THE INTRAVENOUS GLUCOSE TOLERANCE TEST

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Oral glucose tolerance tests have generally been used to differentiate between diabetes mellitus and the various forms of non-diabetic glycosuria (1). On the basis of such oral tests alterations in carbohydrate metabolism have also been reported in numerous disorders other than diabetes mellitus. These include endocrine, intracranial and hepatic diseases (2), arthritis (3), and convulsive disorders of various types (4). Oral tests, however, necessarily fail to distinguish between effects due to changes in intestinal absorption and those due to alterations in carbohydrate metabolism. Variations in gastric emptying time and in intestinal absorption are in fact known to influence the results of oral tests (5). An intravenous glucose tolerance test automatically eliminates variations due to gastro-intestinal factors. The present study describes the results obtained with a standard intravenous glucose tolerance test. The extent of variation of the test was first determined in normal individuals. It was then applied to patients with a variety of conditions in which the carbohydrate metabolism might possibly be deranged.

METHODS

Sixty normal adult subjects were studied. All were in the post-absorptive state and remained in a recumbent position throughout the morning. After a fasting venous blood sample had been obtained, 50 ml. of a 50 per cent solution of glucose in distilled water were injected intravenously during a period of two minutes. Samples of venous blood were obtained at intervals during the next two or three hours. In the majority of cases hourly urine samples were collected as well. A modification of Benedict's macro-method (6) was used for blood sugar analyses, protein-free filtrates of whole blood being employed. Protein was removed by the zinc precipitation method of Somogyi (7), which also removes most of the non-fermentable reducing substances. Rothberg and Evans' (8) tubes were used in the final visual colorimetric comparison. Urine samples were analyzed for glucose by the quantitative method of Benedict (9).

The same procedure was applied to 271 patients in the New Haven Hospital. Only a few with outright diabetes were included. The majority were selected either because, on clinical grounds, some abnormality of carbohydrate metabolism was suspected or because they had some one of a variety of disorders reputedly attended by derangement of carbohydrate metabolism.

RESULTS

(A) Analysis of results in sixty normal subjects

The original data are presented in Table I. The form of the curve derived from these data relating blood glucose values to time is indicated in Figure 1. The heavy line passes through the mean values, while the lighter upper and lower curves represent the extreme limits of variation. The blood glucose rises sharply immediately following the intravenous injection of glucose, then begins to fall with almost equal rapidity. The rate of fall is, however, progressively retarded during the next two hours. The rate of fall of the blood glucose varied considerably. In some of the subjects the blood glucose fell to the fasting value within half an hour, while in others it was still elevated after an hour and a half. In all subjects, by two hours the blood sugar was within the normal fasting range.

In every instance the blood glucose fell below the initial fasting concentration at some time within the first two hours. This feature of the individual curves of Table I is lost when the average curve of Figure 1 is drawn. In many instances the blood sugar subsequently rose above the minimum point. The low point was reached at forty-five minutes in four tests; at sixty minutes in eight tests; at ninety minutes in thirteen tests and at two hours in thirty-one more. In four of the ten curves in which the blood sugar was determined after three hours, the concentration was still lower than it had been after two hours.

Hypoglycemia therefore regularly occurs in the normal individual following the intravenous in-

TABLE I

Raw data of intravenous glucose tolerance tests on sixty normal subjects

Number	Age	Sex	Height	Weight	Blood glucose level at minutes indicated after intravenous injection of 25 grams of glucose									Urinary excretion of glucose at hours indicated after injection			
					0′	5′	15′	30′	45′	60′	90′	120′	180′	1	2	3	Total
	years		*cm.*	*kgm.*	*milligrams glucose per 100 ml. blood*									*grams*			
1	25	F	163	63.5	94	222	167	87	78	78		87					
2	39	M	173	59.0	92	286	182	131	90	74		68		1.17	0		1.17
3	29	F	165	51.5	100	304	213	177	142	126		78		1.95	0.04		1.99
4	43	F	168	68.0	110	273	204	153	129	101		77		1.59	0.66		2.25
5	52	M	160	63.0	82	254	208	145	127	99		67		1.13	0.08		1.21
6	22	F	168	53.5	82	296	234	191	153	102		87		0.83	0		0.83
7	24	M	173	62.5	92	263	191	141	95	76		78		1.82	0		1.82
8	21	F	180	69.0	91	206	177	112	68	65		82		0.88	0		0.88
9	25	F	173	57.5	98	282	203	154	110	100		85		1.27	0.35		1.62
10	26	M	185	90.5	86	263	144	88	76	67		89		0.93	0		0.93
11	27	M	180	81.5	90	255	200	175	146	120		83		1.06	0.09		1.15
12	26	F	160	49.0	87	286	195	139	110	100		80					
13	22	F	156	51.0	92	328	229	174	97	69		78		2.06	0.06		2.12
14	34	F	160	54.5	84	291	193	119	90	60		67		1.83	0		1.83
15	33	F	160	50.0	87	271	164	76	53	58		80		1.66	0		1.66
16	30	M	188	81.5	80			110	92	86	82	90		0.73	0		0.73
17	28	M	173	70.0	86			98	67	68	86	87		1.31	0		1.31
18	41	M	170	76.5	110			207	165	147	107	84		0.59	0		0.59
19	49	M	160	60.5	79			125	108	78	67	71		0.89	0		0.89
20	65	M	173	57.0	89			165		136	107	90					
21	44	M	168	60.5	82			143		99	89	82					
22	40	M	173	60.5	84			137		90	68	67					
23	47	M	165	80.0	92			131		102	91	90					
24	40	M	168	54.0	86			171		135	95	79					
25	35	M	173	64.0	79			157		138	106	89					
26	49	M	183	96.0	75			96	77	71	82	85		0.51	0		0.51
27	35	M	173	64.5	117			74	60	66	67	83					
28	29	M	180	64.5	79			126	93	78	57	67		0.83	0		0.83
29	37	M	152	49.5	82			135	95	79	76	78					
30	26	M	157	55.5	85			128	89	76	78	85					
31	52	M	165	79.0	91			158	135	117	96	89					
32	74	M	168	59.0	90			130	111	102	78	80		0.36	0.11		0.47
33	35	M	157	52.0	75			141	109	90	70	65		1.43	0		1.43
34	53	M	180	87.5	105			180	135	129	103	84		0.77	0.12		0.89
35	54	M	160	67.0	82			131	112	99	79	68		1.31	0		1.31
36	53	F	165	105.0	85			121	105	95	83	82		0.5	0		0.5
37	60	M	165	54.5	79			166	143	122	85	75		0.79	0.04		0.83
38	49	M	178	90.5	78			115	84	72	71	76		0.47	0.09		0.56
39	39	F	160	74.5	90			163	120	110	85	77		0.92	0.07		0.99
40	21	F	160	55.5	99			215		151	85	74		pooled			1.48
41	46	F	168	76.5	85			149	109	84	68	67					
42	49	F	165	84.0	92			133	117	97	86	89		0.64	0		0.64
43	24	F	157	53.0	85			126	94	86	82	85		1.13	0		1.13
44	42	M	183	78.5	95			163	150	117	77	71					
45	49	M	185	82.0	93			106	88	71	70	85		0.68	0		0.68
46	39	M	163	60.5	82			152	131	112	67	66		pooled			1.16
47	23	M	170	68.0	89			108	77	76	85	86		1.29	0		1.29
48	48	M	157	71.0	100			162	115	93	78	78		1.39	0		1.39
49	24	M	175	63.5	84			79	68	71	81	84		0.58	0		0.58
50	59	M	185	93.0	88			136	105	105	84	75		0.90	0		0.90
51	58	M	170	73.5	82					127	96	82	81	0.27	0	0	0.27
52	40	M	170	54.5	101					114	82	72	79	1.68	0	0	1.68
53	50	M	163	78.5	72					115	93	74	67	1.05	0.10	0.07	1.22
54	52	M	165	77.5	100					131	96	75	76	0.71	0	0	0.71
55	43	M	165	57.0	87			168		120	89	77	72	0.30	0	0	0.30
56	44	M	165	71.5	85			136		78	75	81	81	0.51	0	0	0.51
57	52	M	170	78.0	85					80	75	78	81				
58	44	M	175	57.0	96					116	79	75	76	0.93	0	0	0.93
59	26	M	168	61.0	108					111	86	84	71	1.50	0	0	1.50
60	56	M	168	67.0	88					94	76	67	71	1.21	0.36	0.08	1.65

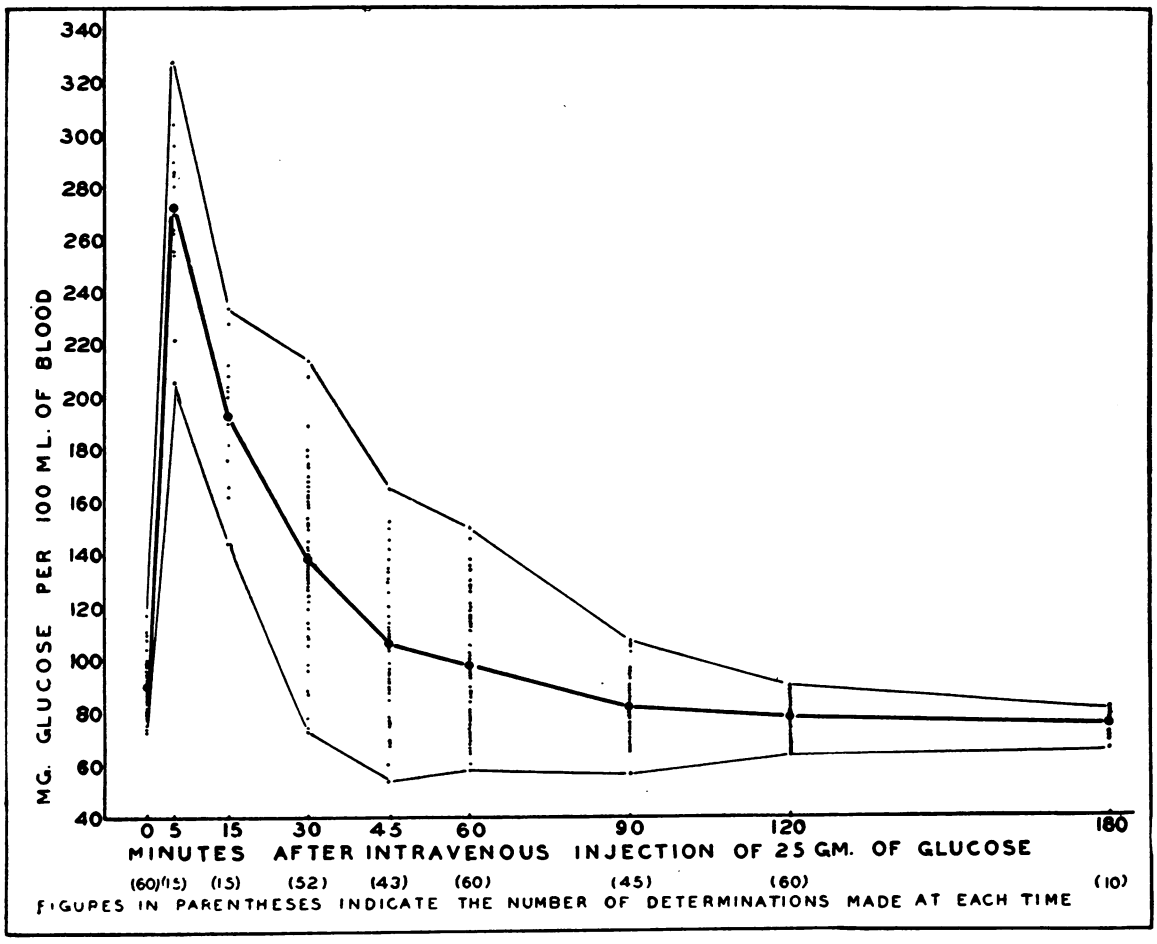

FIG. 1. RESULTS OF INTRAVENOUS GLUCOSE TOLERANCE TESTS ON SIXTY NORMAL SUBJECTS

Upper and lower light solid lines indicate maxima and minima, respectively. Heavy solid line connects arithmetical means.

jection of glucose. The extent of this hypoglycemic response could not be correlated with the fasting blood sugar. Hypoglycemia was as apt to appear promptly in individuals with high initial blood sugar concentrations as in those with low initial concentrations. Indeed the initial blood sugar could not be correlated with any characteristic of the curve.

For statistical purposes the standard deviation of the mean at each point was computed by the formula,

$$\text{S.D.} = \sqrt{\frac{\Sigma d^2}{N-1}},$$

Σd^2 representing the sum of the squares of the individual deviations and N the number of observations at each point. The mean, the standard deviation of the mean, and the maximum and minimum values at each point are presented in Table II. The standard deviation is comparatively

TABLE II

Analysis of glucose tolerance tests on sixty normal subjects

Minutes after injection	Number of subjects	Mgm. glucose per 100 ml. blood			
		Maximum	Minimum	Arithmetical mean	Standard deviation
0	60	117	72	89.0	9.1
5	15	328	206	272.0	30.7
15	15	234	144	193.3	24.3
30	52	215	74	138.7	31.8
45	43	165	53	105.6	26.7
60	60	151	58	97.1	23.5
90	45	107	57	82.7	11.5
120	60	90	65	78.8	7.2
180	10	81	67	75.5	5.0

large at the earlier points but becomes progressively smaller, so that by two hours it has become less than it was at the initial observation. The still lower standard deviation at three hours has less significance since data from only ten subjects are available.

Glycosuria, which was absent in only one subject, was usually confined to the first hour, but in three of the subjects it continued during the second hour as well. The maximum amount excreted by any normal subject was 2.25 grams, less than 10 per cent of the amount injected.

The justification of the use of a fixed dose of 25 grams, rather than a dose adjusted to the size of the subject, appears from an examination of Table I. The subjects ranged in weight from 45 to 105 kilograms, in age from 21 to 74 years, and in height from 152 to 188 centimeters. About one quarter of the subjects were females. Nevertheless, in spite of this variation in the physical characteristics of the subjects, no correlation between the results of the tolerance test and sex, age, height or weight could be demonstrated. Adjustment of the dose to weight or height, therefore, is without logical basis.

(*B*) *Analysis of results in 271 patients*

The curves of patients resembled in general characteristics those of normal subjects. Not infrequently the blood sugar fell more slowly than

TABLE III

Analysis of blood glucose levels at 120 minutes after intravenous injection of 25 grams of glucose in 271 patients

Clinical diagnosis	Number of cases	Distribution			
		Normal	Moderately elevated	Markedly elevated	Moderately depressed
		65–99 mgm. per 100 ml.	*100–119 mgm. per 100 ml.*	*120–281 mgm. per 100 ml.*	*38–64 mgm. per 100 ml.*
Tests done because of glycosuria					
(*a*) Definite diabetes mellitus	19	3	6	10	0
(*b*) Probable diabetes mellitus	14	1	1	12	0
(*c*) Possible diabetes mellitus	8	2	2	4	0
(*d*) No evidence of diabetes mellitus	78	67	6	3	2
Tests done because of pituitary disease					
(*a*) Acromegaly (without glycosuria)	6	4	2	0	0
(*b*) Verified chromophobe adenoma	3	3	0	0	0
(*c*) Unverified chromophobe adenoma	2	2	0	0	0
(*d*) Typical basophilism	7	5	2	0	0
(*e*) Atypical basophilism (obesity, hirsutism)	29	27	2	0	0
Tests done because of other endocrine diseases					
(*a*) Typical hyperthyroidism	4	3	1	0	0
(*b*) Atypical hyperthyroidism	3	2	1	0	0
(*c*) Addison's disease	1	1	0	0	0
(*d*) Myxedema	1	1	0	0	0
Tests done for suspicion of hypoglycemia					
(*a*) Verified islet cell adenoma of pancreas	2	1	0	0	1
(*b*) Unverified islet cell adenoma of pancreas	1	1	0	0	0
(*c*) Idiopathic epilepsy	16	14	0	0	2
(*d*) Convulsions without true epilepsy	3	3	0	0	0
(*e*) Syncope with vasomotor disturbances	16	13	2	0	1
(*f*) Syncope without vasomotor disturbances	18	18	0	0	0
Tests done because of pancreatic disease					
(*a*) Steatorrhea	3	1	0	0	2
(*b*) Acute and chronic pancreatitis	3	2	1	0	0
Miscellaneous tests					
(*a*) Anorexia nervosa and marked malnutrition	5	2	1	2	0
(*b*) Verified brain tumor	4	3	0	0	1
(*c*) Unverified brain tumor	4	3	1	0	0
(*d*) Liver disease	7	3	3	0	1
(*e*) Arthritis	5	3	2	0	0
(*f*) Various specific diseases	5	4	1	0	0
(*g*) No organic disease	4	4	0	0	0
Totals	271	196	34	31	10

TABLE IV

Analysis of blood glucose levels 120 minutes after intravenous injection of 25 grams of glucose in 119 patients with glycosuria, with respect to criteria for diagnosis of diabetes mellitus

Evidence for diagnosis of diabetes mellitus	Number of cases	Distribution			
		Normal	Moderately elevated	Markedly elevated	Moderately depressed
		65–99 mgm. per 100 ml.	*100–119 mgm. per 100 ml.*	*120–281 mgm. per 100 ml.*	*38–64 mgm. per 100 ml.*
Definite evidence (19 Cases)					
(*a*) History of treatment with insulin in amounts greater than 30 units per day, usually associated with marked hyperglycemia	14	2	5	7	0
(*b*) History of fasting hyperglycemia greater than 200 mgm. per 100 ml.	5	1	1	3	0
Probable evidence (15 Cases)					
(*a*) History of fasting hyperglycemia between 150 and 199 mgm. per 100 ml.	12	1	2	9	0
(*b*) History of fasting hyperglycemia between 120 and 149 mgm. per 100 ml. together with glycosuria, polyuria and polydipsia	3	0	0	3	0
Possible evidence (7 Cases)					
(*a*) History of glycosuria, polyuria and polydipsia without history of fasting hyperglycemia	2	0	1	1	0
(*b*) History of fasting hyperglycemia between 120 and 149 mgm. per 100 ml. without symptoms	5	2	0	3	0
No evidence other than glycosuria	78	67	6	3	2
Grand totals	119	73	15	29	2

did that of normal subjects; only rarely did it fall more rapidly. Deviations from normal were most evident at the two-hour point, since here the range of normal variation was so small. In statistical phraseology, the standard deviation of the mean reached its minimum significant value at this point (Table II). Any individual value differing from the mean normal value by an amount greater than three times the standard deviation of this mean was considered outside the normal range. In any series having a normal frequency distribution, only one in a hundred of the individual values will differ from the arithmetical mean by an amount exceeding three times the standard deviation.

The patients were therefore divided into four groups on the basis of the blood sugar concentration two hours after the injection of glucose. These are: (*a*) a group with blood glucose concentrations within the normal range, from 65 to 99 mgm. per 100 ml.; (*b*) a group with moderate elevation of the blood sugar, ranging between 100 and 119 mgm. per 100 ml.; (*c*) a group with markedly elevated blood sugar values, ranging between 120 and 281 mgm. per 100 ml.; and (*d*) a group with blood glucose below the lowest concentration in the normal group, *i.e.*, less than 65 mgm. per 100 ml. Values in group (*a*) differed from the normal mean by less than three times its standard deviation; those in group (*b*) by more than three but less than six times; and those in (*c*) by more than six times. Of the 271 patients, 196 fell into class (*a*), thirty-four into class (*b*), thirty-one into class (*c*) and ten into class (*d*). After the patients had been divided into these four groups on the basis of the glucose tolerance test alone, their clinical records were consulted. Diagnoses were then assigned to each patient, using all available clinical and pathological criteria *except* the results of the glucose tolerance test itself. The results of this analysis are presented in Table III. The group of patients in whom the test was carried out because of glycosuria was further analyzed with respect to criteria used in making or excluding the diagnosis of diabetes mellitus. The results are presented in Table IV. The small proportion of cases with outright diabetes is due to the fact that the test was usually not done in such cases. Borderline cases form an unusually high percentage of the entire group, since such cases were deliberately selected. Had the tests been done rou-

tinely on all glycosuric patients, a very much larger proportion of cases with clear-cut diabetes would have been included.

DISCUSSION

The type of test used in this study is similar to the usual type of oral test, in that its interpretation depends upon the concentration of sugar in the blood after considerable excretion, storage and combustion of carbohydrate have taken place. Jörgensen (10) and others (11) have used intravenous glucose tolerance tests similar in principle to this one. McKean, Myers and Von der Heide (12) relied solely on changes in the blood sugar during the first hour or so after injection, and emphasized particularly the changes during the first quarter hour. Their own data reveal a marked variability in the first hour; during this period numerous changes in distribution and excretion take place which have little relationship to the utilization of glucose. It appears that at least an hour must pass before a true picture develops of the manner in which the individual handles a test dose of glucose.

There is little need to explain the advantages of the intravenous glucose tolerance test over the oral variety. The remarkably small normal variation of the blood sugar two hours after the injection of glucose indicates the desirability of eliminating gastro-intestinal factors, since no comparable point of equal constancy can be found after oral administration (13). This point is strikingly brought out by results obtained in a patient with steatorrhea who was subjected to both an oral and to an intravenous test. The two curves are shown in Figure 2. The blood sugar remained nearly constant during the two hours after the oral ingestion of 50 grams of glucose, while it rose and fell normally following the intravenous injection of 25 grams. The discrepancy can most reasonably be attributed to defective or delayed absorption of glucose in the oral test, rather than to any incapacity to deal with the glucose after reabsorption.

A variety of disturbing factors produce large standard deviations of the mean at all points during the first hour (Table II), so that during this period it is difficult to be sure whether or not a given curve is abnormal. Certainly in no case does the " rapid fall " observed in some patients exceed

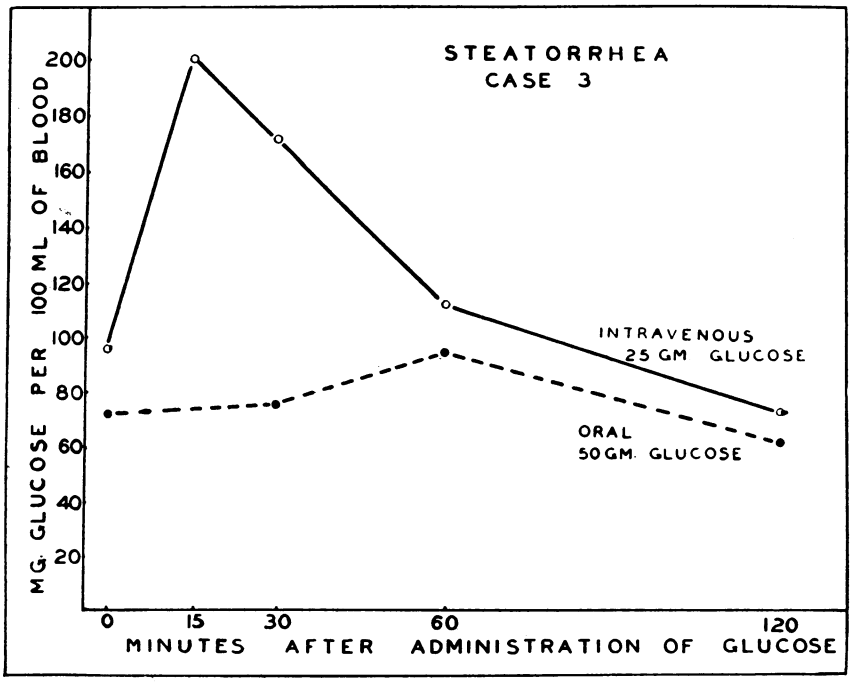

FIG. 2. COMPARISON OF ORAL AND INTRAVENOUS GLUCOSE TOLERANCE TESTS ON A PATIENT WITH IDIOPATHIC STEATORRHEA

the rate of fall of the blood sugar in some normal individuals. On the other hand, if sufficient time be allowed, the blood sugar will normally return to a very restricted range, and deviations from normal are easily demonstrated. The data presented here indicate that the value of the blood sugar two hours after injection is the most satisfactory index for differentiating between normal and abnormal curves.

Before proceeding to a discussion of Tables III and IV the term " diabetes mellitus " must be accurately defined. This term is in fact used in two senses: (*1*) as a disorder of metabolism; and (*2*) as a disease entity. In the first sense the term " diabetes " is applied to any and all subjects whose maximum attainable rate of carbohydrate combustion is less than normal. The intravenous glucose tolerance test is almost by definition diagnostic for " diabetes " in this sense, since, in general, failure of the blood sugar to fall at its usual rate means some retardation of combustion. Consequently, all patients with elevation of the blood sugar two hours after injection of glucose presumably have diabetes in this functional sense of the word. From the clinical standpoint, however, the second definition of diabetes, *i.e.,* diabetes as a disease entity, is of greater importance. Anyone with hyperglycemia, with or without glycosuria, who on the basis of past clinical experience may sometime develop certain characteristic clinical manifestations, suffers from the disease " diabetes mellitus ". These manifestations include polyuria and polydipsia associated with malnutrition and, under some circumstances, ketosis and coma. These disturbances disappear under appropriate therapy. Many individuals potentially liable to the development of these difficulties may not actually suffer from them for long periods of time, if ever. A clinical diagnosis of diabetes not depending on a glucose tolerance test can be made in such persons in only two ways. First, there may be a history of clinical manifestations of diabetes in the past. Second, the individual, though symptom-free, may have hyperglycemia of so pronounced a degree that, on the basis of past experience, he is potentially liable to develop diabetic symptoms. The diagnosis of diabetes in this series was based on one of these two kinds of evidence independently of the glucose tolerance test itself. In order to avoid a circular argument in correlating the results of the intravenous test with the diagnosis, the test itself was never used to derive the diagnoses in the left-hand columns of Tables III and IV.

From Tables III and IV it is clear that twenty-six out of thirty-one, or 84 per cent, of the patients with markedly elevated blood sugar levels after two hours had some independent evidence of the disease " diabetes mellitus ". Of the remaining five patients, two had anorexia nervosa associated with extreme malnutrition, leaving only three with no evidence of disturbed carbohydrate metabolism other than the glycosuria. The analysis of Table IV indicates that the evidence for diabetes mellitus was somewhat uncertain in only four of twenty-six classified in Table III as having diabetes mellitus; in the remainder the evidence was unequivocal. The disturbed carbohydrate metabolism in the two individuals with anorexia nervosa and marked malnutrition was presumably associated with starvation (14). Obviously, these patients had " diabetes " in the functional sense of the term, but did not have the *disease* " diabetes mellitus ". The importance of the definitional distinction made above is here apparent.

Of the 119 patients in whom the tests were done because of glycosuria, seventy-three had normal sugar tolerance curves (Table IV). Of these seventy-three patients, sixty-seven, or 92 per cent, had no evidence of diabetes mellitus. On the other hand, only ten of the nineteen patients with the most definite evidence of diabetes had markedly elevated sugar tolerance curves. The reason for this apparent anomaly can be found in the mode of selection of the cases, since the test was only rarely performed in clear-cut cases of diabetes. The nine patients without markedly elevated curves included the cases of so-called " acute " or " cured " diabetes. Evidence of diabetes was non-existent at the time the tests were performed, but had been unmistakable at an earlier date. A more detailed clinical account of these patients will be presented elsewhere. The tests were performed because at the time there was no available collateral evidence of diabetes. Only nine of the seventy-eight patients with no evidence of diabetes other than glycosuria had either moderately or markedly elevated curves. This group of nine

is especially interesting, since only the future can decide whether these patients will develop the disease " diabetes mellitus ". In spite of these borderline cases, the conclusion is justified that a delayed fall in the blood sugar is correlated with an independent clinical diagnosis of the disease " diabetes mellitus " in about 90 per cent of the cases. The percentage would have been much higher had fewer dubious cases been included; as the figures stand, the odds are at least ten to one that a patient with a markedly elevated curve has diabetes mellitus. Conversely, the odds are ten to one that the patient does not have diabetes if the blood sugar falls to normal within two hours. In the present state of knowledge, moderately elevated curves are of little diagnostic value.

No markedly elevated curves were encountered in patients with conditions other than diabetes or suspected diabetes (Table III). Moderately elevated curves are found not infrequently in such diverse states as acromegaly, basophilism, hyperthyroidism, syncope, pancreatic disease, brain tumor, anorexia nervosa, liver disease and arthritis. In all these conditions occasional abnormalities of carbohydrate metabolism have previously been reported, usually on the basis of oral tests (1, 2). In acromegaly this impairment may be so severe as to produce the disease " diabetes mellitus " (15); the one case of this type in Table III is listed among the diabetics. In liver disease there may be a limitation of capacity to metabolize glycogen, which in turn may affect the glucose tolerance test (16). The occasional presence of a moderately elevated curve is, however, of little diagnostic value in these conditions, since at least an equal number of persons within each disease group have normal curves.

The value of this type of intravenous glucose tolerance test in the detection of pathological hypoglycemia is not great. This is in accord with the experience of Wilder (17) and others. In almost all the normal subjects the blood sugar fell below its fasting level within two hours after the injection of glucose, and in this sense some measure of hypoglycemia is physiological. The blood sugar, however, never fell low enough to be associated with symptoms. In the present series the test was carried out on fifty-six subjects suspected of hypoglycemia because of their symptoms. Four of these had hypoglycemia at the end of two hours, including one case with true islet cell adenoma. On the other hand, the two remaining patients with islet cell adenomata (one unverified) had entirely normal curves. Furthermore, definite depression of the blood sugar at two hours was found in six patients not suspected of hypoglycemia, including two subjects with glycosuria and suspected diabetes, two with steatorrhea, one with brain tumor and one with liver disease. In these subjects no symptoms were associated with the hypoglycemia induced by the test.

Obviously, a test which is normal in two out of three cases of islet cell tumor of the pancreas is of little value in this diagnosis. This is consistent with the results obtained in this condition with the three-hour oral glucose tolerance test, for normal, delayed and accelerated curves have been reported, depending on the previous nutritional state (14). All three cases of islet cell tumor, however, developed marked hypoglycemia with severe symptoms when the period following the ingestion of glucose was prolonged for several hours. It therefore seems logical to apply a modified test if evidence of this diagnosis is sought. The modification would omit samples prior to the two-hour point; hourly samples would then be obtained for at least five hours following the injection, or until the appearance of symptoms. Wilder (17) recommends even longer periods of fasting.

The value of the present test in the diagnosis of hypoglycemia not due to islet cell tumor, but associated with symptoms, is also doubtful. In the first place, a positive result is obtained in a variety of disorders in which there are no symptoms of hypoglycemia. Secondly, a negative result has little meaning, since normal curves may be found in cases having true islet cell adenomata. The rarity in this series of hypoglycemia exceeding the normal range suggests either that the condition is rare, or that this is not the proper way to demonstrate it. The prolonged test suggested above might logically be substituted for the two-hour test whenever hypoglycemia from any cause is suspected.

The intravenous glucose tolerance test, of course, requires an operator with some skill in intravenous technique. Occasionally, local irritation along the vein follows the injection of con-

centrated glucose. These technical difficulties are, however, slight, and the advantage derived from an exact knowledge of the amount of glucose to be metabolized is considerable. Perhaps much of the controversy concerning the tolerance for carbohydrate in specific diseases would be resolved if an intravenous test such as is here described were more universally adopted.

SUMMARY AND CONCLUSIONS

1. An intravenous glucose tolerance test is described and normal standards are defined.

2. A single blood sugar drawn two hours after the intravenous injection of 25 grams of glucose is a reliable guide in distinguishing between benign glycosuria and diabetes mellitus. If the blood sugar is greater than 120 mgm. per 100 ml., the patient probably has diabetes mellitus, while if it is less than 100 mgm. per 100 ml., he probably does not. If it falls between 100 and 120 mgm. per 100 ml., the test is indeterminate.

3. In this series the only condition among patients without glycosuria in which the blood sugar after two hours exceeded 120 mgm. per 100 ml. was anorexia nervosa with marked malnutrition. The blood sugar fell between 100 and 120 mgm. per 100 ml. in a variety of conditions, including acromegaly, basophilism, hyperthyroidism and arthritis. Little diagnostic value could be assigned to the test in these states, since blood sugar values less than 100 mgm. per cent were equally common in each group.

4. Hypoglycemia of moderate degree, unassociated with symptoms, appeared in the majority of normal subjects. The blood sugar was normal in subjects with islet cell adenomata and subnormal in subjects without symptomatic or other evidence of endocrine disease. The two-hour blood sugar is therefore of little value in the diagnosis of pathological hypoglycemia.

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