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The Significance and Interpretation of Mildly Abnormal Oral Glucose Tolerance

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Summary. Intravenous glucose tolerance, release of immunoreactive insulin and the hypoglycaemic response to exogenous insulin were investigated in nine normal, fifteen maturity-onset diabetic and twenty-five subjects (equivocal group) with a mild abnormality of oral glucose tolerance (Fasting blood glucose < 110 mg%, and two hour levels < 170 mg%). — Intravenous glucose tolerance ($K_{G.T.T.}$) and insulin sensitivity ($K_{I.T.T.}$) of subjects in the equivocal group ranged from normal to low values, but were significantly different from the normal and frank diabetic groups. Within the equivocal group, eleven subjects had normal, eight diabetic and six borderline $K_{G.T.T.}$ values. — Plasma insulin responses within the equivocal group varied widely: seven normal and seventeen typical diabetic responses occurred in individuals with either normal or reduced intravenous glucose tolerance. Despite this heterogeneity, a definite diagnosis was established in eleven of the twenty-five subjects with the present method of investigation. — Significant positive correlations were demonstrated both between $K_{G.T.T.}$ and plasma insulin and $K_{G.T.T.}$ and insulin sensitivity, suggesting that overall glucose tolerance is dependent on both insulin sensitivity and on the amount of circulating plasma insulin.

Signification et interprétation d'une tolérance au glucose oral légèrement anormale

Résumé. La tolérance intraveineuse au glucose, la libération d'insuline immuno-réactive et la réaction hypoglycémique à l'insuline exogène furent examinées chez neuf sujets normaux, chez quinze sujets diabétiques de l'âge adulte et chez vingt-cinq sujets (groupe équivoque) ayant une anomalie bénigne de la tolérance au glucose par voie orale (glucose à jeun < 110 mg% et des taux de deux heures < 170 mg%). La tolérance intraveineuse au glucose ($K_{G.T.T.}$) et la sensibilité à l'insuline ($K_{I.T.T.}$) du groupe équivoque allaient des valeurs normales à des valeurs peu élevées mais étaient nettement différentes des groupes normaux et franchement diabétiques. Dans le groupe équivoque, onze sujets eurent des valeurs normales, huit des valeurs diabétiques et six des valeurs limites de $K_{G.T.T.}$ — Les réponses de l'insuline plasmatique dans le groupe équivoque eurent de grandes variations: sept réponses normales et dix-sept réponses typiquement diabétiques apparurent chez les individus ayant soit une tolérance normale au glucose intraveineux, soit une tolérance réduite. Malgré cette hétérogénéité, un diagnostic définitif fut établi chez onze des vingt-cinq sujets avec cette méthode d'enquête. — Des corrélations d'une signification positive furent démontrées à la fois entre $K_{G.T.T.}$ et l'insuline plasmatique et entre $K_{G.T.T.}$ et la sensibilité à l'insuline, suggérant que la tolérance complète au glucose dépend à la fois de la sensibilité envers l'insuline et de la quantité d'insuline plasmatique qui circule.

Die Deutung und Bedeutung leicht abnormaler Glucosebelastungen

Zusammenfassung. Die intravenöse Glucose-Toleranz, die Sekretion von immunreaktivem Insulin und die hypoglykaemische Reaktion auf exogenes Insulin wurde bei einer Reihe von Patienten untersucht: von diesen waren 9 normal, 15 hatten im reifen Alter einen Diabetes entwickelt, und 25 (eine Mittelgruppe) zeigten eine geringe Anomalie der oralen Glucose-Toleranz. (Blutzucker, nüchtern < 110 mg%, Werte nach 2 Std < 170 mg%). Die Messung der intravenösen Glucose-Toleranz ($K_{G.T.T.}$) und der Insulin-Empfindlichkeit ($K_{I.T.T.}$) von Patienten in der Mittelgruppe ergaben normale oder niedrige Werte, aber sie waren deutlich verschieden von denen in der normalen oder diabetischen Gruppe. Innerhalb der Mittelgruppe hatten 11 Patienten normale, 8 diabetische und 6 Grenzlinien $K_{G.T.T.}$ Werte. — Die Anstiege des Plasma Insulins in der Mittelgruppe fielen sehr verschieden aus: 7 normale und 17 typisch diabetische Reaktionen fanden sich bei Patienten, die eine normale oder erniedrigte intravenöse Glucose-Toleranz hatten. Trotz dieser Unterschiede war es möglich, eine definitive Diagnose bei 11 der 25 Patienten mit Hilfe dieser Untersuchungsmethode zu stellen. — Signifikante positive Beziehungen wurden festgestellt zwischen $K_{G.T.T.}$ und Plasma Insulin einerseits und $K_{G.T.T.}$ und Insulin-Empfindlichkeit andererseits. Daraus folgt, daß die Gesamt-Glucose-Toleranz abhängig ist nicht nur von der Insulin-Empfindlichkeit, sondern auch von der Menge des Plasma-Insulins im Blutkreislauf.

Key-words: Equivocal oral glucose tolerance, intravenous glucose tolerance, insulin tolerance tests, immunoreactive insulin levels, insulin sensitivity.

The practical problems that arise in an individual in differentiating a possibly benign abnormality of glucose tolerance from diabetes mellitus have been excellently discussed in a recent review by Schwartz (1968). The biochemical criteria used at present for the diagnosis of diabetes mellitus vary widely (Fajans and Conn, 1959, British Diabetic Association — Fitzgerald and Keen 1964, W.H.O. Publications 1965, American Diabetes Association 1967 and 1969) and the difficulties and possible dangers inherent in such definitions were highlighted in the prospective study of O'Sullivan and Mahan (1968). These workers showed that over a

twelve year period, a group of individuals assessed by several criteria as having mildly abnormal glucose tolerance had widely differing rates of progression to clinical diabetes.

Many workers have suggested that alterations in the pattern of insulin release following a glucose load may be diagnostic of diabetes mellitus (Yalow *et al.* 1965, Cerasi and Luft 1967a, Colwell and Lein 1967, Perley and Kipnis 1967, Seltzer *et al.* 1967, Simpson *et al.* 1968). However, it has also been shown that glucose tolerance depends as much on the effective hypoglycaemic action of insulin as on the amount of circulating insulin (Martin *et al.* 1968, Heard and Henry 1969, Reaven and Farquhar 1969, Alford *et al.* 1970). As early as 1939, Himsworth and Kerr 1939, using a combined glucose-insulin tolerance test, had differentiated two types of diabetics — the insulin sensitive and the insulin insensitive type.

This report describes the study of patients with mildly abnormal oral glucose tolerance tests by a combined intravenous glucose tolerance/insulin tolerance test. The results indicate that in an individual with a mild abnormality of glucose tolerance, there is usually decreased insulin sensitivity compared with normal subjects, but that the patterns of the insulin responses are variable.

Table 1. *Summary of patients studied by intravenous glucose tolerance and insulin tolerance tests*

Group	Number	Age (mean)	Sex	Ponderal index*	$K_{G.T.T.}$*	$K_{I.T.T.}$*
I			M:F			
Normal	9	27	7:2	2.2	2.83	7.80
Control				± 0.01	± 0.27	± 1.06
II						
Diabetic	15	50	11:4	2.3	0.68	2.73
Control				± 0.01	± 0.05	± 0.36
III						
Equivocal	25	46	11:14	2.3	1.28	4.59
				± 0.05	± 0.12	± 0.42

* mean ± S.E.M.

Methods

Patients studied. Forty-nine subjects aged 15 to 75 years were investigated (Table 1). The subjects were divided into three groups: *Group I.* Nine normal, non obese subjects, seven males and two females aged 17 to 46 years (mean 27 years), with no family history of diabetes and no evidence clinically of endocrine or vascular disease. Oral glucose tolerance tests were normal. *Group II.* Fifteen maturity-onset diabetics aged 40 to 72 years (mean 50 years) with unequivocal biochemical and symptomatic disease. Family history of diabetes was present in eight subjects, and one subject was obese. Diabetic microangiopathy was present in three cases. Control of the diabetes was by diet and/or oral hypoglycaemic agents in all subjects except two patients who were currently receiving insulin and in whom heterologous insulin antibodies prevented the measurement of immunoreactive insulin levels. At the time of the investigation all were well controlled, being free of infections and ketosis. *Group III* (Table 2). Twenty-five subjects, eleven males and fifteen females aged 15 to 75 years (mean 46 years), who had mildly abnormal oral glucose tolerance tests. A family history of diabetes was present in nine cases, but none were overweight. Case No. 5 had a degenerative exudative retinopathy, Cases 17 and 18 mild ischaemic heart disease (angina and non-specific T wave changes on E.C.G.), and Case 20 had clinically asymptomatic mild peripheral neuritis. All other subjects in this group were free of large and small vessel vascular disease on clinical examination and by E.C.G. as assessed independently by a cardiologist.

Normal oral glucose tolerance was defined by the W. H.O. Criteria (W.H.O. Publications 1965). Patients were classed as having mild oral glucose intolerance if fasting blood glucose levels were less than 110mg%, and the two hour level was greater than 130 mg% but less than 170 mg% after a 50 g glucose load. Capillary blood samples were used, measuring whole blood reducing substance by the alkaline ferricyanide auto-analyser method.

Body build was expressed as the Davenport-Ponderal Index — weight (g)/height^2(cm), which correlates directly with adiposity (Whyte 1965). The normal Australian mean for subjects aged 20 to 30 years is 2.37 and 40 to 60 years is 2.62 (Whyte 1965).

Intravenous glucose tolerance and insulin tolerance tests. Prior to investigation, all patients were on a diet containing at least 200 g carbohydrate daily for four days, and had ceased oral hypoglycaemic agents for at least 72 h or had omitted insulin therapy for 24 h (American Diabetes Association 1969). The majority of subjects were studied as outpatients, the test being commenced between 8 and 9.30 a.m. after a 15 to 30 min period of recumbency.

Following an overnight fast, an intravenous glucose tolerance test was performed, using a 750 mg per kg

body weight glucose load which was injected over 4 min. Samples were collected for blood glucose and plasma insulin at 0, 2, 5, 10, 15, 20, 30, 45 and 60 min, from an indwelling needle in the opposite forearm vein. Glucose tolerance, $K_{G.T.T.}$ (the rate of glucose decay per unit time) was calculated from the expression $K_{G.T.T.} = \frac{0.693}{T\frac{1}{2}} \times 100$ (Lundbaek 1962). The half life ($T\frac{1}{2}$) of glucose disappearance was estimated from the line of best fit for glucose decay from the fifteenth to sixtieth minute after the glucose load when plotted on semi-log paper

At sixty minutes, 0.1 unit per kg body weight of crystalline bovine insulin was injected into a vein in the opposite arm. Insulin sensitivity, $K_{I.T.T.}$, (the hypoglycaemic potency of exogenous insulin) was calculated from samples collected every five minutes over the next forty-five minutes (Martin *et al.* 1967). The validity of the insulin sensitivity test ($K_{I.T.T.}$), with prior glucose loading was examined in the control group. No significant difference was found between paired $K_{I.T.T.}$ values obtained after fasting or 60 min after the glucose load (mean 5.75 versus 6.83, $t = 0.61$, $p > 0.6$).

Plasma insulin was estimated in duplicate by the charcoal method of Herbert *et al.* (1965) as modified by Pearson *et al.* (1968) in samples rapidly frozen and stored at $-15°$C. The presence of heterologous insulin antibodies are determined routinely in this assay system (Pearson and Martin 1970).

$K_{G.T.T.}$ values greater than 1.20 were classed as normal, allowance being made for the relatively large intravenous glucose load used (Moorhouse *et al.* 1963, Wahlberg 1966, Kahn *et al.* 1967). $K_{G.T.T.}$ values less than 1.00 were considered to be in the diabetic range. The range of insulin sensitivity ($K_{I.T.T.}$) previously determined in fifty normal Australians aged 20 to 50 years of age was 2.5 to 9.3, mean 6.23 (Martin and Stocks 1968). Fasting plasma insulin of 2 to 25 μU/ml and a rise of greater than 30 μU/ml above fasting levels 2 to 5 min after the intravenous glucose load were considered normal.

Statistical analyses were by the Students' T test and by simple coefficient correlation analysis using the Olivetti computer programme. Logarithmic transformation of the plasma insulin levels was carried out to convert the data to a more "normal" distribution with stabilisation of the variance (Welborn *et al.* 1966, Reaven and Miller 1968).

Results

Groups I and II. Control and diabetic subjects: Intravenous glucose tolerance ($K_{G.T.T.}$) in the controls ranged from 1.60 to 3.47, with a mean of 2.83 ± 0.27 (S.E.M.). Glucose decay after exogenous insulin ($K_{I.T.T.}$) was rapid in the control subjects, $K_{I.T.T.}$ values being greater than 3.10 with a mean of 7.80 ± 1.06 (Table 1, Figs. 1 and 2). The two eldest subjects aged 40 and 46 years had $K_{G.T.T.}$ values of 3.30 and 1.60 and $K_{I.T.T.}$ values of 8.70 and 9.90 respectively. Plasma insulin showed a normal brisk early rise to a peak two to five

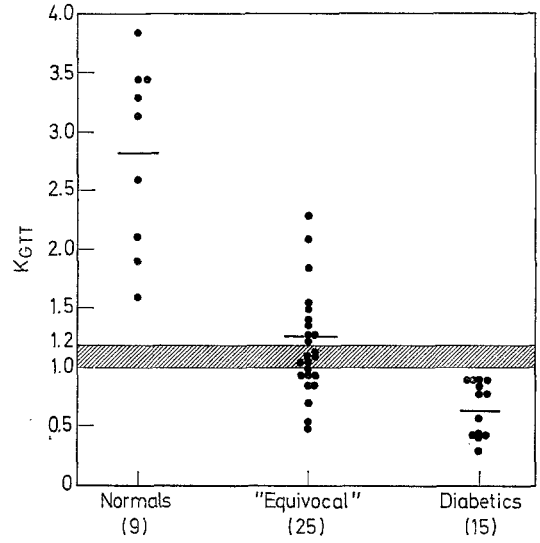

Fig. 1. Comparison of intravenous glucose tolerance ($K_{G.T.T.}$) of the normal and diabetic controls — Groups I and II — with the "equivocal" Group III. The shaded area shows the borderline range of $K_{G.T.T.}$ between normal (> 1.20) and diabetic (< 1.00) values. The horizontal line represents the mean for each group

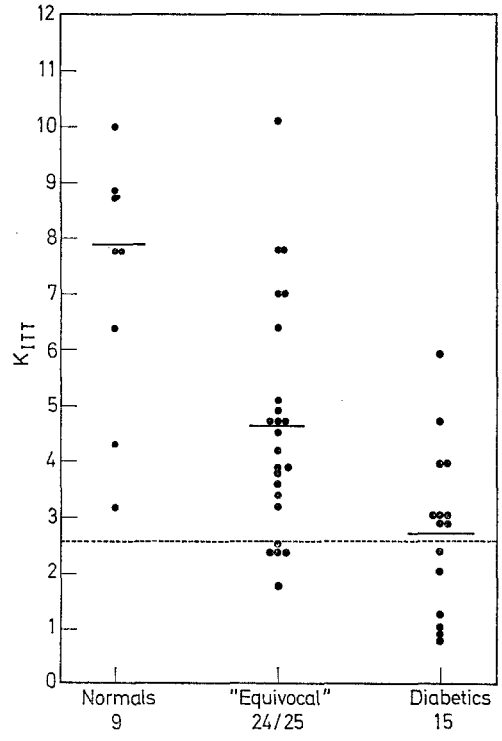

Fig. 2. Comparison of insulin sensitivity of the normal and diabetic control Groups I and II, with the "Equivocal" Group III. The dotted line represents the lower limit for normal $K_{I.T.T.}$, and the horizontal lines the mean for each group

minutes after the glucose load (mean ± S.E. peak rise 75 ± 12 μU/ml), falling towards fasting levels by sixty minutes (Fig. 3).

In the diabetics (Group II), intravenous glucose tolerance was very low, $K_{G.T.T.}$ values being below

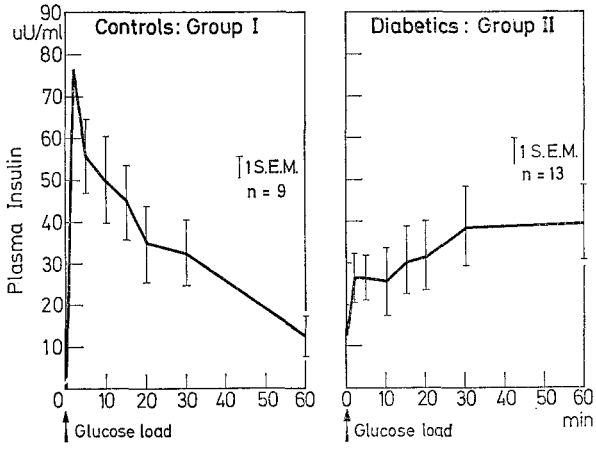

Fig 3. Mean plasma insulin levels following the intravenous glucose load in Groups I and II

were significantly different from both the controls and the frank diabetics (Tables 1 and 2; Figs. 1 and 2). The mean $K_{G.T.T.}$ value, 1.28 ± 0.12 was lower than the normal controls ($t = 5.811$, $p < 0.001$) but was significantly higher than the diabetics (Group II) ($t = 5.459$; $p < 0.001$). In addition, insulin sensitivity was significantly reduced compared with the control Group I (mean $K_{I.T.T.}$ 4.59 ± 0.42 versus 7.80 ± 1.06, $t = 3.333$, $p < 0.002$), but was higher than the diabetics (4.59 ± 0.42 versus 2.73 ± 0.36; $t = 3.516$, $p < 0.005$) (Fig. 2).

Within Group III, several sub groups were noted. Eleven subjects had $K_{G.T.T.}$ values within the normal range, six had $K_{G.T.T.}$ values between 1.00 and 1.20 and in eight, $K_{G.T.T.}$ was in the frank diabetic range, less than 1.00 (Fig. 1, Table 2). There was no significant difference between the insulin sensitivity of the three sub-groups. However, when insulin sensitivity of Group III subjects with diabetic $K_{G.T.T.}$ values, less than 1.00, were compared with the frank diabetics (Group II), no significant differernce was now evident (mean $K_{I.T.T.}$ 3.76 ± 0.52 versus 2.73 ± 0.36; $t = 1.737$, $p > 0.05$).

The plasma insulin response to the glucose load of

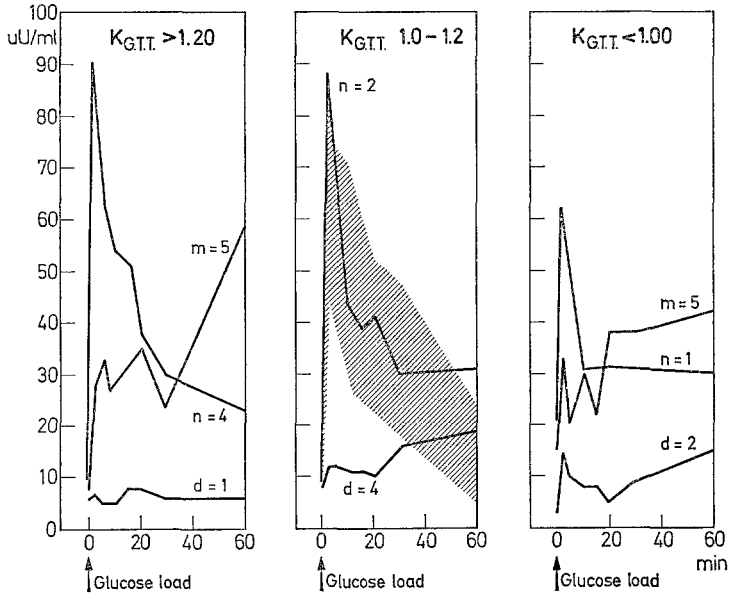

Fig. 4. Mean plasma insulin levels following the intravenous glucose load in the "equivocal" Group III. The group has been subdivided according to intravenous glucose tolerance, as indicated in the text. n = normal insulin response; m = maturity-onset diabetic response; d = insulin-deficient diabetic response. The shaded area represents the range of response in normal controls (Group I)

1.00 with a mean of 0.68 ± 0.05. Insulin sensitivity was significantly reduced, mean $K_{I.T.T.}$ 2.73 ± 0.36, compared with the control group ($t = 5.099$, $p < 0.001$) (Table 1, Figs. 1 and 2). The mean plasma insulin response in the diabetics is shown in Fig. 3. Two types of response were seen: the delayed, sustained response of the maturity-onset diabetic and the flat response of the insulin-deficient diabetic.

Group III. In this group overall intravenous glucose tolerance ($K_{G.T.T.}$) and insulin sensitivity($K_{I.T.T.}$) Group III subjects was unpredictable (Table 2, Fig. 4). Normal patterns of release were seen in subjects with normal (Cases 1,2, 6 and 11) and reduced (Cases 12, 15 and 22) intravenous glucose tolerance. However, the insulin response was normal in only four of the eleven subjects with normal intravenous glucose tolerance, and three of the fourteen subjects with reduced intravenous glucose tolerance had normal plasma insulin levels (Fig. 4). Flat or delayed insulin responses occurred in seven of the eight patients with a family

history of diabetes, but in only eight of the seventeen individuals with no family history. There was no evidence in this series that the plasma insulin response was influenced by the age of an individual.

Relationship between glucose tolerance, plasma insulin responses and insulin sensitivity. When the forty-nine patients were considered as a whole, a significant positive correlation between glucose tolerance ($K_{G.T.T.}$) and the five minute plasma insulin level ($r = 0.475$, $p < 0.001$) and a significant negative correlation with the sixty minute plasma insulin level ($r = -0.376$, $p < 0.01$) were found (Figs. 5 and 6). It would therefore seem that normal glucose tolerance is associated with an early peak rise of plasma insulin which falls rapidly towards fasting levels. On the other hand, decreased glucose tolerance is associated with a low early insulin response and a sustained elevation of plasma insulin levels, sixty minutes after the glucose load.

A significant positive correlation between overall glucose tolerance and insulin sensitivity ($K_{I.T.T.}$) was also demonstrated for the forty-nine subjects ($r = 0.647$, $p < 0.001$) (Fig. 7). This relationship was still evident when either the frank diabetic Group II ($r = 0.461$, $p < 0.05$) or the equivocal Group III ($r = 0.506$, $p < 0.01$) were considered separately.

Discussion

This report has shown that intravenous glucose tolerance ($K_{G.T.T.}$) varies widely in subjects with only mildly abnormal oral glucose tolerance. The intravenous glucose tolerance test was employed in this study because the oral glucose tolerance test is imprecise and poorly reproducible in any one individual (McDonald *et al.* 1965). Although the rate of glucose decay is affected by age (Wahlberg 1966, Franckson *et al.* 1966), Wahlberg showed that despite less frequent high normal $K_{G.T.T.}$ values in subjects over seventy years of age, there was no increase in the number of diabetic $K_{G.T.T.}$ values (Wahlberg 1966). The test is not physiological, but isotope studies have shown that the $K_{G.T.T.}$ value represents a constant and useful measure of overall glucose tolerance (Forbath and Hetenyi 1966).

In the equivocal Group III, eleven subjects (44%) had normal $K_{G.T.T.}$ values, six (24%) were borderline, and eight (32%) were in the diabetic range. Insulin sensitivity ($K_{I.T.T.}$) of the equivocal group as a whole (Group III), as measured by the hypoglycaemic potency of exogenous insulin, was significantly different from the normal control and the frankly diabetic sub-

Table 2. *Details of the Twenty-five Subjects of Group III*

Case No.	Age	Sex	$K_{G.T.T.}$	$K_{I.T.T.}$	Intravenous G.T.T. Plasma Insulin (μU/ml)							
					0′	2′	5′	10′	15′	20′	30′	60′
1.	21	F	1.87	7.70	24	204	139	99	88	55	44	37
2.	36	F	2.31	6.3	18	88	68	84	82	64	45	25
* 3.	65	M	1.54	—	—	—	—	—	—	—	—	—
* 4.	37	M	1.33	4.85	9	9	13	21	20	21	23	33
5.	70	F	1.41	2.47	11	70	91	71	73	86	—	171
6.	45	F	3.30	4.45	2	36	34	28	24	20	17	10
7.	17	F	1.50	7.70	2	20	16	14	9	13	13	10
* 8.	24	F	2.10	4.60	6	7	5	5	8	8	6	6
* 9.	44	F	1.28	3.64	5	15	11	21	25	22	20	41
*10.	39	M	1.27	2.31	10	12	—	8	12	18	26	28
11.	51	M	1.26	2.31	10	33	17	15	24	22	27	22
*12.	63	F	1.07	4.60	10	89	78	35	36	37	30	26
13.	15	F	1.05	4.62	5	5	5	5	5	5	12	22
14.	21	F	1.09	6.93	9	19	19	20	16	—	12	17
15.	63	M	1.00	3.47	9	87	72	53	42	45	31	36
16.	35	M	1.05	10.00	10	18	14	10	15	13	19	23
17.	69	M	1.12	4.08	6	6	10	8	8	11	12	14
*18.	69	F	0.72	3.15	22	56	27	108	38	52	65	75
19.	33	M	0.53	1.77	20	35	28	43	43	50	59	69
20.	69	F	0.83	3.30	3	26	9	7	6	5	9	12
21.	43	F	0.50	6.93	44	—	21	25	17	26	19	22
22.	75	M	0.93	2.31	16	62	50	26	—	33	32	33
23.	54	M	0.95	3.85	2	7	3	3	6	21	25	18
24.	36	F	0.96	3.85	12	12	24	18	2	35	21	28
*25.	58	M	0.86	4.95	2	2	10	8	10	—	10	19
			$K_{G.T.T.}$	$K_{I.T.T.}$	Plasma insulin (μU/ml)							
Mean ± S.E.M.			1.28±12	4.59±0.42	11±2	40±10	33±7	31±6	25±5	30±4	25±3	33±7

* Family history of diabetes mellitus

jects. However, the insulin sensitivity ($K_{I.T.T.}$) of the individuals in Group III with diabetic $K_{G.T.T.}$ values (less than 1.00) was similar to the frank diabetics. Factors thought to affect insulin sensitivity — large and small vessel disease (Martin and Stocks 1968, Stocks and Martin 1969), obesity (Franckson *et al.* 1966) and malnutrition (Heard and Henry 1969) — were not

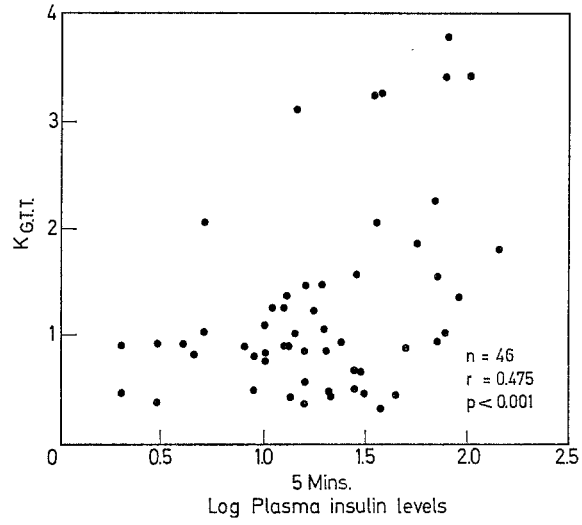

Fig. 5. Relationship between glucose tolerance ($K_{G.T.T.}$) and the logarithm of the plasma insulin at five minutes in all groups

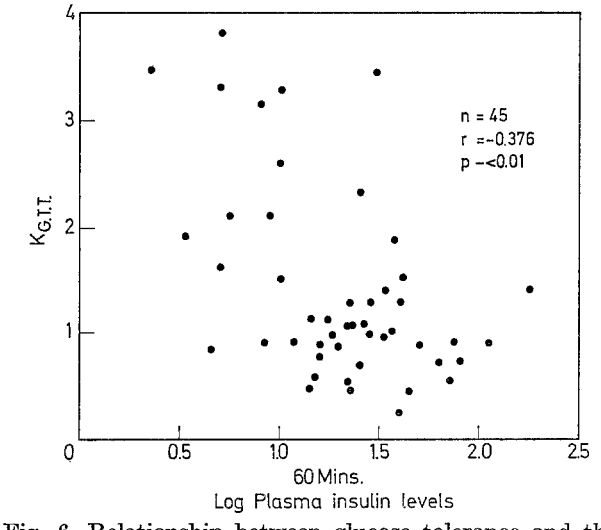

Fig. 6. Relationship between glucose tolerance and the logarithm of the plasma insulin at sixty minutes in al groups

clinically present in these subjects and therefore cannot be evoked as the cause of the observed insulin resistance.

Immunoreactive plasma insulin levels after glucose loading in the normal and diabetic subjects (Groups I and II) were similar to other reports (Yalow *et al.* 1965, Cerasi and Luft 1967a, Seltzer *et al.* 1967, Simpson *et al.* 1968). In contrast the individual plasma insulin responses of the Group III subjects varied widely, normal and typically diabetic patterns of insulin release being found in subjects with normal, diabetic or equivocal $K_{G.T.T.}$ values. Although all these subjects had mildly abnormal oral glucose tolerance, age did not influence the pattern of insulin response to the glucose load (Reaven and Miller 1968, McKiddie *et al.* 1969).

By means of the combined intravenous glucose tolerance and insulin sensitivity test further separation of the subjects with doubtful oral glucose tolerance was possible. Within Group III, four subjects had normal intravenous glucose tolerance, insulin sensitivity and plasma insulin levels and are considered to be non-diabetic. Seven subjects were diabetic by all criteria with abnormal plasma insulin responses, decreased insulin sensitivity and very low intravenous glucose tolerance. The remaining thirteen patients with $K_{G.T.T.}$ values greater than 1.00, had variable insulin sensitivity and both normal and abnormal plasma insulin responses. No definite diagnosis can be made at this stage,

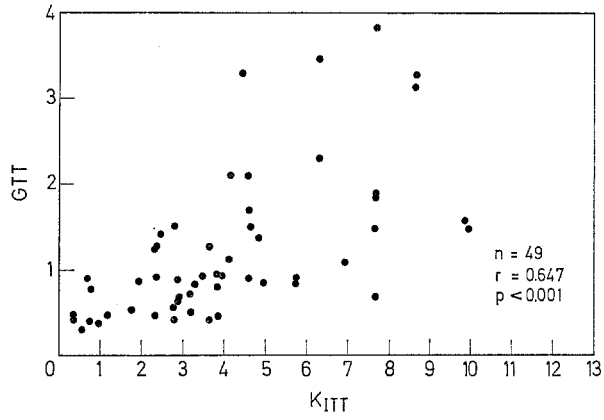

Fig. 7. Correlation between glucose tolerance ($K_{G.T.T.}$) and insulin sensitivity ($K_{I.T.T.}$) in all subjects

and only long term follow up of these individuals will determine with any certainty their true diagnosis.

The factors which lead to the onset of glucose intolerance in an individual are unknown. The close relationship between individual blood glucose and immunoreactive insulin levels after an intravenous glucose load is well established (Colwell and Lein 1967, Wahlberg 1966, Williams *et al.* 1966, Kahn *et al.* 1967, Seltzer *et al.* 1967, Boden *et al.* 1968) but the dependence of *overall* glucose tolerance on the magnitude of insulin release is less clearly defined. Some of this confusion may have arisen because of the numerous methods employed to interpret the magnitude of an insulin response (Seltzer *et al.* 1967, Perley and Kipnis 1967, Bagdade *et al.* 1967, Cerasi and Luft 1967b). Thus Kahn & Associates (1967) reported that in 10 subjects intravenous glucose tolerance ($K_{G.T.T.}$) correlated with the early 10 min insulin release in the same individual with varying dose levels of glucose.

However, these workers were unable to find any correlation between $K_{G.T.T.}$ values and early insulin release in different individuals. This is at variance with other reports describing a significant correlation between intravenous glucose tolerance and early insulin release (Wahlberg 1966) and integrated oral glucose tolerance and total insulin release (McKiddie *et al.* 1969). Some of these discrepancies may be due to the fact that overall glucose tolerance is probably related to the pattern of insulin secretion rather than the actual levels of plasma insulin (Reaven and Miller 1968).

In the present study, glucose tolerance ($K_{G.T.T.}$) was positively correlated with plasma insulin levels at five minutes and negatively correlated at sixty minutes, suggesting that decreased glucose tolerance is associated with an altered *pattern* of insulin response to a glucose load. However, a significant correlation between glucose tolerance and insulin sensitivity in normals and diabetics was also observed. Heard and Henry (1969) found in animals a similar positive relationship between insulin sensitivity and overall glucose tolerance, concluding that the rate of intravenous glucose decay was dependent on insulin sensitivity and was independent of the levels of immunoreactive insulin. In man it has been shown that insulin sensitivity also influences glucose tolerance (Martin *et al.* 1968, Alford *et al.* 1970). The demonstration in the present study of a direct relationship between glucose tolerance and insulin sensitivity indicates that the overall glucose tolerance of an individual is as much dependent on the insulin sensitivity as on the amount of circulating insulin. The diagnosis of "early" diabetes based solely on the pattern of the insulin response to a glucose load should therefore be viewed with suspicion.

The difficulty in diagnosing "diabetes mellitus" in an individual from a mild abnormality of oral glucose tolerance alone remains (O'Sullivan and Mahan 1968, Carter and Maynard 1970, Schwartz 1968). As glucose tolerance has a unimodal distribution (Hayner *et al.* 1965), one would not expect a sharp division between a "normal" and an "abnormal" test. The postulate that active treatment of a "potential" diabetic might delay the onset of islet cell failure and overt diabetes with its serious long term sequelae, is of considerable importance (Stowers 1966, Murphy *et al.* 1969, Rull *et al.* 1970). However, the testing of such an hypothesis must depend on the ability to diagnose with absolute certainty an "early" diabetic abnormality of glucose tolerance. From the present study it is evident that a confident diagnosis of diabetes mellitus in patients with mild abnormalities of oral glucose tolerance alone cannot be made readily.

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