. TUSTISON, W. A., A. J. BOWEN AND J. H. CRAMPTON. Clinical interpretation of plasma glucose values. Diabetes 15: 775, 1966.
14. MORGAN, C. R., AND A. LAZAROW. Immunoassay of insulin. Two antibody system. Diabetes 12: 115, 1963.
15. SOELDNER, J. S. Diagnosis and treatment of diabetes mellitus. Postgrad. Med. 43: 76, 1968.
16. ANDERSON, J. W. Mechanism for improved glucose tolerance in diabetics fed high carbohydrate diets. Clin. Res. 22: 580A, 1974.
17. FARQUHAR, J. W., A. FRANK, R. C. GROSS, et al. Glucose, insulin, and triglyceride responses to high and low carbohydrate diets in man. J. Clin. Invest. 45: 1648, 1966.
18. HERMAN, R. H., D. ZAKIM AND F. B. STIFEL. Effect of diet on lipid metabolism in experimental animals and men. Federation Proc. 29: 1302, 1970.
19. BIERMAN, E. L., AND J. T. HAMLIN. The hyperlipemic effect of a low-fat, high-carbohydrate diet in diabetic subjects. Diabetes 10: 432, 1961.
20. STONE, D. B., AND W. E. CONNOR. The prolonged effects of a low cholesterol, high carbohydrate diet upon the serum lipids in diabetic patients. Diabetes 12: 127, 1963.
21. WEINSIER, R. L., A. SEEMAN, M. G. HERRERA, et al. High and low-carbohydrate diets in diabetes mellitus. Study of effects on diabetic control, insulin secretion, and blood lipids. Ann. Internal Med. 80: 332, 1974.
22. ERNEST, I., E. LINNER AND A. SVANBORG. Carbohydrate-rich, fat-poor diet in diabetes. Am. J. Med. 39: 594, 1965.
23. ERNEST, I., B. HALLGREN AND A. SVANBORG. Short term study of effect of different isocaloric diets in diabetes. Metabolism 11: 912, 1962.
24. VAN ECK, W. F. The effect of a low fat diet on the serum lipids in diabetes and its significance in diabetic retinopathy. Am. J. Med. 27: 196, 1959.
25. HEATON, K. W., AND E. W. POMARE. Effect of bran on blood lipids and calcium. Lancet 1: 49, 1974.
26. Editorial. Dietary fibre and plasma-lipids. Lancet 2: 353, 1975.