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Glucose Kinetics in Human Obesity*

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Summary. The kinetics of glucose utilization have been studied in 325 normal subjects, and 150 obese patients free from diabetes or other endocrine diseases. The investigation included measurements in the basal state by isotope dilution technique, determinations of glucose utilization rate induced by endogenous insulinic response (intravenous glucose load and tolbutamide) and by administration of various doses of exogenous insulin. — Results showed that whatever the test used, the disappearance rate constants (slope values or fractional disappearance rate) and the total uptakes (absolute value) of the obese patients were systematically lower than the corresponding values in the normal subjects. This metabolic abnormality is not favoured by ageing, but is not due to a diminished ability of the pancreas to release insulin: basal levels of plasma insulin and rises induced by glucose and by tolbutamide were significantly higher in obese patients. — The deficiency is better revealed by increasing the utilization rate by insulinic stimulation: the greater the slope value, the larger the impairment. In fact, there is a straight line relationship showing direct proportionality between the impairment of the glucose utilization rate constant and the velocity of the process, irrespective of the amount of insulin present or added. This feature strongly suggests in human obesity that the metabolic disturbance primarily affects the glucose uptake process itself rather than the action of insulin.

Cinétiques du glucose dans l'obésité humaine.

Résumé. La cinétique de l'utilisation du glucose a été étudiée chez 325 sujets normaux et 150 obèses exempts de diabète ou d'autres affections endocriniennes. L'investigation a comporté la détermination des vitesses de production et d'utilisation basales par dilution isotopique ainsi que les mesures des vitesses d'utilisation réactionnelles induites par stimulation pancréatique (injection intraveineuse d'une surcharge glucosée ou de tolbutamide) et par administration de doses variables d'insuline exogène. — Nos résultats montrent que quel que soit le type d'épreuve réalisé, les constantes de vitesse (constante K ou vitesses de disparition fractionnaires) et les vitesses d'utilisation (valeurs absolues) enregistrées chez les obèses sont systématiquement inférieures aux valeurs correspondantes des normaux. Ce trouble métabolique n'est ni favorisé par le vieillissement, ni dû à une diminution de la capacité secrétoire du pancréas: les taux plasmatiques de base et les accroissements insuliniques induits par injection de glucose et de tolbutamide sont significativement plus élevés chez les obèses que chez les normaux. Le trouble est d'autant plus facilement mis en évidence que l'on force la vitesse d'utilisation par stimulation insulinique. Il existe, en effet, une relation de proportionnalité directe entre l'altération des vitesses d'utilisation glucidique des différentes épreuves chez les obèses et ces vitesses elles-mêmes. Cette relation, qui n'est pas influencée par la quantité d'insuline présente ou ajoutée, suggère que le trouble primitif est plus lié au processus de captation tissulaire qu'à l'action de l'insuline.

Die Kinetik der Glucoseutilisation bei der Fettsucht des Menschen.

Zusammenfassung. Die Kinetik der Glucoseutilisation wurde bei 325 Normalpersonen und 150 fettleibigen Patienten untersucht, die weder an Diabetes noch an anderen endokrinen Erkrankungen litten. Die Untersuchung umfaßte Messungen im Nüchternzustand mit der Isotopenverdünnungstechnik, Bestimmungen der Glucoseutilisationsrate unter dem Einfluß endogener Insulinfreisetzung (nach i.v. Glucosebelastung und Tolbutamid) und nach Gabe verschiedener Dosen exogenen Insulins. — Die Ergebnisse zeigten, daß die Konstante der Verschwinderate (K-Werte oder fraktionierte Verschwinderate) und die totale Aufnahme (in Absolutwerten) bei den fettleibigen Patienten bei allen verwendeten Testen übereinstimmend niedriger waren als die entsprechenden Werte der Normalpersonen. Diese Stoffwechselabnormität wird durch das Alter nicht begünstigt; sie kann auch nicht auf eine verminderte Fähigkeit des Pankreas zur Insulinfreisetzung zurückgeführt werden: die Ausgangswerte des Plasmainsulins und der Anstieg des Insulins nach Glucose und Tolbutamid waren bei den fettleibigen Patienten signifikant höher. — Diese Störung zeigt sich noch besser bei Ansteigen der Utilisationsrate durch Stimulation der Insulinsekretion: je größer die K-Werte, um so deutlicher die Verschlechterung. In der Tat läßt sich eine geradlinige Beziehung herstellen, die eine direkte Abhängigkeit zwischen der Verschlechterung der Konstante der Glucoseutilisationsrate und der Geschwindigkeit des Prozesses zeigt, unabhängig von der Menge des vorhandenen oder zugeführten Insulins. Diese Ergebnisse lassen vermuten, daß die Stoffwechselstörung bei der menschlichen Fettsucht primär eher den Prozeß der Glucoseaufnahme selbst als die Insulinwirkung betrifft.

Introduction

That obesity entails an impairment of the glucose metabolism has often been recorded in man (Paullin and Sauls, 1922; John, 1929; Newbury and Conn, 1939; Boulin, 1949; Berkowitz, 1964; Butterfield et al., 1966). However, most of the authors were more interested in describing the gross alterations of the "glucose tolerance" after oral loading than in evaluating the changes in the glucose utilization process itself, and their studies principally aimed at either obtaining a diagnosis of glucose metabolism abnormality or comparing the latter with the level of plasma insulin (Grodsky et al., 1963; Karam et al., 1963; Samaan et al., 1965; Samols, 1965) or free fatty acids (Beck et al., 1964; Gordon et al., 1960; 1963; Morse and Mahabir, 1964).

On the contrary, our aim is to analyse the changes in glucose kinetics occuring in obesity. For this purpose a large number of normal subjects and obese

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patients were submitted to a series of dynamic tests including the venous route of administration for glucose, insulin and an insulin-releasing drug. These tests provide an easy estimate of the velocity of the glucose uptake by the whole tissues at various levels of insulin stimulation; they may permit a more exact expression of the possible relationship between the amount of hormone present and the importance of the nutrient disturbance and correspond to the following metabolic conditions.

1. Measurement of glucose utilization and production rates in the basal condition and steady state by administration of a tracer dose of labelled glucose.

2. Estimation of glucose utilization rate under endogenous insulinic response. Mild pancreatic stimulation was obtained by injection of a small, standardized glucose load. Greater stimulation was provoked by intravenous injection of tolbutamide. Measurements were performed on an initially normal glucose pool by injecting the drug alone, or on an increased pool by simultaneous injection of the drug and the standardized glucose load.

3. Determination of the activity of exogenous insulin on the glucose utilization rate. Measurements were carried out either on a normal glucose pool by intravenous injection of insulin alone, or in loading conditions by combined administration of insulin and glucose.

The use of a glucose load ensures 2 advantages. First, when a small amount of insulin is delivered or released, difficulty may arise in the determination of the utilization rate due to the occurence of a low rate and of an important residual glucose release from the liver (FRANCKSON, 1958; FRANCKSON et al., 1962). By stopping the sugar output, hyperglycaemia cancels out this interference (BONDY et al., 1949; FRANCKSON et al., 1962; OOMS et al., 1962; SOSKIN et al., 1938). Secondly, on injection of large amounts of insulin, hyperglycaemia prolongs the duration of the blood-sugar decay allowing a more accurate estimation of the rate of glucose uptake.

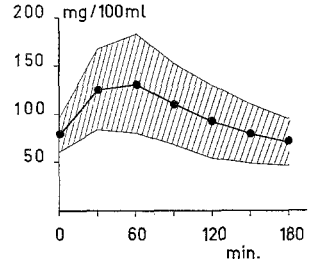

Fig. 1. Distribution of oral glucose tolerance curves in 50 individuals sampled at random in our obese group. Figures given are the means surrounded by $t_{0.05}$ x S.D.

Material

Three hundred and twenty five normal subjects and 150 obese patients have been investigated. The normal subjects were convalescent patients, having recovered from a benign illness; the obese patients were selected on the basis of an overweight greater than 25% of their theoretical weight (LORENTZ, 1929), and an absence of biological signs of diabetes: fasting blood-sugar level lower than 100 mg/100 ml, no glycosuria, and an oral glucose tolerance test within the normal range (CONN and FAJANS, 1961) (Fig. 1). All the subjects examined were free from endocrine, hepatic or febrile disease; they were given no treatment; nearly all were in-patients from the Medical Clinic receiving a 2000—2500 calories diet, rich in carbohydrates. After an identical 15 hour fast, they were submitted in groups of similar age distribution to several of the above mentioned investigations.

Metabolic parameters

After rapid intravenous injections of labelled and unlabelled glucose, of insulin and tolbutamide, the following parameters can be drawn from the blood glucose disappearance curves.

1. The disappearance rate constant or fractional rate of transfer (commonly called K value) can be directly obtained by graphical procedure; it corresponds to the slope of the final exponential disappearance:

$$K=\frac{1}{t}\times \lg_n (C_1/C_2)$$

equation in which C_1 and C_2 are the blood glucose concentrations recorded for the interval of time t. Its derivative form clearly indicates that it expresses the ratio between the velocity of utilization ($-dC/dt$) and the blood glucose concentration:

$$K=-d\,C/dt:C \text{ or } K=-d\,C/C:dt$$

It represents thus the fraction of the glucose pool or concentration transferred outside the pool per unit of time.

2. In steady state (glucose pool constant) the K value of the labelled glucose allows the calculation of the turn-over rate or absolute rate of transfer, which can be expressed in relation to either the concentration (C) or the total glucose pool (M)

$$F=KC \text{ or } F=KCV$$

In the latter case, it represents the total movement of glucose into or out of the extracellular space (V). These last equations are the simplified form of a more general formula that holds when the size of the glucose pool undergoes a slow unidirectional change (slight increase or slight decrease):

$$F=K(Ce^{kt}-C_o)/e^{kt}-1$$

where C_0 and C are respectively the initial and final blood glucose concentrations for the period of time t.

3. In the case of a decreasing glucose pool, the exponential decay of the blood glucose concentration makes it possible to estimate at any time (t), the amount of glucose taken up by the tissues, i.e. transferred outside the extracellular pool. When hypoglycaemic agents are injected alone, it corresponds to:

$$C_u=C_o\,(1-e^{-kt}),$$

where C_0 is the fasting blood-sugar level.

After intravenous glucose loading, the initial concentration becomes the sum of the basal one and of the ratio of the injected amount Q to the extracellular space (v):

$$C_u = (C_o + Q/V)\ (1 - e^{-kt}).$$

Techniques

The characteristics of the dynamic tests investigating the glucose metabolism in the whole body are summarized in Fig. 2.

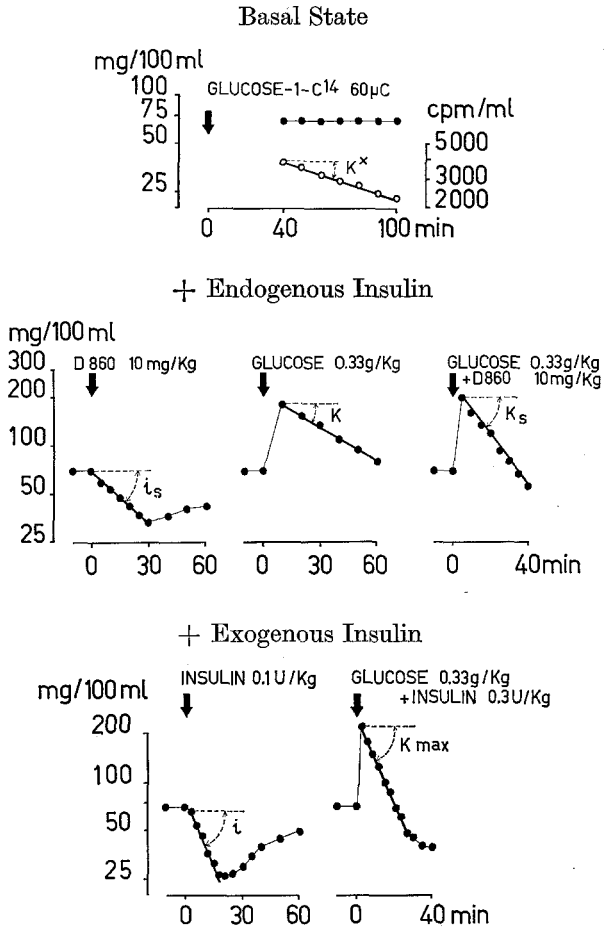

Fig. 2. Semi-logarithmic representation of the blood-sugar disappearance curves observed in the various dynamic tests

Labelled glucose turn-over studies. The conditions we used have been previously described (OOMS et al., 1961, 1962): simultaneous injection of 60 μC of glucose-1-^{14}C (2 mC/mM) and of 10 ml sodium thiocyanate (N/1) for estimation of extracellular space (CACHERA and LAMOTTE, 1950); venous blood sampling from the 40th to the 100th min following injection; radioactivity of the glucose-1-^{14}C isolated by fermentation with leuconostoc mesenteroides (BERNSTEIN et al., 1955; DEMOSS et al., 1951), the $^{14}CO_2$ being counted on planchets as barium carbonate in thin layer in a proportional flow counter.

Intravenous glucose tolerance test was performed according to CONARD et al. (CONARD, 1955): glucose injection of 0.33 g/kg body weight, venous blood sampling every 10 minutes from the 10th to the 60th minutes, and direct estimation of the K value on a semi-logarithmic graph. In obese patients the glucose load was proportioned to the body weight up to 75 kg; for heavier weights a constant amount of 25 g was delivered.

Determination of the diffusion space of free glucose was achieved graphically by a classical extrapolation method (CONARD et al., 1965).

Insulin sensitivity test. The procedure was the one described by Franckson (1958): rapid intravenous injection of insulin (100 mU/kg), and venous blood sampling every 3 minutes for 30 minutes.

The slope (i) expressing the rate of glucose uptake was obtained either by direct graphical method or by calculation; indeed the blood sugar disappearance curve corresponds to the sum of a decreasing exponential process (tissue uptake) and an increasing linear process (residual hepatic output), this latter term often reducing to zero in normal subjects (FRANCKSON, 1958).

Glucose insulin tests. Simultaneous intravenous injection of the glucose load and either a small insulin dose (30 mU/kg) or a dose inducing maximal utilization velocity (300 mU/kg) was followed by serial withdrawals of venous blood every 5 minutes for 40 minutes or every 3 minutes for 30 minutes respectively. The slopes expressing the blood glucose disappearance rates (K_i and K_{max}) were estimated by graphical procedure.

Tolbutamide response tests were performed according to BELLENS (1961): rapid intravenous injection of tolbutamide (10 mg/kg), and venous blood sampling at 5 minutes interval for 40 minutes. When the drug was injected alone, calculation of the slope was made as previously mentioned (cf. insulin sensitivity test). Simultaneous injection of the drug and of the usual glucose load allowed direct graphical estimation of the reactive K value.

Blood sugar estimations were carried out by HOFFMAN's method (1937) using a Technicon Autoanalyzer.

Plasma insulin was estimated either by bioassay or immunoassay. Insulin-like activity was determined on the fat pad by the manometric method of BALL et al. (1959). Measurements were carried out in the absence and in the presence of an excess of guinea pig anti-insulin serum added to the incubation medium. Immunereactive insulin was measured according to the method of MORGAN et al. (1964), slightly modified.

Results

^{14}C-glucose-studies. Two groups of 20 young adults — normal and obese — were examined (Table 1). In the obese group, small but significant changes in the basal kinetics of glucose were observed: a mean

increase of 8 per cent in fasting blood sugar level with a marked augmentation in fasting plasma insulin level averaging 100 per cent; and decreases both in K value and in transfer rate, averaging respectively 22 and 17 per cent. The total inflow-outflow of glucose in obese patients was not statistically different from the normal, due probably to a moderate enlargment of their extracellular space; on the contrary, when expressed in relation to the body weight or surface area (69 mg/m²/min for the normal as against 54 for the obese), the values of this parameter were strikingly depressed in obesity.

Table 1. *Glucose-I-^{14}C data in normal and obese subjects. Figures given are the mean and S.E.M. Statistical significance of difference between means is indicated in the last column:* [1] *0.05 > P > 0.01,* [2] *P > 0.01*

		Normal	Obese
Age	(year)	34 ±3.1	34 ±3.1
Weight	(kg)	64 ±2.0	92 ±4.1[2]
Thiocyanate space	(l)	14.5 ±0.4	15.3 ±0.4
Fasting blood sugar	(mg/10 ml)	77 ±1.4	83 ±2.1[1]
Immunereactive insulin	(μU/ml)	16 ±1.6	31 ±2.3[2]
K value	(% per min)	1.08±0.05	0.84±0.03[1]
Transfer rate	(mg/100 ml/min)	0.83±0.05	0.69±0.03[1]
Total inflow-outflow	(mg/min)	121 ±7.0	105 ±4.6
	(mg/kg/min)	1.94±0.11	1.13±0.06[1]

The regressions of the K values, plotted on a logarithmic scale, on age are illustrated by figure 3 and statistical data are reported in Table 2. In each group, a consistent relationship between ageing and alteration in K value was observed, the slopes of the regression lines were significantly different from zero. Tested by the covariance analysis (SNEDECOR, 1956), the 2 regression lines could be considered as parallel and the difference in height between them was significant.

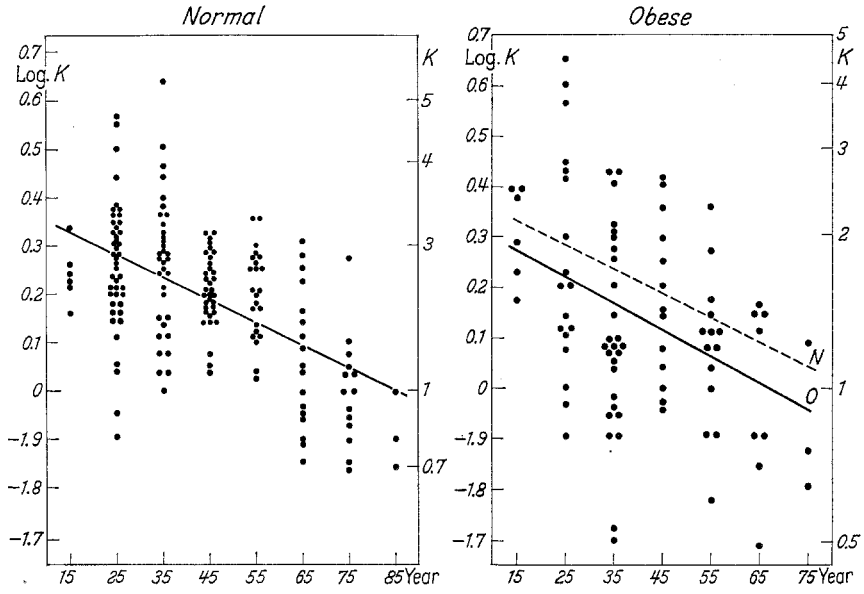

Fig. 3. *Intravenous glucose test*: relationship between age and K values in normal and obese subjects. The straight lines represent the regressions of the logarithms of the K values on age

Intravenous glucose tolerance test. This test was applied to 175 normal and 91 obese individuals. The comparison of the results was achieved by studying the regression of the logarithms of the K values in respect to age in both groups. This procedure was used because it was previously demonstrated in a normal population that ageing impaired progressively the K value (CONARD, 1955) and that the frequency distribution of the K values corresponded to an asymetrical pattern, which could be normalized by substituting the logarithms of K to the experimental values (BASTENIE et al., 1963).

In each of these large groups of normal and obese individuals, 16 young adults were selected according to similar ages and K values, and the total insulin-like

activities (ILA) of the serum were determined at various times of an intravenous glucose tolerance test. As shown by Table 3, hyperglycaemia induced a marked and protracted insulinic response in the obese group whereas no changes were recorded in normals for the explored times, in spite of the fact that the constant glucose load (25 g) injected into the obese patients caused a smaller rise in their blood sugar level than the proportioned one (0.33 g/kg) did in the normals.

These results reveal that ageing has the same depressive influence on the glucose utilization rate in normal and obese subjects; in the latter — whatever their age — a constant metabolic impairment of small magnitude can be systematically demonstrated. This deficiency is not related to a reduced ability of the pancreas to release insulin in response to hyperglycaemia.

Tolbutamide response tests. In the upper part of

Table 2. *Intravenous glucose test: comparison of the regressions of K values on age in normal and obese subjects.(For statistical significance, see table 1)*

	Normal	Obese	Normal-Obese Statist. Comparison
Number of subjects	175	91	
Mean Age (year)	42.7±17.4	40.6±15.4	$t = 0.455$
lg K/age regression			
1. mean value (corresponding K in % per min)	1.58	1.36	$t = 3.814$[2]
2. Slope of regression b_1	−0.0046[2]	−0.0052[2]	$F = 13.617$[2]
t_{b_1}	8.523[2]	4.060[2]	

Table 3. *Intravenous glucose test: Changes in serum insulin-like activity in normal and obese subjects (For statistical significance, see table 1)*

		Normal	Obese
Number		16	16
Age	(year)	31±2.3	32±2.4
Weight	(Kg)	68±2.2	91±4.0[2]
Glucose data			
Blood-sugar at 0 min.	(mg/100 ml)	81 ±2.1	78 ± 1.4
at 10 min	(mg/100 ml)	275 ±7	233 ±12[2]
K value	(% per min)	1.60±0.10	1.70± 0.14
Insulin data			
ILA at 0 min	(μU/ml)	65± 9	62±10
10 min	(μU/ml)	67±11	111±17[1]
30 min	(μU/ml)	67± 9	130±17[1]
60 min	(μU/ml)	79±17	117±21

Table 4. *Tolbutamide response tests in normal and obese subjects. Upper part: effect of the drug on the utilization rate of glucose load. Lower part: rate of decline in blood-sugar and change in insulin-like activity induced by the injection of the drug alone (for statistical significance, see table 1)*

		Normal	Obese
Number		20	47
Age	(year)	35 ± 3.8	38 ± 2.4
Basal rate (K_1)	(% per min)	1.53± 0.17	1.41± 0.07
Drug effect (K_2-K_1)	(id.)	2.18± 0.27	1.49± 0.10[2]
Uptake (C_u)	(mg/100 ml/30 min)	145 ±12	106 ± 8[2]
Number		15	15
Fasting blood sugar (C_0)	(mg/100 ml)	72 ± 1.7	77 ± 1.5[1]
Induced slope (i)	(% per min)	2.70± 0.31	1.53± 0.11[2]
Uptake (C_u)	(mg/100 ml/min)	38 ± 2.8	28 ± 1.4[2]
ILA at 0 min	(μU/ml)	41 ± 9	50 ± 9
at 10 min	(id.)	66 ±12	105 ±14
at 30 min	(id.)	70 ±27	154 ±32

Table 4 are recorded the data for the tests performed in hyperglycaemia. The normal and obese groups had similar age distributions and the mean K values (K_1) defining their basal utilization rate were not significantly different. On the contrary, the intravenous glucose tolerance tests performed immediately following the administration of tolbutamide revealed a diminution of the effect of the drug in the obese: both the mean reactive K value (K_2) and the total amount of glucose taken up by tissues after 30 minutes (C_u) were significantly lowered.

A similar impairment of the hypoglycaemic action of tolbutamide was observed after injection of the drug alone (table 4, lower part): both the transfer rate constant (i) and the amount transferred (C_u) were reduced in the obese group. These troubles cannot be related to a diminution of the effect of the drug upon the β cells of the pancreas: the serum rises in total and suppressible ILA were indeed more marked in the obese patients.

Insulin activity tests. Fig. 4 illustrates the data recorded in 100 normal subjects (mean age and S.D.: 40.5 $\pm$ 14.9 years) and 42 obese patients (35.7 $\pm$ 12.4 years) submitted to an insulin sensitivity test involving the intravenous injection of 100 mU/kg of insulin alone. In both groups, the influence of ageing upon the insulin effect on the decrease in blood-sugar was not marked: the slopes of regression lines of the transfer rate constant (i) plotted on a logarithmic scale against age reached the limit of the significance in the normal group ($t = 1.962$) and was less in the obese group ($t = 1.730$). On the contrary, the difference between the mean values of the 2 samples was highly significant ($t = 5.040$); this logarithmic difference corresponded to an i value of 7.56% per min for the normal group and 5.15 for the obese group.

panied by a reduction in the peripheral action of exogenous insulin on the glucose utilization rate. This metabolic defect can be revealed by injecting either inframaximal amounts of hormone (30 and 100 mU/kg) or a dose larger than the one inducing the greatest blood-sugar lowering effect (300 mU/kg). These results are more especially significant as the injected quantities of insulin were proportioned to the subjects body weight.

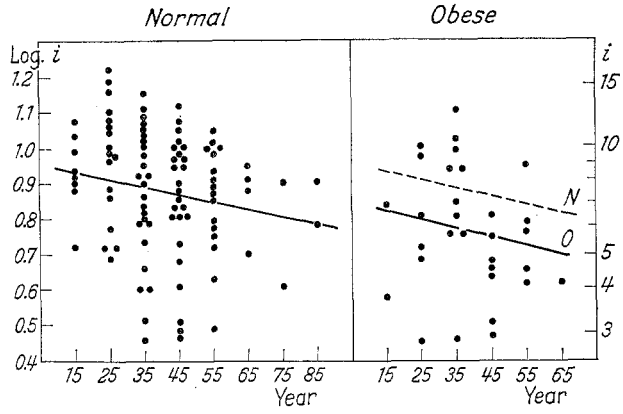

Fig. 4. *Insulin sensitivity test*: relationship between age and slope values (i) in normal and obese subjects (same representation as in Fig. 3)

Discussion

Our data concerning the various dynamic tests performed by rapid intravenous injection of glucose, insulin and insulin-releasing drug among normal and obese subjects may be summarized as follows.

In the basal state obesity entails a diminution of glucose uptake by the whole tissues, demonstrated by

Table 5. *Combined glucose-insulin tests in normal and obese subjects: influence of 2 doses of insulin on the reactive K value and on the amount of glucose taken up by the tissues in 30 minutes (for statistical significance, see table 1)*

		Normal	Obese
Ins. 300 mU/Kg			
Number		42	21
Age	(year)	38 $\pm$1.5	33 $\pm$2.3
Induced slope (K max)	(% per min)	7.8$\pm$0.45	5.4$\pm$0.40[2]
Uptake (C_u)	(mg/100 ml/30 min)	210 $\pm$6.9	181 $\pm$7.7[2]
Ins. 30 mU/Kg			
Number		13	12
Induced slope (K_i)	(per % min)	5.3$\pm$0.42	3.2$\pm$0.37[2]
Uptake (C_u)	(mg/100 ml/30 min)	175 $\pm$6.1	153 $\pm$7.7[1]

Comparable results were obtained with the combined glucose-insulin tests (Table 5). Whatever the administered dose of insulin, the mean glucose utilization rates (K_1 and K_{max}) recorded in the normal groups were significantly higher than the corresponding ones of the obese groups.

This investigation shows that obesity is accom- the lowering of the transfer rate constant of ^{14}C-*glucose*, and of the transfer rate of glucose when expressed in relation to the volume of blood, body weight or body surface area. The absolute value of the difference between the mean slopes of the normal and obese groups is of small magnitude ($K = 0.26\%$ per min), but is highly significant due to the narrow dispersion of individual

figures about their means. The reduction in ^{14}C-glucose uptake closely agrees with the lowering of the $^{14}CO_2$ production from labelled glucose found by Gordon (1962; Gordon et al., 1963).

When performed in two large samples of normal and obese patients both having a broad range of age, the *intravenous glucose test* shows that the reduction of the glucose utilization rate in obesity is not a late occuring alteration or an alteration favoured by ageing. Indeed, the regression lines defining the relationship between age and K value are parallel in normal and obese subjects. So obesity *per se* — whatever the age of the obese patient — involves a small but constant impairment of the utilization rate of the glucose load.

It must however be emphasized that the impairment can only be disclosed by comparing large samples of population, owing to the small difference in mean K values ($K = 0.22\%$ per min) and to the wide variations of individual figures. Indeed comparisons performed on groups of smaller size may provide similar K values, as for instance in the groups of 15—20 individuals whose results were presented in Tables 1 and 3 and in another group studied by Balasse (1966).

With the glucose tests performed after injection of *tolbutamide* or *exogenous insulin* the impairment of the reactive utilization rate is more easily demonstrated among obese patients; the reductions in slope values are of greater magnitude and a clear-cut significance is attained even when comparing samples of small size (10 to 20 individuals).

In Fig. 5 are summarized the whole of the data recorded in the present investigation of glucose utilization: on the abscissa are plotted the mean values of the transfer rate constants (slope values) obtained for each type of dynamic test performed on normal subjects and on the ordinate, the mean values of the corresponding tests performed on the various obese groups.

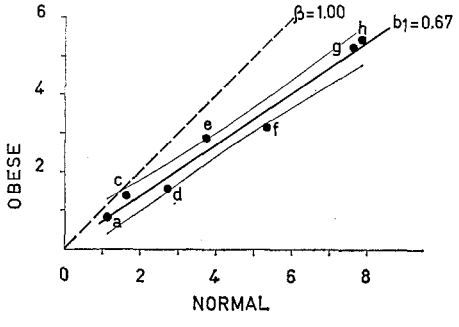

Fig. 5. Mean transfer rate constants (slope values) of corresponding glucose dynamic tests performed in several groups of normal and obese sujects: a = ^{14}C-glucose, c = ^{12}C-glucose, d = tolbutamide response, e = glucose-tolbutamide response, f = glucose-insulin (30 mU/kg), g = insulin (100 mU/kg), h = glucose-insulin (300 mU/kg), b_1 = observed regression line, β = theoretical regression for null hypothesis, l = confidence belts of regression line

The progressiveness of the metabolic disturbance is evident at a glance. Statistical analysis shows that the regression of the transfer rate constants of the obese on the corresponding normal ones has a slope of 0.67 ± 0.03, which is significantly different from the theoretical slope $\beta = 1.00$ testing the null hypothesis ($t = 10.87$). This relationship reveals that whatever the investigation test used, the transfer rate constant which can reasonably be expected among the obese would represent an impairment of $\frac{1}{3}$ of the corresponding normal value. It indicates the value of increasing the glucose utilization rate with insulin to obtain an easily measurable defect, since the greater the slope value the greater is the difference.

Finally, it must be emphasized that the alteration of the rate constant is not related to a stoichiometric effect. Indeed the sizes of the fasting glucose pool of the normal and obese groups were very close (mean difference 5 mg/100 ml or 1.2 g), and the rise in extracellular glucose concentration induced by the loading was similar in both groups due to the fact that the obese patients were injected with a constant load of 25 g instead of an amount proportioned to the body weight (mean extracellular increase 163 mg/100 ml in the obese as against 155 in the normal). As was previously demonstrated (Conard, 1955; Franckson, 1966), such minute changes are without effect on the value of the utilization rate constant.

Plasma insulin estimated by bioassay and immunoassay showed an increased fasting level (IRI) and an increased pancreatic response to intravenous glucose and tolbutamide (ILA) in the obese groups. These data are in accordance with the literature (Grodsky, 1963; Karam, 1963; Samaan, 1965; Samols, 1965). However, this increase both in basal secretion and in pancreatic response is unable to modify the characteristic impairment of the glucose kinetics. Indeed, comparing the ratios between the utilization rates of normal and obese patients, measured after injection of proportioned amounts of exogenous insulin, with the ratios recorded at various levels of endogenous insulin secretion, one obtains similar values (cf. Fig. 4).

Thus there is a direct proportionality between the impairment of the glucose utilization and its velocity, irrespective of the type and amount of insulin (endogenous or crystalline exogenous). This feature strongly suggests that in human obesity the disturbing influence primarily affects the glucose uptake process itself rather than the action of insulin.

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