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RESPONSE TO INSULIN AS AN INDEX TO THE DIETARY MANAGEMENT OF DIABETES

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Recently there has developed a widespread trend toward allowing relatively large amounts of carbohydrate in the diabetic diet. It should be emphasized, however, that the use of higher carbohydrate diets is not new; Donkin's milk treatment (1874) may have provided 250 grams of carbohydrate daily, and the "cures" of von Düring, Mosse, von Noorden and others match in carbohydrate content many of those advised today (1). Despite the good results obtained in some cases with such diets, the treatment of diabetes was in general carried out upon principles established by Naunyn (2), who found it usually necessary to limit carbohydrate to very small amounts. It was still the common opinion of students of the disease that deleterious results followed the excessive consumption of carbohydrate, with loss of sugar tolerance and deterioration in the clinical condition of the patient.

Strict limitation of the carbohydrate in the diet has in general proved quite satisfactory treatment, and its use is based upon long clinical experience and is supported by excellent laboratory evidence. The lowest carbohydrate diets, introduced by F. M. Allen et al. (3), were based upon the observation that partially depancreatized dogs lost tolerance with high carbohydrate intake, but gained tolerance with low carbohydrate. Patients under Allen's observation seemed to act similarly. The low caloric, low carbohydrate diets of the "Allen era" were followed for years quite generally and with considerable success. It was the common opinion that excessive carbohydrate ingestion might exhaust the diabetic's pancreas.

More recent efforts to find the optimum diabetic diet have led in widely divergent directions. Newburgh and Marsh (4) and Petrén (5) found that high fat was well tolerated by many patients, and advised keeping the carbohydrate very low. Rosenberg (6) reports good results with a similar regime. The introduction of insulin permitted the use of higher carbohydrate and encouraged many at least temporarily to forget the principle of "sparing" the carbohydrate metabolism. The leaders in the recent movement toward higher carbohydrate diets (Sansum; Adlersberg and Porges; Geyelin; and Rabinowitch (7)) have demonstrated that many diabetics experience a definite improvement in health and may gain in sugar tolerance upon diets higher in carbohydrate than previously thought advisable. This has been a significant advance in our knowledge, reemphasizing the observations of earlier workers and tending to modify previously accepted conceptions of the pathological physiology of the disease. It has been observed that many patients do not gain tolerance with high carbohydrate, but the fact that many do requires a revision of the idea that "pancreas-sparing" is necessary in the treatment of all patients with diabetes.

It is quite generally accepted that as concerns total calories, normal or slight undernutrition is advisable, and that 0.75 to 1.25 grams protein per kilogram per day should be given. Concerning the carbohydrate-fat ratio, however, on one side we find advocates of high fat to rest the pancreas, and on the other those recommending high carbohydrate to stimulate the pancreas. That this is true now, twelve years after the introduction of insulin, emphasizes that the use of the pancreatic hormone has so far not helped much in solving the problem. With so many theoretical, practical and experimental arguments on each side, it is not surprising to find the conservative, moderate fat, moderate carbohydrate regime as advocated by Joslin (8) so widely used, since it represents a compromise between the two extremes.

It seemed to us, however, an important observation that some of our diabetic patients gained tolerance with high carbohydrate, while others showed no tendency to gain, or even lost tolerance. It seemed possible that there might be some fundamental difference in the type of diabetes in pa-

tients who responded so differently. The widespread use of the conservative, compromise type of diet might conceal latent possibilities of great improvement in glucose tolerance, or might in some cases even cause loss of tolerance.

Accordingly an investigation was undertaken to determine whether diabetics who will gain tolerance on high carbohydrate can be clinically distinguished from those who will not. The primary object was to find, if possible, a method for deciding upon the optimum type of diet for each individual diabetic. The optimum diet should supply the necessary calories in palatable form with the lowest possible insulin dosage, and should permit the development of the greatest possible carbohydrate tolerance.

RELATIVE INSULIN RESPONSE

Three years ago studies were reported (9) confirming the observations of Falta and Boller (10) upon the frequency of relative insulin-resistance in diabetes. Since then we have found that the diabetics we have studied have tended to fall into two groups, the relatively insulin-sensitive, and the relatively insulin-resistant. The insulin-resistance here described is not that commonly indicated by the term, in which several hundred units per day are required. Infection, coma, hyperthyroidism, pituitary and adrenal disorders, hepatic and various cutaneous diseases account in most instances for temporary marked unresponsiveness to insulin. The resistant patients in this study showed a relative lack of response to insulin slight to moderate in degree and not explainable upon the basis of any discernible complications. The relative degree of insulin sensitivity tended to remain as a persistent characteristic of the individual.

Studies were planned to determine whether the two groups differed in their response to high carbohydrate diets. Fifteen patients were chosen, each of them being intensively studied for three weeks to three months in the hospital, and from three months to three or more years in the outpatient department. The only criterion employed in the selection of cases was the individual's willingness to cooperate. Observations have been made upon the response of these patients to high and low carbohydrate diets, and the influence of these diets upon the concentration of blood sugar, the glycosuria, the ketonuria, the insulin requirement, the glucose tolerance and relative insulin sensitivity.

METHODS OF STUDY

The studies are best described under three headings: (1) determinations of relative insulin-sensitivity; (2) hospital studies; (3) observations in the outpatient department.

1. Relative response to insulin

(*a*) Blood sugar curves for four hours following the subcutaneous injection of one unit of insulin per 10 pounds body weight into the fasting patient were determined.

(*b*) Intravenous insulin tolerance was determined as a check upon the subcutaneous method. One-fifteenth unit per kilogram body weight was given intravenously to the fasting patient, blood samples for sugar analysis being collected every fifteen minutes for one and one-half hours.

(*c*) Tolerated overdose. After the insulin requirement upon the standard diet was determined, the total dose of insulin was gradually increased from day to day until the patient experienced a hypoglycemic reaction. The tolerated overdose may be defined as the amount of insulin above the insulin requirement which a patient will tolerate per day without having a reaction.

(*d*) Glucose equivalent. The glucose equivalent, representing the number of grams of glucose metabolized per unit of insulin, was calculated by dividing the number of grams excreted by the number of insulin units required to eliminate the glycosuria.

Laboratory methods:

(*a*) Blood sugar determinations were performed on capillary blood by the method of Somogyi (11). These are "true sugar" readings and average 15 to 20 mgm. per 100 cc. lower than those obtained by the older methods. Ante- and post-cibos blood sugars (fasting, and 2½ hours after breakfast) served as frequent checks upon changes in tolerance.

(*b*) The twenty-four hour urines were tested daily for glucose and acetone bodies. The quantitative excretion was determined by the Shaffer-Hartmann method (12).

(*c*) Glucose tolerance tests were performed by estimation of the fasting blood sugar, and at one-half, one, two and three hours after the ingestion of 0.8 gram dextrose per pound of body weight. For comparison with the figures of others the relative rise in the blood sugar is indicated by the percentage increase above the fasting figure. A more accurate measurement expresses the differences in area of the curves in "milligram-minutes" (Table IV). The figures given represent the rise above the fasting level in each case, a rise of 20 milligrams lasting for one hour, for example, being expressed as a rise of 1200 milligram-minutes.

(*d*) The total glucose value of the diets was calculated as 10 per cent of the fat plus 58 per cent of the protein plus 100 per cent of the carbohydrate.

Accurate dietary regulation and prompt collection and preservation of specimens for analysis was carried out by the trained staff of the Tirrill Metabolism Ward.

2. Studies on patients in the hospital

(*a*) Control diets were given supplying 27.3 calories per kilogram body weight. This was considered a maintenance energy value for patients spending most of their time in bed, but permitted to be up and about in the ward. One gram of protein, 1.7 grams of fat and 2 grams of carbohydrate per kilogram per day were chosen as representing an average between the high fat and high carbohydrate types of diet. The protein supplied 15 per cent, the fat 56 per cent and the carbohydrate 29 per cent of the total caloric value. In the high carbohydrate "normal type" diet used by Geyelin (7) fat furnishes 33 per cent of the calories or less, and the carbohydrate 53 per cent or over. Rabinowitch's high carbohydrate diets (7) supplied 22 per cent of the calories from fat, 63 per cent from carbohydrate. In the Newburgh high fat diets (4) fat formed 75 per cent, carbohydrate 10 per cent, of the caloric intake.

The daily glycosuria in grams was measured, and the daily amount of insulin necessary to keep the blood sugar within approximately normal limits, and the glycosuria below 10 grams per 24 hours was determined. No effort was made to get the urine absolutely sugar-free, since we should then have been unable to tell whether the actual daily insulin requirement was being exceeded.

After a period upon the control regimen sufficiently long to avoid marked variations in daily blood sugar or daily glycosuria, the effect of alterations in the diet was studied. These were arranged in such a way as to involve no change in the protein or total caloric intake or in the insulin dosage. Test diets of the high fat type and of the high carbohydrate type were given, and the effects upon glycosuria and glycemia noted.

In some of the cases studied, glucose tolerance and insulin tolerance tests, while on the control regime and after the high carbohydrate period, were performed.

In certain instances the addition of fat or carbohydrate to the control diet was employed to determine the effect of adding calories above the control level in the form of carbohydrate or fat.

(*b*) In some cases a second type of control diet was used supplying 60 grams protein, 125 grams fat, and 150 grams carbohydrate, 1965 calories, without regard to the patient's weight. The effect of added carbohydrate and fat could then be studied without regard to certain theoretical objections to the first method. In thin patients receiving only 1500 or 1600 calories on the first type of control diet, for example, changes in tolerance might be ascribed to undernutrition, while obese patients receiving 2700 calories would certainly be subject to possible tolerance changes from excessive food intake as well as to possible influences of the high carbohydrate or high fat diets.

3. Outpatient observations

The effects of varying the proportions of fat and carbohydrate in the diet of patients measuring and preparing their own food at home and seen at intervals of a week or more could not of course be as closely judged as those in the hospital. Certain facts, however, make these observations of considerable importance, and permit placing them on a plane of equal significance with the hospital studies.

All of the outpatients had previously been in the hospital where the technique of weighing and measuring diets and of testing the urine for sugar had been well learned. Each outpatient had also been a subject of one of the hospital studies, so that hospital and outpatient studies serve as checks on each other. Frequent urine tests at home, at least once daily, were recorded, and the record brought with the patient on each visit. Frequent blood sugar determinations were made. On each visit an analysis of the patient's dietary control was made by the dietitian. Adherence to the prescribed total caloric intake could be checked by the frequent records of body weight.

With these considerations in mind, plus the fact that changes in carbohydrate tolerance observed over long periods of time should naturally be more significant in the study of diabetes, the results seem particularly significant.

RESULTS

1. Relative response to insulin

(*a*) Subcutaneous insulin tolerance. The patients fell into two groups, the relatively insulin sensitive and the relatively insulin resistant (Table I). The sensitive group of eight patients exhibited a marked fall in the blood sugar, ranging

TABLE I

Insulin tolerance (1.0 unit per 10 pounds subcutaneously)

Case number	Blood sugar (*mgm. per 100 cc.*)					Per cent fall
	Fasting	1 hour	2 hours	3 hours	4 hours	
INSULIN-SENSITIVE TYPE						
1	156	124	71	41(r)*	41	74
2	234	179	143	66	58	75
3	176	134	39(r)*	52	70	70
4	119	88	46	45	45	62
5	218	133	87	59	63	73
6	212	147	111	61	71	71
7	142	119	100	42	48	70
8	202	175	123	68	81	61
INSULIN-RESISTANT TYPE						
9	164	132	111	125	128	32
10	134	137	119	110	80	40
11	191	166	128	91	102	53
12	119	96	99	71	82	40
13	115	96	80	80	76	34
14	212	206	155	100	110	53
15	173	155	115	102	111	40

* (r) indicates symptoms of hypoglycemia.

from 61 to 75 per cent of the fasting levels. All of them reached a blood sugar level of 68 or below, the average of the lowest determinations being 52 mgm. per cent. Definite signs of hypoglycemia were observed in every patient of this group and two of them experienced quite severe reactions.

The relatively resistant patients showed much less response. The per cent fall ranged from 32 to 53; none of them reached a point below 71 mgm. per 100 cc., and the average of the lowest determinations was 90 mgm. Signs of hypoglycemia were minimal or absent.

(*b*) Intravenous insulin tolerance tests upon three of the patients in each group indicated that possible differences in absorption of the subcutaneous insulin could not explain the observed differences in response. In each instance a patient sensitive to subcutaneous insulin was found also to be sensitive to intravenous insulin. Those relatively resistant showed relatively poor response to both the subcutaneous and the intravenous hormone (Table II). The relative fall in per cent ranged from 34 to 45 in the sensitive group, and from 12 to 22 in the resistant type.

TABLE II

Insulin tolerance (1/15 unit per kilogram body weight intravenously)

Case number	Blood sugar (*mgm. per 100 cc.*)							Per cent fall
	Fasting	15 minutes	30 minutes	45 minutes	60 minutes	75 minutes	90 minutes	
INSULIN-SENSITIVE TYPE								
1	213	200	166	159	141	145	160	34
3	156	127	110	96	86	94	98	45
8	189	170	156	145	130	112	135	40
INSULIN-RESISTANT TYPE								
11	182	177	175	174	170	168	158	13
14	206	202	199	181	182	192	194	12
15	194	190	173	157	163	151	160	22

(*c*) The tolerated overdose in those patients found to be sensitive in the insulin tolerance tests was in every case practically zero. An increase of as much as three or five units produced hypoglycemia, while a reduction of three or five units below the required amount led promptly to glycosuria and hyperglycemia (Table III).

TABLE III

Clinical characteristics and insulin requirements

Case number	Age	Sex	Nutrition	Blood pressure	Insulin requirement	Tolerated overdose	Glucose equivalent
	years			*mm. Hg*	*units per 24 hours*	*units per 24 hours*	
INSULIN-SENSITIVE							
1	31	M	Thin	104/70	30	0	1.3, 2.5, 2.1
2	46	M	Thin	106/74	75	0	1.9, 2.3
3	47	F	Slightly obese	138/74	0		3.2
4	29	M	Normal	110/70	50	0	1.1
5	38	F	Normal	105/70	50	0	1.8
6	44	F	Thin	105/70	38	0	2.9
7	53	F	Obese	174/88	0		
8	33	M	Thin	120/70	70	0	1.2
INSULIN-RESISTANT							
9	56	F	Normal	135/70	25	30	0.80, 0.90
10	68	M	Normal	140/80	60	75	0.22, 0.33
11	43	F	Very obese	190/120	50	60	0.37, 0.35, 0.40
12	53	M	Very obese	140/80	40	35	1.1
13	33	F	Obese	130/85	45	60	0.56, 0.50
14	53	F	Obese	135/70	55	65	0.70, 0.77
15	55	F	Obese	135/80	70	15	0.30

In the resistant group, however, increase in the insulin dosage had a relatively slight effect. In the seven patients in this group (Cases 9 through 15) the tolerated daily overdose ranged from 15 to 75 units. In Case 9 the requirement was 25 units, the tolerated overdose 30 units, so that 55 units daily were required to provoke hypoglycemia. In Case 10, the requirement was 60, the tolerated overdose 75, a total of 135 units causing the first evidences of insulin excess. In Cases 11, 13 and 14 the required dose could also be more than doubled without producing symptoms of hypoglycemia.

(*d*) The glucose equivalents, representing the number of grams of glucose metabolized per unit of insulin, would be expected to be higher in the insulin-sensitive group. Such was found to be the case, the values in this group ranging from 1.1 to 3.2 and averaging over 2 grams (Table III). In the resistant type the values averaged 0.55 gram, ranging from 0.22 to 1.1. On the average, then, by this criterion, there appears to be approximately four times as much effect per unit in the sensitive group as in the resistant group.

Clinical characteristics

While it is our impression that the clinical features in the two groups differ significantly (9), there is considerable overlapping of clinical characteristics (Table III). Those patients showing relative resistance are usually older, frequently are obese, and often have vascular hypertension. There is little tendency to acidosis, while the sensitive group develop acidosis and coma much more easily. The sensitive group are usually younger, are often thin, and have as a rule low blood pressures. It is doubtful, however, whether clinical features alone will serve to distinguish the two types. They cannot be distinguished as to severity, since the insulin requirement is on the average higher in the resistant group, but acidosis occurs more frequently in the sensitive type.

TABLE IV

Effect of high carbohydrate diets upon insulin tolerance and glucose tolerance

Case number*	Diet (27.3 calories per kgm.)	Subcutaneous insulin tolerance	Intravenous insulin tolerance	Glucose tolerance	
	grams carbohydrate per kilogram	*per cent fall*	*per cent fall*	*milligram-minutes*	*per cent rise*
1 (S)	2 (6 days)	74	34	21,705	67
	3 (7 days)	70	32	29,145	125
4 (S)	2 (6 days)	62		23,220	251
	3 (9 days)	58		37,995	280
8 (S)	2 (11 days)	61	40	18,600	103
	3 (14 days)	60	38	23,170	104
11 (R)	2 (7 days)	53		13,560	92
	3 (6 days)	58		12,120	68
14 (R)	2 (16 days)	53	12	37,380	122
	3 (9 days)	60	28	25,410	82
15 (R)	2 (18 days)	40	22	24,270	96
	3 (8 days)	49	30	9,060	51

* Cases 1, 4 and 8 (S) are relatively insulin-sensitive. Cases 11, 14 and 15 (R) are relatively resistant to insulin.

The clinical characteristics, with the insulin requirements, tolerated overdoses, and glucose equivalents are summarized in Table III. Cases 1 through 8 are those who showed relative sensitivity in the insulin tolerance tests. Cases 9 through 15 were relatively resistant.

Results of dietary studies

In Tables IV, V and VI analyses are given of the responses to the various test diets. Of eight relatively insulin-sensitive patients studied in the hospital, seven showed no gain or a loss of tolerance following high carbohydrate diets; one sensitive patient gained tolerance. High fat, however, was relatively well borne and was followed in several instances by improved tolerance.

Seven relatively resistant patients studied in the hospital all showed definitely improved tolerance following high carbohydrate diets. Fat was as a rule poorly tolerated by this group and tended to impair tolerance.

In the outpatient studies over long periods of time five of six sensitive patients failed to gain tolerance with increased carbohydrate intake; one showed improved tolerance.

Five relatively resistant patients gained tolerance in a definite and remarkable manner upon progressively increasing the carbohydrate ingestion.

The cause of improved carbohydrate tolerance resulting from high carbohydrate diets

It is evident from these experiments that some patients with diabetes may be expected to gain tolerance when allowed large amounts of carbohydrate, while others either fail to gain or actually lose tolerance.

The early observation of Hamman and Hirschman (13) that the hyperglycemia resulting from the second of two equal ingested amounts of glucose by a normal subject is less than that following the first dose has been confirmed by Staub (14), Traugott (15), Foster (16), du Vigneaud and Karr (17), and Lennox (18). Lennox demonstrated that this was true whether the glucose be given orally or intravenously. This effect is now commonly referred to as the Staub-Traugott phenomenon.

Sweeney (19) investigating the effects of various diets upon normal subjects, and using the glucose tolerance test as an indicator, concluded that starvation or a high fat diet decreased the tolerance, protein diets had little effect, and high carbohydrate raised the tolerance. He explained this effect by supposing that the mechanism secreting insulin becomes increasingly sensitive to stimulation when frequently subjected to the higher blood sugar resulting from the high carbohydrate diets, while the absence of such stimulation caused insulin to be secreted less readily and in smaller amounts.

TABLE V

Responses to various test diets

Case number	Age and sex	Diet number	Days on diet	Protein	Fat	Carbohydrate	Calories	Total glucose value	Insulin	Blood sugar (a.c./p.c.)	Glycosuria	Ketonuria	Remarks
	years			*grams*	*grams*	*grams*		*grams*	*units per 12 hours*	*mgm. per 100 cc.*	*grams per 24 hours*		
1	31 M	1	6	60	102	120	1640	165	30	100/93	2.1		Control period
		2	4	60	89	150	1640	194	30		29.2		High carbohydrate; quantitative excretion, 27.1 of 29 grams
		3	3	60	60	215	1640	256	30	/391	79.9	++	Higher carbohydrate; quantitative excretion, 50.7 of 62 grams
		4	4	60	102	120	1640	165	30	/99	6.8		Control diet, loss of tolerance after high carbohydrate; glycosuria higher than in control period
		5	4	60	138	40	1640	88	30(R) 10	/90	0		High fat, insulin decreased
		6	4	60	150	40	1750	90	10	/85	0		Higher fat (108 calories), insulin unchanged. No change in glycosuria
		7	4	60	120	120	1640	165	30	/90	0.9		Control, gain in tolerance after high fat
		8	4	60	89	150	1640	194	30	/163	20.2		High carbohydrate, better borne after high fat
		9	4	60	138	150	2082	199	30		20.2		Higher fat (442 calories above diet 8)
		10	4	60	180	150	2460	203	30	/172	21.4		Higher fat (820 calories above diet 8); no change in glycosuria
		11	4	60	180	175	2560	228	45		1.3		Increase in carbohydrate with fat high, requires quantitative insulin
		12	5	60	180	200	2660	253	60	/130	2.1		
2	46 M	1	7	66	113	132	1809	181	75	123/186	1.2		Control period
		2	3	66	99	165	1815	213	75	/336	32.3	++	Quantitative excretion, 31 of 32 mgm.
		3	3	66	84	198	1812	244	75	/410	53.3	+++	Quantitative excretion, 21 of 31 grams
		4	3	66	113	132	1809	181	75	/210	3.6		Control diet. Loss of tolerance after high carbohydrate
		5	3	66	143	66	1815	118	75(R)	106/115			Insulin reactions with lower carbohydrate, high fat, same calories
		6	3	66	156	40	1804	94	20(R)	/118			Insulin reactions, with insulin greatly reduced
		7	3	66	113	132	1809	181	55	/120			Control diet, gain in tolerance after high fat
3	47 F	1	4	60	125	150	1965	198	0	160/192	1.3		Control period
		2	3	60	188	150	2530	204	0	155/196	3.0		Fat added; slight increase in glycosuria
		3	3	60	125	150	1965	198	0	176/210	3.8		Control diet, no change in tolerance after high fat
		4	5	60	125	200	2165	248	0	186/290	32.0	++	High carbohydrate, quantitative excretion, 28 of 50 grams
		5	2	60	125	285	2505	333	0	190/313	71.4	+++	Higher carbohydrate, excretion of 39 of 85 grams
		6	4	60	125	150	1965	198	0	/223	4.5		Control diet, no gain, loss of tolerance after high carbohydrate
4	29 M	1	6	76	130	145	2075	202	50	152/166	4.4		Control period
		2	9	76	112	190	2075	245	50	/316	37.7	++	High carbohydrate; quantitative excretion, 33 of 43 grams. No gain in insulin effect
		3	7	76	130	145	2075	202	50	/234	22.1	+	Control diet, loss of tolerance after high carbohydrate, higher blood sugar, more glycosuria
		4	6	76	152	100	2075	159	50	164/183	3.8		Apparent gain in tolerance on high fat
		5	2	76	170	60	2075	121	50(R)	/78			
		6	2	76	170	60	2075	121	30				
		7	2	76	170	60	2075	121	20	/120	1.0		

TABLE V—*Continued*

Case number	Age and sex	Diet number	Days on diet	Protein	Fat	Carbohydrate	Calories	Total glucose value	Insulin	Blood sugar (a.c./p.c.)	Glycosuria	Ketonuria	Remarks
	years			*grams*	*grams*	*grams*		*grams*	*units per 18 hours*	*mgm. per 100 cc.*	*grams per 24 hours*		
5	38 F	1	7	60	125	80	1685	128	40	218/	1.6		Low carbohydrate
		2	13	60	125	150	1965	198	50	242/218	1.2		Control diet
		3	3	60	188	150	2530	204	50	/198	1.1		No loss of tolerance with high fat added
		4	3	60	125	150	1965	198	50	/205			Perhaps gain in tolerance after high fat
		5	3	60	125	200	2165	248	50	/242	47.3	++	Quantitative excretion, 47 of 50 grams carbohydrate added
		6	3	60	125	235	2305	283	50	/414	68.1	++	Excretion of 21 of 25 grams carbohydrate added
		7	3	60	125	150	1965	198	50	/230	1.2		No gain in tolerance after high carbohydrate
6	44 F	1	14	60	125	150	1965	198	38	/131	14.0		Control period
		2	3	60	188	150	2530	204	38	/136	14.0		No loss of tolerance with added fat
		3	3	60	125	150	1965	198	38	/110	10.7		Control diet, gain in tolerance after high fat, less glycosuria, blood sugar lower
		4	3	60	125	200	2165	248	38	/246	57.1	++	Increase of 50 grams carbohydrate, glycosuria increased 47 grams
		5	3	60	125	285	2505	333	38	/424	102.3	++++	Increase of 85 grams carbohydrate, glycosuria increase of 55 grams
		6	3	60	125	150	1965	198	38	/212	23.4		Loss of tolerance after high carbohydrate. Increased glycosuria and higher blood sugar
9	56 F	1	6	57	98	114	1518	157	25	161/130	5.7		Control period
		2	4	57	67	171	1518	211	25	/152	9.9		High carbohydrate, excretion of 4.2 of 54 grams
		3	4	57	35	245	1518	282	25	/194	15.7		Higher carbohydrate, excretion of 5.8 of 71 grams
		4	4	57	98	114	1518	157	25	/101	1.7		Control diet, gain in tolerance after high carbohydrate
		5	4	57	126	38	1518	84	25	/93	1.0		High fat, low carbohydrate
		6	4	57	98	114	1518	157	25	/146	7.5		Control diet, loss of tolerance following high fat
		7	4	57	98	285	2250	328	25	/245	22.5		Increase of 171 grams in carbohydrate, increased excretion of only 15 grams
		8	4	57	98	285	2250	328	50	/141	3.2		Insulin increase of 25 units. 19.3 grams ÷ 25 = glucose equivalent of 0.8
10	68 M	1	7	60	102	120	1638	165	60	134/161	3.1		Control period
		2	3	60	60	217	1648	258	60	/184	13.1		High carbohydrate; increased excretion of only 10 of 93 grams
		3	3	60	40	262	1648	301	60	/192	17.1		Higher carbohydrate; increased excretion of only 4 of 43 grams
		4	3	60	102	120	1638	165	60	152/154	0		Control diet, gain in tolerance, lower blood sugar, less glycosuria
		5	3	60	138	40	1642	89	60	/186	1.0		High fat, blood sugar higher, more glycosuria
		6	3	60	102	120	1638	165	60	/180	3.5		Control diet, loss in tolerance after high fat, higher blood sugar, more glycosuria
11	43 F	1	8	60	125	150	1965	198	50	/138	5.2		Control period
		2	4	60	188	150	2530	204	50	/141	6.4		Added fat, increased glycosuria
		3	3	60	125	150	1965	198	50	/191	6.4		Control diet, higher blood sugar, increased glycosuria after high fat
		4	4	60	125	200	2165	248	50	/158	10.6		High carbohydrate; excretion of only 4.2 of 50 grams
		5	4	60	125	300	2565	348	50	/230	16.8	+	Higher carbohydrate, excretion of 6.2 of 50 grams

TABLE V—*Continued*

Case number	Age and sex	Diet number	Days on diet	Protein	Fat	Carbohydrate	Calories	Total glucose value	Insulin	Blood sugar (a.c./p.c.)	Glycosuria	Ketonuria	Remarks
	years			*grams*	*grams*	*grams*		*grams*	*units per 12 hours*	*mgm. per 100 cc.*	*grams per 24 hours*		
11	43 F	6	4	60	125	150	1965	198	50	/110	0		Control diet, no glycosuria, lower blood sugar following high carbohydrate
12	53 M	1	6	60	125	150	1965	198	40	/68	2.6		Control period
		2	3	60	188	150	2530	204	40	/215	6.7		Increased glycosuria, higher blood sugar with high fat
		3	3	60	125	150	1965	198	40	/132	1.8		Control diet, decreased tolerance after high fat
		4	3	60	125	200	2165	248	40	/232	8.3		High carbohydrate, excretion of 6.5 of 50 added grams
		5	3	60	125	285	2505	333	40	/265	19.2		Excretion of 11 of 85 added grams
		6	3	60	125	150	1965	198	40	/70	0		Control diet, gain in tolerance following high carbohydrate
14	52 F	1	16	100	170	200	2730	265	55	206/110	3.4		Control period
		2	5	100	148	250	2730	323	55	/151	4.9		High carbohydrate; small excretion increase, 1.5 of 58 grams
		3	9	100	128	300	2730	371	55	200/162	6.6		Higher carbohydrate, increased excretion of only 1.7 of 58 grams
		4	8	100	170	200	2730	265	55	/131	0		Control diet, improved tolerance after high carbohydrate, lower blood sugar, less glycosuria
		5	6	100	170	200	2730	265	40	/91	0		Control diet, gain in tolerance permits lower insulin dose
15	55 F	1	18	70	119	140	1911	193	70	175/166	4.9		Control period
		2	8	70	88	210	1911	260	70	148/163	6.3		High carbohydrate, increased excretion of only 1.4 of 67 grams
		3	7	70	119	140	1911	193	70	/116	0		Control diet, gain in tolerance, lower blood sugar, less glycosuria

Macleod (20) offers a similar explanation of these phenomena, stating that a lower level of hyperglycemia acts as an adequate stimulus to insulin secretion after sensitization of the secreting apparatus by a previous rise in the blood sugar.

It seemed possible, however, as our experiments progressed, that the increased tolerance noted in some of our patients might be due to either of two factors: (1) increased secretion of insulin, or (2) increased sensitivity to endogenous insulin. Abderhalden and Wertheimer (21), and Bainbridge (22) showed that animals on high carbohydrate diets were much more sensitive to insulin than those which were receiving high fat. Hynd and Rotter (23) also noted that hypoglycemic convulsions were more easily produced in animals receiving large amounts of carbohydrate. Those patients who gained tolerance with high carbohydrate intake in this study fell in the relatively insulin-resistant group. It seemed possible that the increased tolerance was due to a better response to endogenous insulin. Insulin tolerance tests were therefore performed upon several resistant patients after periods upon the control diet containing 2 grams carbohydrate per kilogram body weight, and after high carbohydrate periods on 3 grams per kilogram. Glucose tolerance tests were performed before and after the high carbohydrate as a further check upon the effects of the diet, and because the only other similar curves upon diabetics we have been able to find were the rather inconclusive ones of Watson and Wharton (24). Similar insulin and glucose tolerance studies were made upon several of the sensitive group.

The results of these studies are shown in Table IV. Glucose tolerance curves in two of the three sensitive patients showed a higher percentage rise after the high carbohydrate diets, and in one there was practically no change. In all three resistant patients much lower curves were obtained on the high carbohydrate than on the control diets. In-

sulin tolerance curves showed no change in sensitivity in the sensitive patients. A much more marked depression of the blood sugar was evident, however, in the relatively resistant group. This increased sensitivity to insulin was evident whether the insulin was given subcutaneously or intravenously.

While these results do not exclude the possibility of increased insulin production in the relatively resistant group, it seems probable that at least a part of the increased tolerance is due to the patient's greater sensitivity to his own insulin.

The sensitive group, on the contrary, seem rather constantly to respond maximally to endogenous or exogenous insulin, and their response is unchanged by diet. The glucose tolerance, however, is in some of the sensitive patients decreased upon high carbohydrate ingestion. It seems possible, therefore, that in these patients excessive strain upon the pancreatic islets has resulted in a diminished endogenous insulin supply. These patients may be thought of as having diabetes which is primarily pancreatic or insular, since in so many respects their reactions resemble those of Allen's depancreatized dogs.

In the insulin-resistant cases, on the other hand, evidence indicating pancreatic islet insufficiency is by no means so clear. The gain in tolerance upon high carbohydrate diets, accompanied by a definitely increased sensitivity to insulin, suggests that extra-pancreatic factors decreasing the effectiveness of endogenous insulin may be at least partly responsible for this type of diabetes.

Extra-pancreatic factors in diabetes

Our studies emphasize the fact that we can no longer consider diabetes a unitarian disease, caused solely by an inadequate production of insulin. Warren (25) and other pathologists have demonstrated that the non-diabetic pancreas may reveal changes previously described as the cause of diabetes, whereas the diabetic pancreas may in many instances show no definite disease. On the other hand, studies of recent years have shown that a number of other factors must be considered as exerting profound influences upon carbohydrate metabolism.

There is increasing evidence that the pituitary and adrenal glands may play an important part in the etiology of the common type of clinical diabetes (26). Hyperthyroidism is known to be

TABLE VI

Responses to various test diets

Case number	Age and sex	Diet number	Weeks on diet	Protein	Fat	Carbohydrate	Insulin	Blood sugar (a.c./p.c.)	Glycosuria	Remarks
	years			*grams*	*grams*	*grams*	*units per 24 hours*	*mgm. per 100 cc.*		
1	31 M	1	1 year	70	150	200	75	/120		Fat raised in diet, insulin lowered, fat well tolerated
		2	12	60	180	200	60	/130		
		3	4	60	180	220	65		++	Higher carbohydrate, requires increase in insulin dosage, glycosuria and higher insulin requirement persist even when diet returned to previous level
		4	2	60	180	200	65	/164	+	
3	47 F	1	8	60	125	100	0	/180	++	
		2	4	60	80	70	0	/112		Carbohydrate decreased because of glycosuria
		3	32	60	125	150	0	/196	++	Trial of higher carbohydrate
		4	10	60	125	70	0			Carbohydrate decreased because of glycosuria
		5	2	60	110	120	0	/168	++	Trial of higher carbohydrate
		6	2	60	100	100	0	/170	+	No gain in tolerance
5	38 F	1	10 years	60	185	50	10	173/	++	
		2	10	60	100	80	20			
		3	4	50	50	100	25			No gain in tolerance with increase in carbohydrate; proportional doses of insulin required
		4	2	60	125	150	30	242/218	++	
		5	1	60	125	200	40	/260	++	
		6	3	60	125	150	30	/252	+	

TABLE VI—*Continued*

Case number	Age and sex	Diet number	Weeks on diet	Protein	Fat	Carbohydrate	Insulin	Blood sugar (a.c./p.c.)	Glycosuria	Remarks
	years			*grams*	*grams*	*grams*	*units per 24 hours*	*mgm. per 100 cc.*		
6	44 F	1	4	60	125	150	22		++	
		2	8	60	125	150	32			Marked glycosuria and acetonuria with high carbohydrate. Diet 7 same as Diet 2 with practically same insulin requirement. No tendency to gain tolerance
		3	1½ years	70	135	130	32–39			
		4	8	60	135	130	32			
		5	3	60	140	180	40		+++	
		6	3	60	140	200	40		++++	
		7	2	60	125	150	32			
7	53 F	1	4	100	179	200	0	142/205	+	
		2	4	100	134	250	0	/160		Gaining tolerance with high carbohydrate, glycosuria and blood sugar practically unchanged on much higher carbohydrate
		3	4	100	114	350	0	/212	+	
8	33 M	1	2 years	70	150	125	30	138/246	++	
		2	10	57	97	114	45	157/173		Carbohydrate decreased, insulin increased because of glycosuria
		3	4	57	97	150	52	/194	+	Higher carbohydrate requires proportional increase in insulin
9	56 F	1	4	57	98	114	25	161/130		
		2	4	60	90	268	35	/145		Enormous increase in carbohydrate permitted, with practically no increase in insulin required
		3	4	60	100	240	35			
		4	4	60	100	300	35	/148		
		5	4	60	100	300	30	/152		
11	43 F	1	8	60	100	80	10			Reduction of insulin with higher carbohydrate
		2	3	60	125	150	50	/105		Only slight rise in blood sugar and occasional glycosuria with very large increase in carbohydrate
		3	16	60	125	150	30	/154		
		4	1 year	60	60	200	30	/168		
		5	4	60	50	250	30	/180		
13	33 F	1	1	60	125	150	0	146/206	++	
		2	2	60	125	250	45	/80		
		3	8	60	150	150	30	/96		Gain in tolerance with high carbohydrate until insulin could be omitted entirely
		4	4	60	100	170	20			
		5	4	60	80	210	0	/112		
		6	20	60	60	300	0	/126		
14	53 F	1	8	100	170	200	55	206/110		
		2	2	100	170	200	40	/115		Gain in tolerance on high carbohydrate; reduction in insulin
		3	2	70	60	225	40	184/		
		4	2	70	60	225	35	/105		
		5	2	70	60	225	30	/140		
15	55 F	1	6	70	119	140	70	175/166		
		2	2	70	89	210	65	/140		Gain in tolerance as carbohydrate raised; reduction in insulin
		3	2	70	70	250	65	/		
		4	2	70	70	250	55	/130		
		5	6	70	70	250	40	/144		
		6	4	70	70	250	30	/156		
		7	2	70	70	250	15	/149		

accompanied in many cases by decreased sugar tolerance or frank diabetes. Thyroidectomy may diminish the severity of the diabetes and increase the effectiveness of insulin in such patients (*27*).

Claude Bernard's piqûre directed attention to the importance of the nervous system in carbohydrate metabolism. Injury to or tumors affecting the hypothalamus may cause diabetes. Davis (*28*) has been able to produce lesions in the hypothalamus which greatly diminish the severity of the diabetes following pancreatectomy. Animals in which the adrenal medullary tissue has been removed, or the adrenal sympathetic nerve supply has been severed, gain in sugar tolerance

and are hypersensitive to insulin (29). De Takats and Fenn have shown that splanchnic nerve section may increase the effectiveness of insulin in and ameliorate human diabetes (30).

It seems evident that all of the factors mentioned must operate through the liver since it serves as the source of the blood sugar during fasting. Diabetics with various hepatic disorders may require disproportionately large doses of insulin (31). Himsworth (32) concludes from a series of interesting experiments that carbohydrate ingestion increases susceptibility to insulin by causing an increase in an hypothetical insulin activator produced in the liver. The evidence supporting the existence of such a factor is as yet inconclusive.

Present clinical and experimental knowledge indicates that many cases of diabetes may not be due primarily to inadequate production of insulin. The central nervous system, the pituitary, the thyroid, the suprarenals and the liver form a chain of factors influencing the blood sugar level and the storage and combustion of carbohydrate. Extra-pancreatic factors may, by interfering with the action of endogenous insulin, be of importance in the etiology of diabetes.

SUMMARY AND CONCLUSIONS

1. The history of the dietary management of diabetes reveals that the greatest students of the disease have differed widely concerning the optimum balance of the various foodstuffs. The fact that many diabetics will gain tolerance on high carbohydrate diets has been reemphasized by recent workers and has attracted much attention. Less attention has been paid to the equally important fact that other diabetics experience deleterious results when allowed large amounts of carbohydrate.

2. A group of diabetics intensively studied over a three year period fall into two classes, the relatively insulin-sensitive and the relatively insulin-resistant. The resistant type tend to be older, frequently are obese, often have hypertension, and are less subject to acidosis and coma. The sensitive type are usually younger, thin, or of normal nutrition, have low blood pressures and a marked tendency to acidosis. The two groups cannot be separated according to severity, since if the insulin requirement be used as the criterion, the resistant group would seem the more severe, but judged by the tendency to acidosis, the sensitive group would seem to have the more serious type of disease.

3. The insulin-sensitive group failed to gain tolerance on high carbohydrate diets. Only one exception among eight patients was noted to this general rule. Relatively high fat was well borne.

4. The relatively resistant group without exception gained tolerance upon a high carbohydrate intake. In several instances this was shown to be accompanied by increased sensitivity to insulin.

5. Recent studies have shown the probable importance of extrapancreatic influences upon carbohydrate metabolism. It is interesting to note that our insulin-sensitive patients resemble in many respects the partially pancreatectomized animal. They respond well to exogenous insulin, but seem to produce too little of the endogenous hormone. When subjected to the excessive burden of a high carbohydrate intake they may lose tolerance, perhaps as the result of overburdening the damaged or numerically decreased pancreatic islets. Relatively resistant patients, however, react as if the endogenous insulin supply were adequate in amount, but operating under the handicap of inhibiting factors.

6. Studies such as those here described may prove useful in indicating the type of diet which will lead to maximum individual carbohydrate tolerance. The evidence at present indicates that the insulin-resistant type may be expected to gain tolerance with high carbohydrate, while the insulin-sensitive type may either fail to gain or may lose tolerance with excessive carbohydrate ingestion.

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