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The Clinical Value of the Glucogram and a New Approach to the Intravenous Glucose Tolerance Test

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The analysis of 197 glucograms is presented and the authors discuss some new points of clinical importance in the appraisal of the diabetic state. The suggestion is also made that when the sulphonylurea test is done, it should follow sequentially an intravenous glucose tolerance test. Further, it was found that in assessing the result of an intravenous glucose tolerance test it is of importance to take into account the blood sampling method, and whether the patient is ambulant or confined to bed. A simplified intravenous glucose tolerance test is suggested which requires 3 blood samples only, takes less than an hour to perform and derives the K-value from a simple table. The correlation of the various tests and their clinical interpretation is discussed.

Die Arbeit beschäftigt sich mit der Analyse von 197 Glucogrammen. Anhand dieses Materials werden einige neue Gesichtspunkte für die Diabetes-Diagnose diskutiert. Unter anderem wird vorgeschlagen, daß der Sulfonylharnstoff-Test immer anschließend an einen intravenösen Glucosebelastungstest gemacht wird, und, daß bei der Beurteilung des intravenösen Glucosebelastungstests sowohl die Art der Blutprobe, als auch der Unterschied zwischen ambulanter oder stationärer Untersuchung berücksichtigt werden muß. Eine vereinfachte Methode dieses Tests, die nur drei Blutproben verlangt und in einer Stunde beendigt ist, und in der man den K-Wert von einer Tabelle abliest, ist erstmalig beschrieben. Die Beziehung der verschiedenen Tests zueinander und ihre klinische Interpretation wird ausführlich besprochen.

The *glucogram* is a continuous recording of a person's blood glucose level. This can be achieved simply by connecting an intravenous catheter resting in the antecubital vein with an AutoAnalyzer which has been set to analyze glucose by the glucose-oxidase-peroxidase reaction. Details of this procedure have been described by KAWERAU (1) in a previous publication.

Very little use has so far been made of the continuous intravenous sampling technique, and this is surprising, since it was developed in the United States of America, the home of the AutoAnalyzer. Continuous monitoring of the blood glucose level was begun by WELLER et al. (2) for observing the pharmacological effect of the oral hypoglycaemic biguanide Phenformin and by FERRARI et al. (3) for perfusion experiments of various organs of the rabbit. More recently, BURNS and BREGNANT (4) published glucograms of the oral glucose tolerance test ("OGTT") which resemble our own, which we presented to the *Vth International Congress of Clinical Chemistry* in Detroit in 1963; however, these glucograms do not reveal much of clinical interest. In latter years, the continuous technique has been largely developed in France by a team around GALLI, and their glucose work dates from 1961 (5). These French workers have been very active in developing continuous monitoring techniques and their most recent work extends to blood ammonia (6). Glucograms following the intravenous administration of glucose were observed by these French workers to show features which cannot be revealed by the discontinuous technique and it is for this reason that most of our work has been devoted to the continouously recorded intravenous glucose tolerance test ("IVGTT").

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Material and Methods

Normal controls

Healthy young adults were asked especially to take part in the test, and this group we refer to as "*Volunteer Controls*"; the other "Controls" were hospital patients who had no endocrine abnormality and these we refer to as "*Hospital Normals*". All the usual tests fot the diagnosis of diabetes were normal in these patients. All patients showing some disorder of carbohydrate metabolism, or whose clinical or familial background showed a predisposition to diabetes were classified by the system advocated by the British Diabetic Association (7).

Site of sampling

For all tests the same type of disposable pre-sterilized catheter ("Bardic Intracath" Nor. 17,8″ long) was used. To avoid pain it was always introduced into a large antecubital vein with the aid of a small amount of local anaesthetic. Of the 8″ length about 5″ remains in the vein so that sampling is probably from the brachial vein. Most of the patients were given 10 000 Units Heparin i. v., which is sufficient to prevent clotting for 4—5 hours. When there were contraindications to the use of systemic heparin then an external heparinising circuit was used (see (1)), in which case a shorter length of catheter was used.

Glucose

20—25 m*l* of a 50% solution of glucose was injected into an antecubital vein on the other arm through a No. 1 needle, this takes usually 2—3 minutes. With continuous recording the timing of this operation is not critical since the record will show exactly when and for how long the injection was given.

Sulphonylurea

Tolbutamide, and sometimes chlorpropamide were given. These were supplied in readily injectable form, either 10 or 20 m*l* ampoules. Of tolbutamide 1.0 g was given, of chlorpropamide 0.5 g, but the injectable form of the latter drug is only available by special request from the manufacturers. No adverse effects were seen as a result of these injections.

Glucose analysis

Most of our glucograms were recorded with the use of the HOFFMAN ferricyanide reaction (8) and our manifold has been

described (9). Latterly we have redesigned the manifold for use with the glucose-oxidase-peroxidase reaction using the WINCEY and MARKS reagents (1). Satisfactory records can be obtained with either reaction but the true glucose reaction is preferable for diabetic work.

Results

The present work reports on 197 glucograms performed on 126 patients. A summary of the number of tests is given in Table 1.

Tab. 1
Work Analysis

Number of Glucograms after	
intravenous glucose	98
oral glucose	30
intravenous chlorpropamide	38
intravenous tolbutamide	24
insulin	3
leucine	2
ethanol	2
Total	197

The oral glucose tolerance test

We have come to the conclusion that continuous monitoring of the blood glucose level in this test has no advantages over the discontinuous traditional procedure. Figures 1—3 show glucograms of such tests, but apart from small subsidiary peaks that follow the main absorption period, little of additional interest can be derived from these graphic presentations.

Occasionally, it may be useful to do a glucogram in a case of dumping syndrome to obtain clear evidence of rapid absorption and reactive hypoglycaemia. The test must be performed with the patient in the sitting or standing position. This was clearly demonstrated in one of our patients who failed to show any signs of glucose absorption for 30 minutes, when after being sat up straight, his blood glucose level rose abruptly. More than half of the requests for this investigation came to us from the gastric surgery unit, and we think the method has its use in these patients. For the straightforward diabetic suspect, however, a glucogram is not indicated as the less troublesome discontinuous technique adequately copes with the situation. Our glucograms on this type of patient have merely gone to show that what we already know of this test is correct, i. e. the peak absorption period normally covers the 30—60 minute period after the oral intake of glucose, whereas in the diabetic fluctuations are more frequent and the main peak may be deferred beyond the 60 or even 90 minutes post-absorptive point. We are speaking here as clinical pathologists, but there is no doubt that continuous monitoring of oral glucose tolerance tests can be of considerable value to the experimental physiologist, pathologist and pharmacologist.

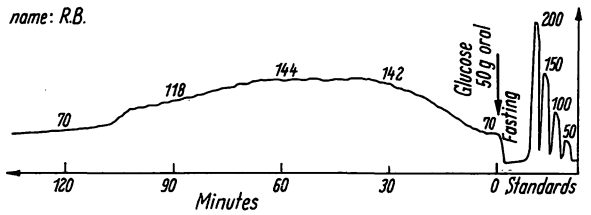

Fig. 1
Glucogram after 50 g. oral glucose in a volunteer normal subject

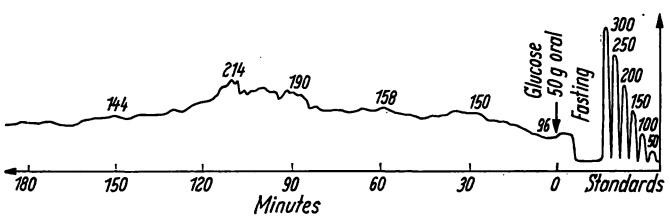

Fig. 2
Glucogram after 50 g. oral glucose in a diabetic patient

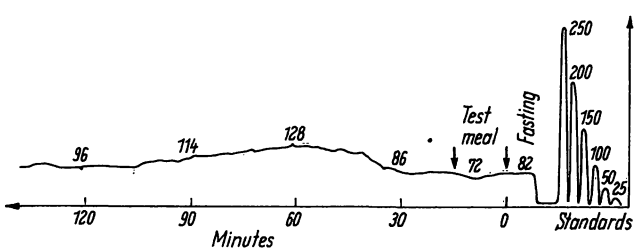

Fig. 3
Record of a test meal in a diabetic patient (the total calorific value was equal to 50 g. glucose); note absence of hyperglycaemia

Insulin, leucine and alcohol tests

Changes following the injection of drugs like adrenaline, insulin, glucagon and the sulphonylureas which cause sudden changes in the blood glucose level can profitably be recorded by a continuous technique. Table 1 does not altogether represent the true state of affairs with regard to *insulin*. In only three cases did we do an isolated insulin test, but on several occasions we tested for insulin sensitivity in comatose and semi-comatose diabetic patients. While the patient is on intravenous therapy it is quite simple to connect him to the AutoAnalyzer, on and off, and we have used the machine in the ward for 50 hours and longer for repeated intermittent periods of testing. It is quite a dramatic demonstration to be able to show how the patient's insulin sensitivity increases as his ketosis lightens.

Although we have tested for *leucine* sensitivity we have not had a positive response. The technique, however, is eminently suited for investigating the alleged hypoglycaemic attack. We have had only one patient in whom an insulinoma was confirmed at operation and her fasting blood sugar level was so low that the diagnosis was never in doubt; but this patient was not sensitive to leucine.

Alcohol hypoglycaemia is a condition that is quite well documented in the United States. FIELD et al. (10) were able to demonstrate this condition in susceptible individuals by giving 35—50 m*l* ethanol as a 10 per cent solution by mouth after a 40 hour fast. In our two patients who were chronic alcoholics, 50 m*l* ethanol given orally after a fast of only 14 hours resulted in a steady fall of the blood sugar reaching levels 10 mg per cent below the fasting value within 5 hours. The slow but steady fall does suggest that hypoglycaemia should be looked for in the chronic alcoholic.

The intravenous sulphonylurea test

Glucograms are particularly helpful in this test. They allow one to prejudge the issue and to rescue the patient with intravenous glucose should the fall become severely hypoglycaemic, they also allow a correct assessment of the nidar to be made. If this lowest point of the blood glucose level reached in the test is deemed to be of diagnostic significance then our curves show that the blood sugar must be determined at not less than 10 minute intervals. It is true, the nidar does occupy the 30 minute point most frequently, but in at least half of the normal curves it may be found anywhere between 20 and 60 minutes. A perusal of the literature on this test will show that outhors have varied in their practice, 15, 20 und 30 minute intervals having been used. The 60 minute level has often been used to determine responsiveness to the homeostatic mechanism, but if the true nidar is not know this assessment cannot really be made with certainty. Our results of this test are summarized in Table 2. The normal figures calculated for the nidar are similar to those reported by ZAROWITZ and EIS (11) for their non-diabetic group, but they are higher than those reported by CREUTZFELD et al. (12). Some difference may arise from the person's preparation prior to the test, i. e. the dietary regimen, the period of preliminary fasting, etc. In our work the test was standardized, it always followed on an intravenous glucose tolerance test.

Test procedure

The patient's dietary history is enquired into and when necessary instructions are given to partake of a liberal carbohydrate diet prior to the test. Chlorpropamide is withheld three days before the test, tolbutamide one day and insulin on the morning of the test. All our tests have been done with the patient fully undressed and in bed even when they were Out-patients. They were resting for at least 30 minutes before they were connected to the AutoAnalyzer and heparinized and they all received 20—25 g glucose into a vein of the other arm in this combined test procedure. When it was observed that the blood glucose level was regaining its fasting level and a steady state was maintained for some time, at least 10 minutes, then the same arm that had received the glucose injection now was injected with either 1.0 g tolbutamide or 0.5 g chlorpropamide intravenously. At this point the manifold was changed over to the high sensitivity recording (1, 9). Three typical recordings after chlorpropamide are shown in figures 4—6. It is usually unnecessary to

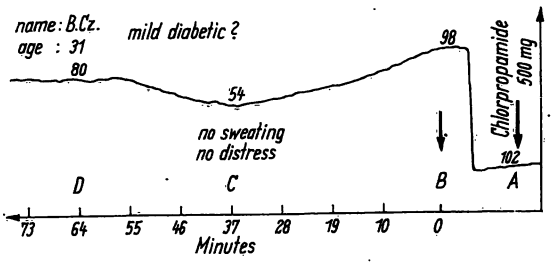

Fig. 4
A characteristic normal response to intravenous chlorpropamide

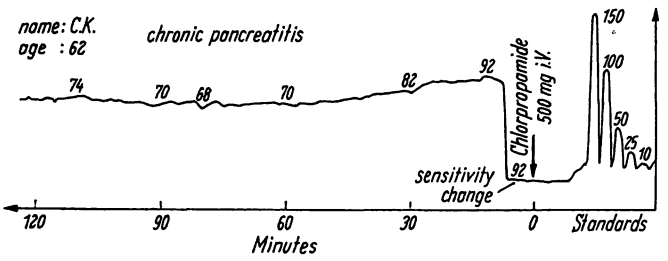

Fig. 5
A moderate diabetic-type of response in a case of chronic pancreatitis

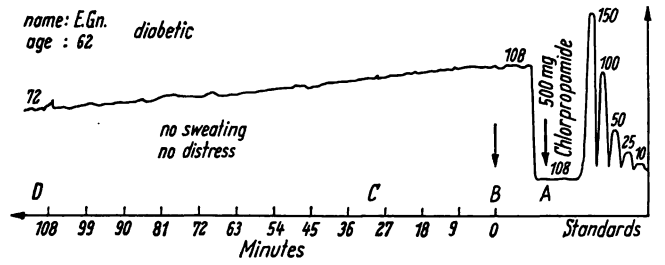

Fig. 6
In this diabetic response the continous recording is particularly useful as it displays the tendency to delayed hypoglycaemia

continue the recording for more than an hour, as in most cases it is quite obvious from the shape of the curve what type of response one is dealing with; should one, however, wish to obtain information regarding the patient's liver function, then the test must be continued for at least two hours (CREUTZFELD et al. (12)). Our own observations do not extend into this field.

Analysis of the results

A summary of the results is given in Table 2. In the work of UNGER and MADISON (13) it is suggested that the percentage fall at 20 minutes is clinically more useful than the fall at 30 minutes. In our figures we can see no suggestion that this is so, and as most other workers have relied on the 30 minute value, we have used this for the statistical analysis. It is evedint that only the clinically diabetic group shows a statistically significant fall and that the tolbutamide test does not differentiate the subgroups of diabetes in the British Diabetic Association Classification. This must be taken to be a provisional statement as the number of patients in each of these subgroups in rather small. It does not mean either that in a particular case, when all clinical facts are taken together a sulphonylurea test might not yield important informamation. The interpretation of this test is obviously more complex than the glucose loading tests.

The intravenous glucose tolerance test

Although the intravenous glucose tolerance test has been known since JACOBSEN (14) introduced it in 1917 and its clinical interest has been revived in recent years (11, 12, 13, 17), it has not become popular for two main reasons: it requires an intravenous injection, and in the calculation of the K-value (the glucose percentage rate of fall per minute) a formula and a graphic method employing semi-logarithmic paper have been employed. In other

Tab. 2. Analysis of the Sulphonylurea Test

Sex	Age	Drug	Kg (authors)	Response to sulphonylurea % fall after minutes 20	30	40	60	Clinical Notes
Diabetic Classification: Normal								
F	33	C	1.47	28	43	28	14	Normal
F	65	C	0.75	20	30	37	39	Occasional faints
F	79	T	1.21	31	45	38	24	Anterior cardiac infarct
F	49	C	1.14	33	31	31	20	Epileptic on phenobarbitone and epanutin
M	69	C	0.82	17	20	24	27	Tussive syncope
F	25	T	0.98	5	16	30	47	Cerebral atrophy, dementia
M	21	T	0.55	11	23	49	33	Low blood pressure, syncope
F	34	C	1.24	17	33	8	10	Several miscarriages
F	41	T	1.25	25	33	38	33	Overweight, neurodermatitis
M	70	T	0.99	19	34	40	32	Coronary thrombosis
M	20	T	1.55	46	54	24	18	Normal
M	47	C	0.80	15	19	24	30	Normal, but high alcohol intake
F	27	T	0.99	21	43	58	50	Hiatus hernia repair 1958, vagal crush. Attacks of weakness
M	56	T	0.47	21	23	29	23	Sudden unconsciouness (epileptic)
M	23	T	0.59	44	39	43	26	Cerebral atrophy, dementia apilepsy
M	36	C	0.84	20	32	36	8	Whipple's disease
F	23	T	1.05	27	53	64	53	Premenstrual nocturnal unconsciousness, sweating, headache
F	75	T	1.62	20	45	42	40	Leg ulcers, lapses of consciousness
F	33	C	1.52	18	39	9	13	Amenorrhoea
Diabetic Classification: Potential Diabetic ($p = 0.70$)								
F	20	C	1.06		19			Great-grandmother diabetic; patient has attacks of unconsciousness
M	79	C	0.65	15	25	33	50	Brother diabetic
M	20	T	0.83	17	28	39	26	Brother diabetic; patient had glandular fever and glycosuria; Attacks of weakness
F	39	T	0.96	49	53	41	26	Father diabetic; Overweight
M	32	T	1.44	13	26	30	9	Father diabetic and maternal grandmother; Vasovagal syncope
Diabetic Classification: Latent Diabetic ($p = 0.20$)								
M	17	C	0.98	4	10	19	13	Obese, fainting attacks
M	35	C	0.94	10	22	12	5	Furunculosis and glycosuria, 1960
F	59	C	1.44	35	33	27	8	Gangrene of toe and glycosuria 1940. Normal G. T. T. now; last 9 months on chlorpropamide
F	49	C	0.57	13	20	25	33	Occasional glycosuria; Coronary thrombosis
M	81	C	0.86	29	31	31	11	Furunculosis; glycosuria recently
M	42	T	2.66	19	15	15	7	Glycosuria in 1959, not since
M	48	T	1.01	15	25	31	36	Glycosuria in 1953, not since; Attacks of sweating and weakness
Diabetic Classification: Asymptomatic Diabetes ($p = 0.4 < p > 0.5$)								
M	49	T	0.70	20	46	50	55	Obese, diabetic oral G. T. T.
M	48	C	1.04	12	24	30	36	Lag oral G. T. T.; glycosuria
F	63	C	0.57	14	21	29	42	Glycosuria, on steroids, arthritis
M	73	C	0.51	15	21	23	26	Foot ulcer, diabetic oral G. T. T.
F	55	C	0.72	21	30	35	29	On steroids, diabetic oral G. T. T.
F	33	C	1.23		20		—	Diabetic oral G. T. T., megaloblastic anaemia
M	50	C	0.94	21	32	40	41	Diabetic oral G. T. T., son diabetic
M	73	C	0.80	11	20	26	42	Lag-type G. T. T.; glycosuria
M	62	T	0.45	33	30	45	48	Lag-type G. T. T.; glycosuria
Diabetic Classification: Clinical Diabetes ($p = 0.02 > p > 0.01$)								
M	81	C	0.53	10	13	9	—	Diabetic for 20 years, on insulin
F	31	C	0.60	22	33	45	21	Diabetic on diet and chlorpropamide for 9 months
M	68	T	0.40	3	3	7	8	*Brill-Symmers* disease, on insulin
M	47	T	0.29	8	14	24	41	Pancreatectomy for insulinoma in 1954; on serpasil, no glycosuria
M	56	T	0.23	12	18	22	30	Diabetic neuropathy, on chlorthiazide
F	75	C	0.47	6	9	11	20	Recurrent urinary infection
F	76	C	0.20	1	2	14	4	On insulin and chlorpropamide
F	70	C	0.37		14		23	Admitted in coma, on insulin
M	85	C	0.18	4	5	6	8	Old diabetic on insulin

words, little of the procedure can be handed over to the technician of the routine laboratory. Our interest in the method was for two principal reasons; one, theoretical, to see whether the glucograms yielded some information related to the pathogenesis of the diabetic state, particularly the pre-diabetic state; the other, technical, to see whether the continuously recorded curve would show some way by which the test could be shortened and simplified so that it could pass more easily into routine use.

After the glucose injection, the initial peak is followed by a rapid fall due to equilibration with the extravascular space and spill-over into the urine; thereafter follows the period during which glucose leaves the blood by direct route to the tissues metabolizing glucose, and none is added or removed through any other channels. We prefer to call this phase the "*steady state*". Later, as the blood sugar is approaching the fasting level, the homeostatic mechanism is brought into play and glucose is released from the liver with a consequent reduction in the rate of fall. These three phases are clearly shown when the analytical results are transferred to semi-logarithmic paper and in many of the glucograms they can also be seen directly, e. g. figure 7. Experimental work by FRANCKSON et al. (15) and by SEARLE et al. (16) has produced convincing evidence that the "*steady state*" is maintained during the 15—60 minute period after the injection of glucose. Analysis of our 98 glucograms has shown that this period is probably even shorter in the majority of people and it is on this finding that we have based our abbreviated intravenous glucose tolerance test described at the end of this treatise.

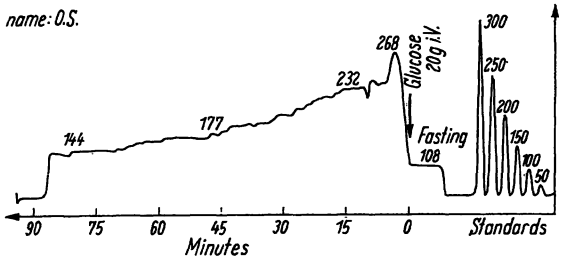

Fig. 7
The three phases in the rate of fall of glucose shown directly in a glucogram

Clinical results

The clinical results are shown graphically in the histogram figure 8. It shows better than statistics that we must draw the line of normality at a Kg of 0.8; both Volunteer Controls and Hospital Normals show an abrupt start here. This may be an artefact because of the relative small number of cases, but as it has repeated itself in two different groups, we think it must be of some significance. The clear gap between the normal and diabetic group has obviously been brought about by the adoption of the *British Diabetic Association* Classification of Diabetes. Our finding here speaks for the soundness of this classification. As one would expect, the overlap is entirely confined to the "potential", "latent" and "asymptomatic" groups.

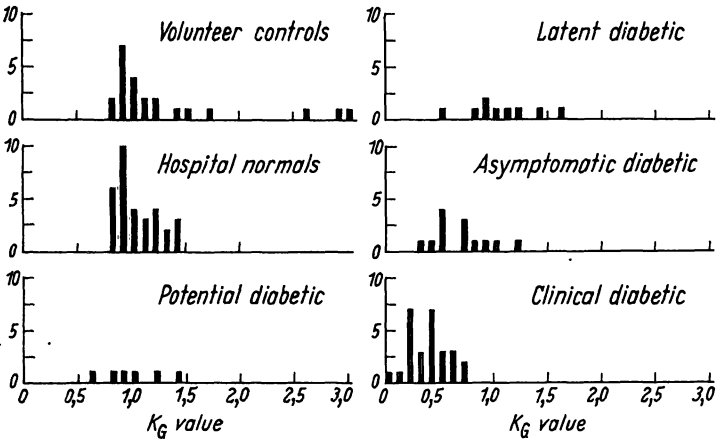

Fig. 8
Distribution of the Kg-value in the Normal and Diabetic Groups

In analyzing our Volunteer Controls and Hospital Normals for age and sex difference of glucose utilization (see Tab. 3) we find that there is an insufficient number of males in each of the age groups; all we can say is that the average Kg value for females is higher than that for a particular group as a whole. However, if we take all normal controls together the number are sufficient and we find a Kg value for males of 1.09 as against 1.27 for females. The age difference for glucose utilization is well established (17, 19). We have grouped our patients in the manner of LUNDBAEK (17) but have failed to notice an appreciable age difference for our Hospital Normal group. The small difference noted is not statistically significant and possibly due to differences in sex distribution for each group. SILVERSTONE et al. in two different test series using the intravenous glucose tolerance test (18 and 18a) reported identical figures for males and females whereas MOORHOUSE et al. (19) report a difference of 0.41 for the two sexes. The discrepancy is probably due to the greater or lesser degree to which the first 15 minute period was excluded from the calculation. We would conclude from our obersvations that in the hospital group age difference is not as important a factor as the sex of the patient.

Figure 8 also explains the difference in the average Kg-value for the Volunteer Controls as compared with the Hospital Normals. The difference is due to the presence of a few individuals with a disproportionately high Kg value in the Volunteer Control group, but basically the histogram for the two groups is approximately the same. STOWERS et al. (20) have pointed out that there is a difference in glucose utilization for ambulant persons as compared with the bedridden patient. Only a few of our Hospital Normals werd bedridden in the narrow sense of this term. Table 3 certainly points to the necessity for making this distinction. It is, of course, arguable on what basis one should assess normality, but as the pathologist is so often asked to investigate the hospital patient who has been in bed for some time, he should be aware of this difference. Conversely, in screening programmes of normal populations standards must be used which relate to the particular group unter test.

Tab. 3. Different Kg-Values

Normal Kg Value for Venous Sampling (Authors)

	Volunter Controls	Hospital Normals		
Age	< 50 years	< 50 years	50—70 years	> 70 years
No. in Group (total)	12	15	11	6
Mean age	31	32	59	79
Mean Kg (total)	1.49	1.11	1.05	1.13
Mean Kg (females)	1.57 (N = 8)	1.14 (N = 8)	1.11 (N = 7)	1.24 (N = 4)
Normal Kg Value for Capillary Sampling (LUNDBAEK)				
No. in Group (total)			140	
Mean Kg (men)		1.67	1.37	1.38
Mean Kg (women)		1.88	1.74	1.29
Mean Kg (total)			1.64	

Normal Kg Values for Venous Sampling (other Authors)

Number of volunteers	Age	Males Kg	Females Kg	Authors
33	50 (?)	1.45	1.86	MOORHOUSE et al. (1963)
12	25—37	1.68		SILVERSTONE et al. (1957)
11	42—58	1.44		SILVERSTONE et al. (1957)
12	65—87	0.98		SILVERSTONE et al. (1957)
	child-bearing age		1.68	SILVERSTONE et al. (1963)

Kg Value of the Diabetic Groups for Venous Sampling (Authors)

Group	Total Number	Mean Age	Mean Kg	T-test against Volunteer Controls	T-test against Hospital Normals
Potential Diabetics	6	45	1.02	$0.3 < p < 0.4$	$0.8 < p < 0.9$
Latent Diabetics	9	45	1.09	$0.3 < p < 0.4$	$0.9 < p$
Asymptomatic Diabetic	13	53	0.71	$0.02 < p < 0.05$	$0.01 < p < 0.02$
Clinical Diabetic	23	64	0.41	$p \ll 0.001$	$p \ll 0.001$

The difference between our results for "Volunteer Controls" and those of LUNDBAEK for hospital normals, we think can be explained on the difference of sampling technique. LAWRENCE pointed out in 1947 (21) that such differences in technique cannot be ignored: on the other hand, MARKS and MARRACK (22) state categorically that there is no difference in the Kg value for venous blood as compared with capillary blood, and in support they cite a number of authors. Although the blood sugar level gives a small and constant arterio-venous difference in the fasting state, the difference can become quite large during glucose loading and BUTTERFIELD and HOLLING (23) have found differences as large as 60 mg/100 m*l*. Hence, one would expect the sampling method to be of paramount importance for the determination of the Kg value.

In this connection it must be mentioned that we do not think that our lower Kg values are due to the use of heparin. On numerous occasions we have first recorded the fasting blood sugar level and then heparinized the patient without noticing any difference in the fasting blood sugar level. On four occasions has it been possible to repeat a test on the same patient without using heparin and in each instance there has been no significant difference in the Kg value. Two of these experiments are recorded in the repeat tests presented in Table 4. Our own experience finds support in BUTTERFIELD's work (24) who also has not been able to demonstrate any marked difference in the rate of glucose utilization in heparinized preparations.

The *Student* "T" test calculation was applied to the figures of Table 3 and the four diabetic groups were

Tab. 4. Repeated Intravenous Glucose Tolerance Tests

No.	Age	Sex	1st Test	2nd Test	Remarks
42	25	M	Kg = 0.87	Kg = 0.99	1st test *without* heparin, 2nd test *with* heparin (interval 4 hours)
52	43	F	Kg = 1.11	Kg = 1.02	1st test *with* heparin, 2nd test *without*
67	70	F	Kg = 0.49	Kg = 0.65	1st result on *venous* blood, 2nd *capillary* blood (same test)
28	82	M	Kg = 1.02	Kg = 1,32	1st *venous* blood, 2nd *capillary* blood (same test)
8	56	F	Kg = 0.99	Kg = 0.79	2nd test one year after first (no treatment)
4	81	M	Kg = 0.56	Kg = 0.53	2nd test done some months later with glucose oxidase
34	50	M	Kg = 0.70	Kg = 0.81	2nd test 3 months after dieting
64	50	M	Kg = 0.94	Kg = 1.25	2nd test after one year on chlorpropamide
30	79	F	Kg = 0.47	Kg = 0.47	2nd test one day after 1st

compared both against the Volunteer Controls and the Hospital Normals. The only two groups for which the results were significant was the "asymptomatic diabetic group" (p 0.01 p. 0.02) and the "clinical diabetic group" (p. 0.001). Hence this test has a slightly higher discriminatory power than the intravenous tolbutamide test.

Correlation between the intravenous glucose and the intravenous sulphonylurea test

In order to test this correlation further we arranged 48 of the combined test results in ascending order of Kg value. These figures are shown in Table 5. They show that for Kg values above 0.80 there is no correlation with the sulphonylurea test. The slight positve correlation bestowed on the group of tests as a whole is largely due to the diabetic component. We have obtained this result in spite of the fact that our sulphonylurea test was carried out under standardised conditions. The implication is that the sulphonylurea test does not help to distinguish the various forms of diabetes in the *British Diabetic Association* classification, although it may give a perfectly valid result in any particular person. Furthermore, it signifies that our interpretation of this test has a not readily grasped component which eludes us at present. It is quite possible that this component is linked to "complexed" circulating insulin which becomes released by sulphonylurea, particularly in the presence of heparin, as it has recently been shown by GUNDERSEN and LIN (25) that heparin can "decomplex" insulin. DOLGER et al. (26) found that the IVTT is no better than the oral GTT in the detection of diabetes in pregnancy and POTE et al. (27) also noted the lack of correlation between the cortisone GTT, oral GTT and intravenous GTT. It thus appears that each test has its own interpretation and that to look for a strict correlation between all of them merely displays our ignorance.

Tab. 5
Correlation between Kg and sulphonylurea test

No.	Kg	% fall	No.	Kg	% fall
66	0.20	2	71	0.80	20
80	0.18	5	65	0.86	31
			52	0.86	32
51	0.23	19	27	0.98	27
67	0.37	14	72	0.80	20
45	0.29	14	74	0.99	43
18	0.40	3	58	0.99	34
75	0.47	23	83	0.84	32
63	0.46	9	26	0.82	18
93	0.45	30	81	0.96	53
47	0.57	20	14	0.94	29
39	0.57	21	77	0.83	29
29	0.55	23			
4	0.56	13	69	1.55	54
50	0.51	22	7	1.55	25
79	0.59	39	44	1.24	33
			41	1.06	20
6	0.75	30	3	1.14	31
54	0.72	30	13	1.21	45
48	0.65	25	2	1.29	43
84	0.70	46	62	1.23	30
15	0.60	33	64	1.25	32
			91	1.62	45
			89	1.05	53
			40	1.44	16
			38	1.04	24
			82	1.44	27
			78	1.11	50
			85	2.66	19
r = + 0.73			r = + 0.01		

Total number = 48; r for total = + 0.44

A simplified intravenous glucose tolerance test

All our glucograms after intravenous glucose were analyzed by the LUNDBAEK technique (17). Ten minute readings were taken from the curves and the values transferred to semi-logarithmic paper, the best fitting line for the first hour points was drawn (fig. 9) and the time noted for the blood sugar to fall to half its value. This time was inserted into the LUNDBAEK formula (see tab. 6) and the Kg value calculated therefrom. The following difficulties were noted: — (1) many times the points lay on a curve, which meant that the straight line could only be drawn by ignoring some upper or lower points and one had a choice of slopes; (2) in diabetics, often extrapolated figures had to be used in order to arrive at a half glucose value, this is both cumbersome and causes inaccuracies; and (3) more than half our lines so drawn have shown definite angulations between the 10 and 20 minute points and between the 40 and 60 minute points; this is illustrated in fig. 10. Such changes in the rate of fall were seen in both normals and diabetics, but they are more common in the normal person. We like to think that these angulation points correspond to the renal and liver thresholds respectively and that the "steady state" is only maintained between these points. In other words a straight line fit cannot be expected between points lying outside this period. Hence, we decided to restrict the period of the test to the 30 minutes that can be expected to lie on this straight line, i. e. the 15—45 minute period after intravenous glucose. In the preparation of this manuscript we came across the interesting paper by WEST and WOOD (28). These authors anticipated this simplified test, unbeknown to us they had advocated it in 1959, quote: — ". . . . we conclude that glucose tolerance could be easily estimated with considerable accuracy by determining the rate of fall of the blood glucose during a period of approximately 30 minutes at a time when the levels of blood glucose are a little below the renal threshold, but above the normal fasting level. Since the per cent per minute fall is constant

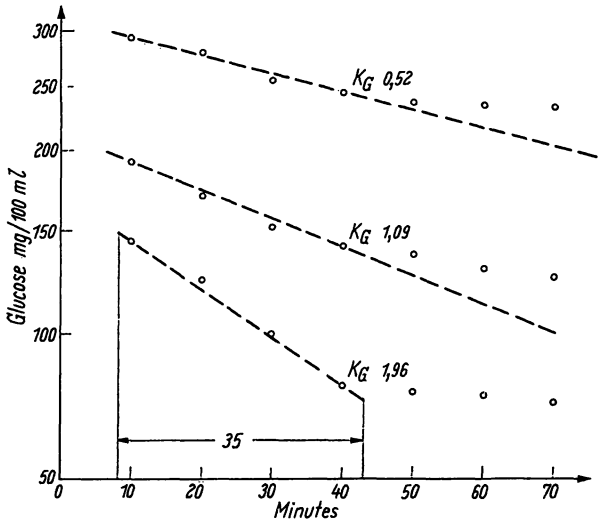

Fig. 9
The best fit line for the first seven points of the test on semi-logarithmic paper.
Note the time for the blood sugar level to fall to half its value

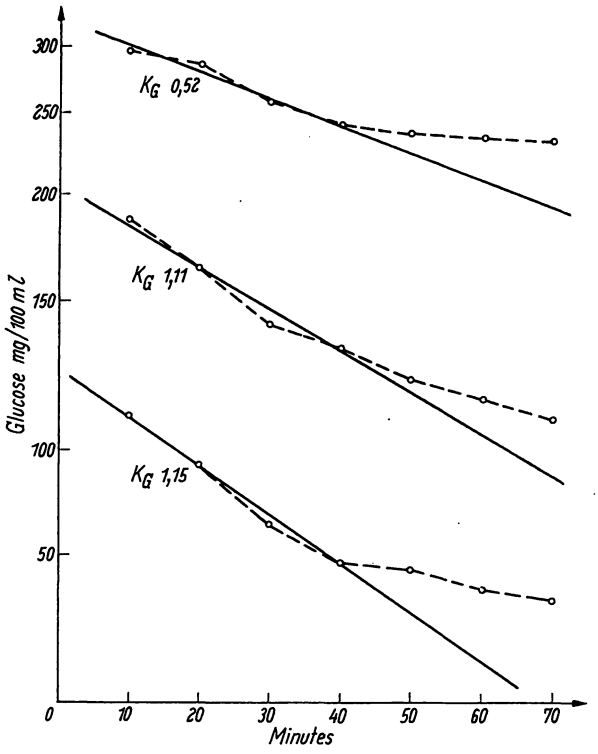

Fig. 10
Some examples of difficult "best-fits" and angulation points

during this period, it seems likely that (the) glucose (fall) could be estimated accurately by performing only two blood glucose determinations." This conclusion they arrived at after careful personal work with the intravenous glucose tolerance test and a most searching enquiry into the results obtained by the other leading investigators in this field — AMATUZIO, CONARD and DUNCAN. We were led to the same conclusion from a careful study of our 98 intravenous glucograms. As far as we are aware the recommendation of WEST and WOOD has never been carried into effect.

Calculation of the result

LUNDBAEK makes use of the simple formula recommended by HAMILTON and STEIN, he simplifies it further by using a predetermined blood sugar value, namely the half-value. We use basically the same formula and simplify it by predetermining the time interval, namely 30 minutes. This is shown in Table 6. Furthermore, by restricting the calculations to the usually encountered range of blood sugar levels found in this test, i. e. 50—300 mg per cent glucose all the k′ values can be reduced to manageable proportions by deducting their value from the k′ value of the 300 blood sugar. The k′ values for glucose levels of 50—300 mg per cent are found in Table 7.

Tab. 6

The LUNDBAEK formula		The authors' formula
For the exponential fall: $BlS_t = BlS_0 e^{-kt}$ $BlS_{t2} = BlS_{t1} e^{-k(t_2-t_1)}$ it follows —		
$k = \frac{\ln BlS_1 - \ln BlS_2}{t_2 - t_1}$	also written	$k = \frac{\ln BlS_1}{t_2 - t_1} - \frac{\ln BlS_2}{t_2 - t_1}$
but by chosing time by which BlS falls to ½ its value —		but by chosing t_2—t_1 to equal 30 minutes —
$k = \frac{\ln BlS_1 - \ln (0.5\ BlS_1)}{t\frac{1}{2}}$		$k = \frac{\ln BlS_1}{30} - \frac{\ln BlS_2}{30}$
then the numerator can be written —		in calculating each half of this expression separately —
$\ln \frac{BlS_1}{BlS_1 \times 0.5} = \ln 2 = 0.693$		$k' = \frac{\ln BlS}{30}$ (× 100) (percentage per minute)
$Kg = \frac{0.693}{t\frac{1}{2}} \times 100$ (percentage per minute)		$Kg = k'_{(45)} - k'_{(15)}$
		(Note: the k′ values for blood sugars — BG— from 50—300 mg/100 m*l* are given in Table 7)

The test procedure

The patient is prepared as for the oral glucose tolerance test. A specimen of blood is taken for the determination of the fasting blood sugar level; this is usually of interest to the physician but has nothing directly to do with the determination of the Kg-value. 25 grams of glucose (50 m*l* of a 50% solution) are then injected into an antecubital vein within a period of 2—3 minutes. By using a No. 1 needle the speed regulates itself on account of the high viscocity of the solution. Blood is taken again 15 and 45 minutes after the injection. Urine is not collected. Taking the fasting blood sample and giving the injection takes usually 6 minutes, it has been found possible thus for one worker to deal with 6 patients in a period of 2 hours giving the injections and taking all the blood samples himself.

When the laboratory results for the blood sugars are available, the k′ value for the 15 minute and 45 minute blood sugar are read from Table 7 and deducted from each other, thus giving the Kg value for the test.

Tab. 7. Table for the calculation of the 30 minute Kg value

B.G.	k'	B.G.	k'	B.G.	k'	B.G.	k'	B.G.	k'	B.G.	k'	B.G.	k'	B.G.	k'	B.G.	k'
299	0.01	274	0.30	249	0.62	224	0.97	199	1.37	174	1.82	149	2.33	124	2.95	99	3.70	74	4.67
298	0.02	273	0.31	248	0.63	223	0.99	198	1.39	173	1.83	148	2.36	123	2.97	98	3.73	73	4.71
297	0.03	272	0.33	247	0.65	222	1.00	197	1.40	172	1.85	147	2.38	122	3.00	97	3.76	72	4.76
296	0.04	271	0.34	246	0.66	221	1.02	196	1.42	171	1.87	146	2.40	121	3.03	96	3.80	71	4.80
295	0.05	270	0.35	245	0.67	220	1.03	195	1.44	170	1.89	145	2.42	120	3.05	95	3.83	70	4.85
294	0.07	269	0.36	244	0.69	219	1.05	194	1.45	169	1.91	144	2.45	119	3.08	94	3.87	69	4.90
293	0.08	268	0.38	243	0.70	218	1.06	193	1.47	168	1.93	143	2.47	118	3.11	93	3.90	68	4.95
292	0.09	267	0.39	242	0.71	217	1.08	192	1.49	167	1.95	142	2.49	117	3.14	92	3.94	67	5.00
291	0.10	266	0.40	241	0.73	216	1.10	191	1.51	166	1.97	141	2.52	116	3.17	91	3.98	66	5.05
290	0.11	265	0.41	240	0.74	215	1.11	190	1.52	165	1.99	140	2.54	115	3.20	90	4.01	65	5.10
289	0.12	264	0.43	239	0.76	214	1.13	189	1.54	164	2.01	139	2.56	114	3.23	89	4.05	64	5.15
288	0.14	263	0.44	238	0.77	213	1.14	188	1.56	163	2.03	138	2.59	113	2.25	88	4.09	63	5.20
287	0.15	262	0.45	237	0.78	212	1.16	187	1.58	162	2.05	137	2.61	112	3.28	87	4.13	62	5.26
286	0.16	261	0.46	236	0.80	211	1.17	186	1.59	161	2.07	137	2.64	111	3.31	86	4.16	61	5.31
285	0.17	260	0.48	235	0.81	210	1.19	185	1.61	160	2.10	135	2.66	110	3.34	85	4.20	60	5.36
284	0.18	259	0.49	234	0.83	209	1.20	184	1.63	159	2.12	134	2.69	109	3.37	84	4.24	59	5.42
283	0.19	258	0.50	233	0.84	208	1.22	183	1.65	158	2.14	133	2.71	108	3.40	83	4.28	58	5.48
282	0.21	257	0.52	232	0.86	207	1.24	182	1.67	157	2.16	132	2.74	107	3.44	82	4.32	57	5.54
281	0.22	256	0.53	231	0.87	206	1.25	181	1.68	156	2.18	131	2.76	106	3.47	81	4.36	56	5.59
280	0.23	255	0.54	230	0.88	205	1.27	180	1.70	155	2.20	130	2.79	105	3.50	80	4.40	55	5.65
279	0.24	254	0.55	229	0.90	204	1.29	179	1.72	154	2.22	129	2.81	104	3.53	79	4.45	54	5.72
278	0.25	253	0.57	228	0.91	203	1.30	178	1.74	153	2.24	128	2.84	103	3.56	78	4.49	53	5.78
277	0.27	252	0.58	227	0.93	202	1.32	177	1.76	152	2.27	127	2.87	102	3.60	77	4.53	52	5.84
276	0.28	251	0.59	226	0.94	201	1.33	176	1.78	151	2.29	126	2.89	101	3.63	76	4.58	51	5.91
275	0.29	250	0.61	225	0.96	200	1.35	175	1.80	150	2.31	125	2.92	100	3.66	75	4.62	50	5.97

Example:

$BlS_{(15)} = 172$ mg/100 ml and $BlS_{(45)} = 124$ mg/100 ml

$k'_{(15)} = 1.85$ $k'_{(45)} = 2.95$

$Kg = 2.95 - 1.85$

$= 1.10$

Reliability of the test

This is simply deduced from a comparison of the LUNDBAEK 6—7 point test procedure with the authors' 2 point procedure on 83 glucograms. The results are shown in Table 8. It would be hard to better the correlation between the two procedures. This is not surprising since they are both based on the same mathematical concept, furthermore, in making the straight-line fit in the LUNDBAEK graphic method, inconvenient points are ignored which also helps in approximating the results by the two methods.

Tab. 8

Correlation between Kg values of LUNDBAEK and Kg values of authors

No.	Lundbaek	Authors	No.	Lundbaek	Authors
1	1.65	1.65	39	0.64	0.57
2	1.47	1.29	40	1.34	1.44
3	0.77	0.73	41	1.06	1.06
4	0.25	0.26	42	1.15	0.99
5	1.15	0.98	43	0.04	0.06
6	0.64	0.75	44	1.32	1.24
7	0.49	0.49	45	0.36	0.29
8	0.84	0.99	46	0.92	0.90
9	0.96	0.91	47	0.61	0.57
10	1.87	1.80	48	0.71	0.65
11	1.97	1.63	49	0.69	0.73
12	0.54	0.42	50	0.49	0.51
13	1.03	1.21	51	0.53	0.23
14	0.96	0.94	52	1.20	1.02
15	0.53	0.60	53	0.59	0.56
17	0.34	0.25	54	0.70	0.72
18	0.11	0.40	55	0.65	0.51
19	0.48	0.66	57	0.40	0.30
20	0.77	0.77	58	1.00	0.99
21	0.40	0.50	60	0.40	0.40
22	2.92	2.92	61	1.72	1.77
23	0.96	1.14	62	1.11	1,23
24	1.15	1.10	63	0.49	0.47
25	1.26	1.17	64	0.92	0.94
26	0.73	0.82	65	0.90	0.86
27	0.86	0.98	66	0.19	0.20
28	0.73	1.02	67	0.49	0.37
29	0.48	0.55	68	0.44	0.37
30	0.44	0.47	69	1.92	1.55
31	0.33	0.32	70	0.84	0.81
32	0.91	0.97	71	0.82	0.80
33	0.31	0.31	72	0.80	0.80
34	0.71	0.70	74	1.03	0.99
36	1.15	1.28	75	0.57	0.47
38	0.92	1.04	77	0.87	0.83
78	1.23	1.11	79	0.61	0.59
81	1.15	0.96	82	1.45	1.44
83	0.76	0.84	85	2.46	2.66
86	2.96	3.06	87	0.96	1.01
89	0.90	1.05	90	0.81	0.82
91	1.23	1.62	92	0.76	0.78
93	0.40	0.45			

Total number of cases: 83; coefficient of correlation r = + 0.97.

We had at one time thought that one additional intermediate point at 30 minutes could serve both as a checkpoint for straightness of the line and a check on the reliability of the laboratory sugar estimation. However, critical examination of this concept revealed that it would involve the operator in quite considerable calculations to achieve this. Such a mid-point in time does not coincide with the arithmetic mean blood sugar fall for the two fractional 15 minute periods since the fall is exponential. If one wished to use the mean value of two separately calculated 15 minute Kg values, a table similar to table 6 could be constructed without much difficulty. It is one thing using an additional point in the test, and it is quite another thing to introduce a *"check-point"*. Not only would the validity of such a point have to be established and its range of accuracy, but it would also have to be interpreted by taking into consideration the accuracy of the individual laboratory's method of sugar analysis. Hence, the test would lose its simplicity. We doubt that clinical accuracy would be improved by going to such a more elaborate procedure. The determination of the Kg value is problematical in a few cases as is best shown in figure 11, fluctuations not infrequently occur during the

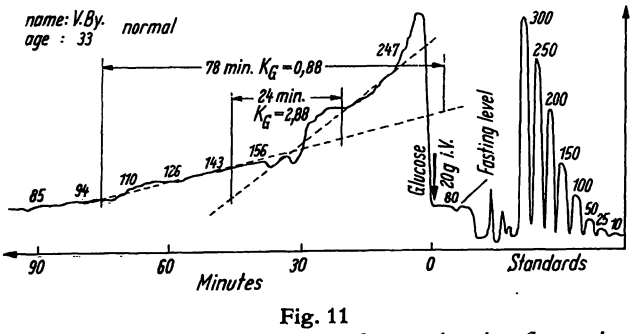

Fig. 11

A normal record after intravenous glucose showing fluctuations during the first 45 minutes

first 45 minutes, and although these are of a minor character they could seriously upset a "check-point" if it was defined within too narrow limits and lead to the rejection of a test which over the half hour period could produce quite an acceptable result. Clinically speaking we do not know whether a change of 0.1 in the Kg value is of significance and the borderline between the normal and abnormal covers 0.3 units of this value, the introduction of more points in the test procedure and additional checks seems therefore to be merely of academic interest at present.

Discussion

The pattern of diabetes in population surveys has been summarized by a publication of the *Office of Health Economics* (29) which has estimated that if screening was applied to the whole population of England and Wales 60.000 new cases would be detected annually. From this knowledge stems the interest in recent years for devising suitable tests for the detection of the early diabetic state, but there has been considerable lack of correlation between the various tests; as is apparent in our own work.— If we make the justifiable assumption that the result of a carefully carried out test procedure has a meaning then it follows that failure to align with other tests can only mean that a strict comparison cannot be made and that interpretation must differ. To say that a test has no meaning because it fails to align with another test is not really a valid argument. Non-alignment requires re-interpretation.

Interpretation of the *oral glucose tolerance test* may need reviewing if the work of TURNER and MCINTYRE (30) can be confirmed which suggests that glucose in contact with the intestinal mucosa in man produces a hormone capable of exerting a powerful stimulus to the insulin output of the pancreas. Their work would seem to confirm the earlier work of ARNOULD et al. (31) on dogs. Alterations in the jejunal mucosa following gastrectomy and starvation may alter such a response. On this basis one would not expect the test to correlate strictly with the intravenous glucose tolerance test. We have not infrequently observed a normal oral glucose tolerance test result coupled with a borderline value for the intravenous glucose tolerance test.

Interpretation of the *intravenous glucose tolerance test* is beset by a great controversy between those workers who maintain that it measures pre-existing tissue held insulin only and those who suggest that it measures a beta-cell response to the circulating glucose load. The former view is chiefly represented by the work of FRANCKSON et. al (15) and the latter in the recent work of SAMOLS and MARKS (32). To the outside observer it is not quite clear why these views should be mutually exclusive. It is fairly common in our observation to find low Kg values associated with high sulphonylurea responses which would argue in favour of the view held by FRANCKSON and his group of workers. It would always depend on what type of patient these test are performed because the presence of insulin antagonists would modify the response. If the latter are present in sufficient amount the tissue could be starved of insulin in the presence of an adequate pancreatic output of insulin. Intravenous sulphonylurea does not only stimulate pancreatic output of insulin, it also releases insulin from its polymer and from binding to protein. Our work suggests that the discrepancy observed between the Kg value and the sulphonylurea response may be due to "complexed" insulinlike activity ("ILA"). The following case would illustrate some of the difficulties:

The patient, an elderly male, 62 years of age, a chronic bronchitic, was found to have glycosuria. The oral glucose tolerance test showed blood glucose values — fasting: 80 mg/100 m*l*; 30 minutes after glucose 210 mg/100 m*l* after 1 hour 100 mg/100 m*l* with 3% sugar in the urine; at 90 minutes 58 mg/100 m*l* blood glucose with 0.2% sugar in the urine and at 2 and 2½ hours a blood sugar of 53 mg/100 m*l* with no sugar in the urine. In the intravenous glucose tolerance test a Kg of 0.45 was obtained which is well within the diabetic region, but in the intravenous tolbutamide test a 30% fall was registered in the first 30 minutes which increased to 51% at 50 minutes reaching low blood sugar levels between 40 and 50 mg/100 m*l* which persisted for a considerable length of time. Although the overall fall was similar to that observed in a healthy person, the fluctuations (see fig. 12) speak for a diabetic disposition (5).

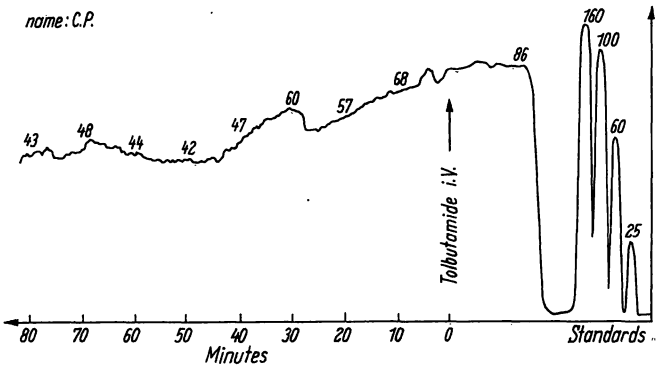

Fig. 12

Fluctuations in the blood sugar level during an intravenous tolbutamide test (read from right to left; glucose oxidase method)

The early part of the response to the oral test, which like the intravenous test relies on the tissue-held insulin gave a diabetic response, the latter part, i. e. after the jejunal hormone transmitted stimulus has come into, play, shows, like the tolbutamide test an almost hypoglycaemic response. This seems a likely interpretation of such a combination of results.

With more knowledge of the mechanism of our tests for diabetes we may need to do *all three tests* discussed above on every patient, as they may give us some guidance not only to diagnosis but also to prognosis.

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Indirekte Bestimmung des Kohlenmonoxyds im Blut

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Eine früher ausgearbeitete Methode zur Bestimmung des ausgeatmeten Kohlenmonoxyds wurde verbessert.
Bei 80 Personen, die beruflich dem Kohlenmonoxyd exponiert waren, wurde gleichzeitig die Konzentration des Gases im Blute sowie das in 5 Min. bei Rückatmung von Sauerstoff ausgeschiedene Gas bestimmt. Die graphische Darstellung der erhaltenen Werte ergibt eine langsam steigende Kurve, die mit einer mittleren Genauigkeit von ± 0,5 m*l* CO-proz. eine indirekte Bestimmung des CO-Hb ermöglicht.
Bei einer 5 Min. währenden Rückatmung werden etwa 2% des gesamten, im Kreislauf befindlichen Kohlenmonoxyds ausgeschieden. Unter den beschriebenen Bedingungen wird ein Grenzwert von 2 m*l* ausgeatmeten Kohlenmonoxyds als annehmbar vorgeschlagen.

Earlier methods for the determination of expired carbon monoxide have been improved.
In 80 persons, who are exposed to CO in their occupations, the concentration of the gas was measured simultaneously in the blood and in the expired gas, following the reinspiration of oxygen. The resulting values show, graphically, a gradually increasing slope, form which the COHb level can be evaluated directly with a maximal dispersion of ± 0.5 m*l* CO%.
During 5 min. reexpiration the sample contains about 2% of the total CO present in the circulation. Under the described conditions, a limit of 2 m*l* of expired CO is suggested.

Die Kenntnis des Gehaltes des Blutes an Kohlenmonoxyd in jedem beliebigen Moment einer gegebenen Zeitperiode — z. B. während der achtstündigen Arbeitszeit — ermöglicht die korrekte Deutung der unspezifischen Symptome, die bei Personen auftreten, die in einer CO-haltigen Atmosphäre arbeiten. Die bekannten, bei der Entnahme von signifikanten Blutproben auftretenden Schwierigkeiten ließen in letzter Zeit das Interesse an der Untersuchung *des ausgeatmeten Gases* wachsen. So schlug 1947 Shepherd (1) vor, die Analyse der ausgeatmeten Luft mit Hilfe eines Molybdat-Palladiumsalz-Indikatorröhrchens durchzuführen. Ein Jahr später versuchte Sjöstrand (2) den CO-Hb-Spiegel indirekt dadurch zu bestimmen, daß er die CO- und O_2-Konzentration in dem ausgeatmeten Gasgemisch nach Rückatmung von reinem Sauerstoff analysierte. — Jones und Mitarbeiter (3) gingen im Jahre 1958 den gleichen Weg und untersuchten das exhalierte Gas nach dem Einatmen von reinem Sauerstoff und darauffolgendem 20 Sek. langem Anhalten des Atems. Beide Verfahren wurden später in verschiedenen Modifikationen zur Erforschung des Kohlenmonoxyd-Sättigungszustandes des Organismus verwendet (4—7).