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## Further Observations on the Diurnal Variation in Oral Glucose Tolerance

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*British Medical Journal*, 1970, 4, 334-337

**Summary:** Diurnal variation in oral glucose tolerance was studied in 122 male volunteers aged 40 years and over who participated in a screening health examination. In those with screening blood sugar levels exceeding 110 mg./100 ml. the degree of diurnal variation was least in those with the highest morning glycaemia; the latter also tended to have lower afternoon fasting blood sugar levels.

In a group of 40 control subjects, afternoon glucose tolerance tests yielded significantly higher post-glucose blood sugar levels. The degree of diurnal variation was significantly and inversely related to the degree of obesity.

### Introduction

The phenomenon of diurnal variation of glucose tolerance in man has been described by several authors (Roberts, 1964; Bowen and Reeves, 1967; Jarrett and Keen, 1969), but little is known about the factors influencing this variation or about its relation to pathological carbohydrate intolerance and diabetes mellitus. We have taken the opportunity provided by a recent health survey of London civil servants to examine further some of the related factors.

### Methods

The health survey, conducted in conjunction with the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine, was open to male civil servants aged 40 and over and working in various Government departments in London. Volunteers were seen between 9.30 a.m. and 1 p.m., having fasted overnight and having drunk 50 g. of liquid glucose (235 ml. of Lucozade) one hour and fifty minutes before attending the screening clinic. Two hours after taking the glucose drink a capillary blood sample (0.1 ml.) was taken from the ear lobe and added to 0.9 ml. of 1% potassium fluoride, and the blood sugar was estimated by the ferricyanide reduction micro-method (Technicon method N-9a) on the AutoAnalyzer.

The usual survey practice was to carry out standard oral glucose tolerance tests on subjects with screening blood sugar levels of 110-199 mg./100 ml. and to refer those with levels of 200 mg./100 ml. or more to their personal doctors. For a period of about six months, however, all those with screening levels of 110 mg./100 ml. or more, including those exceeding 200 mg./100 ml., were recalled for a full glucose tolerance test; they were further asked if they would consent to a second test for the present research project. Though most (96%) consented to the second test, difficulties in arranging

convenient appointments reduced the overall response to 85% (122 subjects).

A random sample of subjects with screening blood sugars below 110 mg./100 ml., stratified for age and two-hour blood sugar level, was selected as a control group, and those concerned were asked to participate in the research project. Replies were received from 68 of the 81 people approached. Twenty-eight of these were either unable or unwilling to participate, so that 40 subsequently had the two glucose tolerance tests.

The morning and afternoon tests were performed in random order not less than three or more than seven days apart and after three days of supplementation of the normal daily diet with an extra 150 g. of carbohydrate. The morning test began, after an overnight fast, at 9.30 a.m. The afternoon test started at 4 p.m., the subjects having fasted since a light breakfast, which in most cases had been completed by 8 a.m. Capillary blood samples were obtained before a 50 g. load of liquid glucose and subsequently at half-hourly intervals for two hours. Subjects remained seated and did not smoke during the test period. Blood sugars were estimated as before.

The area under the glucose tolerance curve was calculated from the formula:  $\text{area} = a + 2b + 2c + 2d + e$ , where  $a$  is the fasting blood sugar and  $b-e$  are the subsequent blood sugar values.

In addition, the possible influence of diurnal variation on screening blood sugar values was examined. Those attending the usual morning survey sessions for a one-week period in January 1970 were asked to volunteer for an extra afternoon screening test, when two-hour blood sugars were estimated on samples collected between 5 and 6 p.m., the glucose having been drunk after fasting from breakfast. In this study, for which no special dietary preparations were made, 107 men participated.

### Results

#### Control Group

The mean glucose tolerance test results are presented in Table I. The results are similar to, though not identical with, those in our earlier "normal" sample (Jarrett and Keen, 1969), which, however, was younger, was composed of both sexes, and in which the afternoon tests were performed at 1 p.m., after a shorter, four to five hours, fast. In both studies the fasting blood sugar values, morning and afternoon, were virtually identical. In the previous series a significant excess of afternoon over morning values was already apparent 30 minutes after the glucose load, was numerically greater at 60 and 90 minutes, but was less at 120 minutes. In the present study there was little difference between morning and afternoon values at 30 minutes, but there was still a considerable and significant difference at 120 minutes.

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The interrelationship of obesity, expressed as the ponderal index, with the degree of diurnal variation in glucose tolerance is shown in Table II. The ponderal index (height in inches divided by the cube root of weight in pounds) is a good index of obesity (Steinkamp *et al.*, 1965), the highest numerical values occurring in the least obese. The group was divided into three tertiles of distribution of ponderal index—high, medium, and low—and the mean glucose tolerance test area calculated separately for both morning and afternoon tests. Clearly the morning "area" increases with increasing degrees of obesity. The statistical significance of this relationship was calculated by performing a linear correlation analysis between the ponderal index and the difference between morning and afternoon glucose tolerance areas—that is the diurnal swing. The correlation coefficient was 0.464 ( $p < 0.001$ ).

The degree of diurnal variation in relation to the degree of morning glycaemia is shown in Table III. While there is some diminution of diurnal swing with increasing morning glucose tolerance area, the effect is considerably less than that observed with increasing obesity (Table II). The interrelationship of age and diurnal variation is examined in Table IV. Neither morning nor afternoon glucose tolerance

areas increase with age; nor is there any apparent trend in the differences between morning and afternoon values.

### Hyperglycaemic (Positive Screening) Group

The mean results of the two glucose tolerance tests in subjects screening with two-hour blood sugars in excess of 109 mg./100 ml. are presented in Table V and the influence of obesity and age is shown in Tables VI and VII. Like the normoglycaemic group, the morning glucose tolerance area increases with the increasing degree of obesity and the difference between morning and afternoon values is inversely related to the degree of obesity. Linear correlation of ponderal index and the diurnal difference, however, proved not significant ( $r = 0.075$ ).

Both morning and afternoon glucose tolerance areas increase with age, but the difference between morning and afternoon values shows no clear relationship with age. The mean morning and mean afternoon glucose tolerance test results are compared in the chart after the subjects have been divided into subgroups according to the level of the two-hour blood sugar in the morning test. Evidently the degree of diurnal variation diminishes as morning hyperglycaemia increases. Furthermore, in the more hyperglycaemic groups the fasting blood sugar level in the afternoon is appreciably, and in several groups significantly, lower than that after the overnight fast.

### Diurnal Variation and Test Results

Two systems of diagnostic classification have been applied. The first (Table VIII) classifies as normal those tests in which the peak blood sugar is 180 mg./100 ml. or less and the two-hour blood sugar is 120 mg./100 ml. or less, which is the classification recommended by the Medical and Scientific Section of the British Diabetic Association (Fitzgerald and Keen, 1964). All the control group had normal morning tests, but 10 (25%) had abnormal afternoon tests. The detailed results for these 10 subjects are given in Table IX. Of the 71 men in the hyperglycaemic group with normal morning tests, 27 (36.6%) had abnormal afternoon tests. In contrast, of 51 with abnormal

TABLE I.—Mean ( $\pm$ S.E. of Mean) Blood Sugar Levels in Morning and Afternoon Glucose Tolerance Tests in the Control Group

	Time (Minutes)				
	0	30	60	90	120
Morning .. ..	72.93 $\pm 1.38$	128.92 $\pm 4.30$	130.65 $\pm 4.48$	95.20 $\pm 4.15$	69.03 $\pm 2.88$
Afternoon .. ..	73.93 $\pm 1.30$	131.63 $\pm 3.32$	161.60 $\pm 6.12$	145.18 $\pm 3.39$	104.98 $\pm 4.64$
Difference .. ..	1.0	2.71	30.95	49.98	35.95

TABLE II.—Comparison of Morning and Afternoon Glucose Tolerance Areas (Mean  $\pm$  S.E. of Mean) by Tertile of Ponderal Index in the Control Group

Mean Ponderal Index	No.	Mean $\pm$ S.E. of Mean Glucose Tolerance Area		Difference
		A.M.	P.M.	
13.15 (high) .. ..	13	796 $\pm$ 29	1,116 $\pm$ 58	320
12.70 (medium) .. ..	14	825 $\pm$ 30	1,048 $\pm$ 40	223
11.20 (low) .. ..	13	914 $\pm$ 47	1,024 $\pm$ 37	110

TABLE III.—Results of Morning and Afternoon Glucose Tolerance Tests in Normal Group Divided into Tertiles of Distribution of Morning Glucose Tolerance Test Area

Mean Ponderal Index	Glucose Tolerance Area Tertile	Mean Glucose Tolerance Area		Difference
		A.M.	P.M.	
12.86 .. ..	< 775 (n=13)	712	960	248
12.58 .. ..	775—885 (n=14)	827	1,078	251
12.47 .. ..	> 885 (n=13)	995	1,147	152

TABLE IV.—Comparison of Morning and Afternoon Glucose Tolerance Area by Age Group in the Control Group

Age Group	No.	A.M.	P.M.	Difference
40—49	18	868.0 $\pm$ 34	1,054.0 $\pm$ 31	186
50—59	14	830.0 $\pm$ 34	1,110.0 $\pm$ 50	280
60+	8	815.0 $\pm$ 51	996.0 $\pm$ 52	181

TABLE V.—Mean ( $\pm$ S.E. of Mean) Blood Sugar Levels in Morning and Afternoon Glucose Tolerance Tests in the Hyperglycaemic Group

	Time (Minutes)				
	0	30	60	90	120
Morning .. ..	99.52 $\pm 3.02$	177.80 $\pm 4.15$	194.88 $\pm 5.82$	156.0 $\pm 5.84$	122.61 $\pm 5.15$
Afternoon .. ..	91.29 $\pm 3.13$	172.85 $\pm 4.09$	210.56 $\pm 4.80$	178.19 $\pm 4.80$	141.13 $\pm 4.63$

TABLE VI.—Comparison of Morning and Afternoon Glucose Tolerance Area by Tertile of Ponderal Index in the Hyperglycaemic Group

Ponderal Index	No.	Mean $\pm$ S.E. of Mean Glucose Tolerance Area		Difference
		A.M.	P.M.	
High .. ..	39	1,225 $\pm$ 71	1,331 $\pm$ 53	106
Medium .. ..	41	1,277 $\pm$ 66	1,369 $\pm$ 55	92
Low .. ..	42	1,329 $\pm$ 59	1,378 $\pm$ 64	49

TABLE VII.—Comparison of Morning and Afternoon Glucose Tolerance Area by Age Group in the Hyperglycaemic Group

Age Group	No.	Mean $\pm$ S.E. of Mean Glucose Tolerance Area		Difference
		A.M.	P.M.	
40—49	23	1,096 $\pm$ 57	1,187 $\pm$ 49	91
50—59	53	1,265 $\pm$ 54	1,321 $\pm$ 40	56
60+	46	1,385 $\pm$ 67	1,491 $\pm$ 67	106

TABLE VIII.—Classification of Glucose Tolerance Tests into Two Categories. See Text for Criteria

		Afternoon			
		Controls		Hyperglycaemics	
		Normal	Abnormal	Normal	Abnormal
Morning	Normal .. ..	30	10	44	27
	Abnormal .. ..	—	—	5	46

TABLE IX.—Morning and Afternoon Glucose Tolerance Test Results for the 10 Individuals with Abnormal Afternoon Tests by the British Diabetic Association Criteria (Table VIII)

	Age	Time of Test	Blood Sugar at Sample Time (Minutes)					Screening Blood Sugar
			0	30	60	90	120	
1	42	A.M.	75	99	126	106	86	72
		P.M.	80	114	194	178	148	
2	46	A.M.	86	166	220	164	116	72
		P.M.	61	128	180	168	128	
3	46	A.M.	66	122	161	138	99	91
		P.M.	68	139	182	162	122	
4	46	A.M.	72	112	112	88	73	55
		P.M.	82	114	186	183	142	
5	49	A.M.	64	138	151	75	50	59
		P.M.	88	166	181	203	125	
6	53	A.M.	86	144	156	118	81	100
		P.M.	92	130	208	230	186	
7	53	A.M.	85	167	157	109	75	78
		P.M.	74	174	226	172	135	
8	56	A.M.	66	134	144	74	51	109
		P.M.	80	162	209	175	131	
9	58	A.M.	70	139	144	99	57	90
		P.M.	79	168	225	188	136	
10	62	A.M.	70	118	130	88	63	79
		P.M.	66	101	154	185	154	

morning tests, all but five also had abnormal tests in the afternoon.

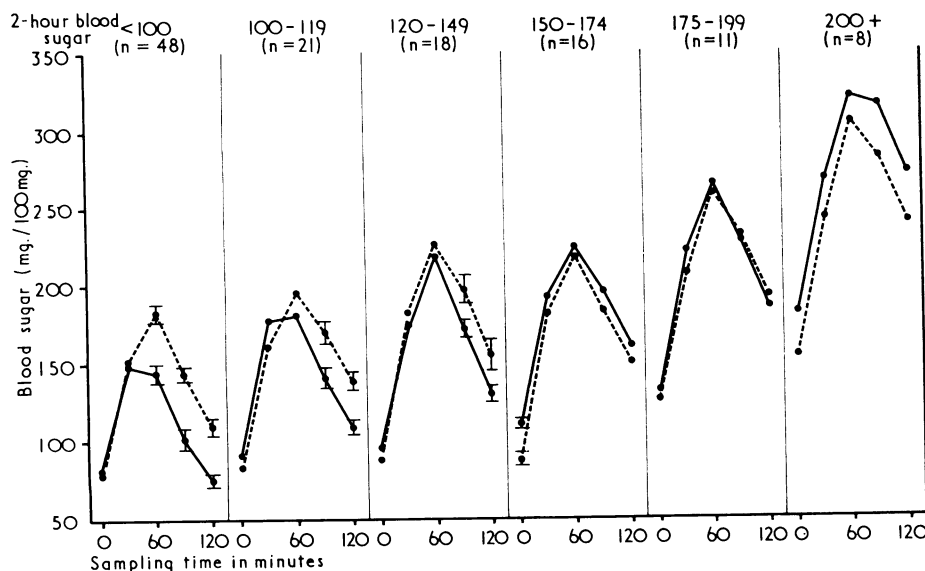
The second classification (Table X) is one suggested by the European Diabetes Epidemiology Study Group (Jarrett, 1970), and this divides the response to glucose into three categories:

(1) normal response to glucose (N.R.G.)—peak blood sugar level and two-hour blood sugar level less than 161 and 121 mg./100 ml., respectively; (2) pathological response to glucose (P.R.G.)—peak blood sugar level and two-hour blood sugar level more than 219 and 149 mg./100 ml., respectively; and (3) borderline response to glucose (B.R.G.)—combinations of peak and two-hour blood sugar levels not falling in category 1 or 2.

The results from this classification were broadly similar, with more borderline and pathological responses occurring in the afternoon.

TABLE X.—Classification of Glucose Tolerance Tests into Three Categories. See Test for Criteria.

		Afternoon					
		Controls			Hyperglycaemics		
		N.R.G.	B.R.G.	P.R.G.	N.R.G.	B.R.G.	P.R.G.
Morning	N.R.G.	14	18	1	8	26	1
	B.R.G.	—	7	—	3	43	10
	P.R.G.	—	—	—	—	7	24



Mean blood sugar levels in morning (solid line) and afternoon (interrupted line) glucose tolerance tests in the positive screening individuals. The six groups are categorized by the level of the two-hour blood sugar in the morning test. Representation of the S.E. of mean indicates a difference significant at 1 in 20.

### Diurnal Variation and Screening Levels

In the group of 107 men in whom the two-hour blood sugars were measured under screening conditions there was little difference between the mean level of blood sugar in the morning (76.5 mg./100 ml.) and that in the afternoon (79.1 mg./100 ml.). There was, however, much more variation in the afternoon levels, the standard deviation being 20.6 mg./100 ml. against 7.5 mg./100 ml. in the morning.

### Discussion

We have previously discussed (Jarrett and Keen, 1969) the possible general implications of the diurnal rise in blood sugar levels in response to an oral glucose load. In particular, we feel strongly that, in *critical* instances, it is not valid to assume normal glucose homeostasis on the basis of one or even more than one normal standard morning test. Clearly, a considerable degree of hyperglycaemia may occur in the afternoon in the presence of unequivocally normal morning tests, and the findings in our "normal screening" group suggest that this may occur in a quarter of the subjects examined. The potential importance of this lies in the relationship between hyperglycaemia and the prevalence and subsequent incidence of atherosclerotic arterial disease (Keen and Jarrett, 1969). At present there is insufficient information available to determine whether the same relationship exists with afternoon hyperglycaemia. Clearly this is an area for further exploration on an epidemiological scale, and it is to be hoped that it may form part of the experimental design of future studies concerned with this relationship.

Evidently, a *relatively* hyperglycaemic response in the afternoon must be regarded as a normal phenomenon, occurring in most normoglycaemic subjects, but raising the blood sugar to the conventionally hyperglycaemic range in about a quarter. It is, inevitably, reminiscent of the cortisol-stressed response to glucose, and it would be of great interest to know whether those subjects who show the greatest diurnal swing are also those who respond most strongly to cortisol.

In contrast, the dimensions of the diurnal swing lessen with increasing degrees of (morning) glucose intolerance. This perhaps indicates a progressive impairment of the capacity to restore the afternoon "relaxation" of glucose homeostasis to normal during the night. It is these subjects with morning hyperglycaemia who also tend to have lower afternoon fasting blood sugar levels. This might represent the phenomenon of late hypoglycaemia after oral glucose, described as an early manifestation of the disordered insulin release which culminates in clinical diabetes (Seltzer *et al.*, 1959; Faludi *et al.*,

1968). Alternatively, it may represent the diurnal variation in fasting blood sugar levels in established diabetics shown by Faiman and Moorhouse (1967). These workers reported that during three-day fasts five diabetic subjects showed a diurnal cycle in their blood glucose levels, with the peak levels occurring around 8 a.m.; no such cycle could be discerned in five healthy controls.

The inverse relation of obesity, as measured by the ponderal index, with the degree of diurnal variation in glucose tolerance, was significant only in the normoglycaemic group, but was also evident in the hyperglycaemic group. Since the morning glucose tolerance area is itself associated directly with the degree of obesity, it is difficult to decide how much of the loss of diurnal variation to attribute to obesity per se and how much to the associated hyperglycaemia. The analyses of the control group in Tables II and III, however, suggest that obesity is the more potent factor when morning glycaemia is within the normal range and is perhaps an independent one.

Diagnostic classification of the tests yields many abnormalities by afternoon testing in the group preselected for normoglycaemia. By one system of classification (Table VIII) all the morning tests were normal, but 10 afternoon tests were abnormal. Table IX lists the paired tests in these 10 subjects, and in all but one (No. 2) the morning tests are unequivocally normal. In some, however, the diurnal swing is so great—for example, Nos. 6, 7, and 9—as to bring the test results into what most would regard as the conventionally diabetic range. The present and potential significance of this phenomenon can only be hypothetical. This *exaggerated* swing may possibly represent an earlier stage in the failure of glucose homeostasis than the *reduced* swing seen in those with morning hyperglycaemia. Obviously, only longitudinal studies can provide the answer, and these are fraught with difficulties, not least logistical ones. A suggested working hypothesis, however, is that afternoon hyperglycaemia is the first stage of

glucose intolerance, followed by increased morning glycaemia (and reduced diurnal variation), then proceeding to morning hyperglycaemia, sufficient eventually to warrant the description of diabetes mellitus.

The small diurnal difference in mean two-hour blood sugar levels measured under screening conditions agrees with our previous experience (Keen, 1966) and presumably accounts for the failure of others to find diurnal variation in population surveys (Hayner *et al.*, 1965; Marine *et al.*, 1969). The reason for the relative lack of diurnal variation under these conditions is probably related to the lesser degree of standardization obtaining. Though the mean blood sugar levels were similar, the variation was very much greater in the afternoon, so that afternoon screening would be likely to yield more subjects exceeding an arbitrary cut-off level.

We are grateful to the many men who volunteered to participate in this study, and to our colleagues at the London School of Hygiene for their co-operation. Our contribution to the main survey and follow-up is financed by a grant from the Department of Health and Social Security. R. J. J. wishes to thank Lilly Laboratories for additional financial support.

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## Exercise Asthma and Disodium Cromoglycate

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*British Medical Journal*, 1970, 4, 337-339

**S**ummary: Exercise-induced asthma (defined as a fall in PEF of at least 25% of the pre-exercise value) was studied in adult patients with uncomplicated asthma. This was found to occur in 22 out of 52 patients. Pre-exercise inhalation of disodium cromoglycate reduced the mean fall in PEF after maximal exercise from 50% of the pre-exercise value to 23% (open assessment in 11 cases). After submaximal exercise for eight minutes the reduction was from 18% to 10% (double-blind crossover study in 28 cases). It is concluded that disodium cromoglycate partly inhibits the increase of airways resistance after exercise in asthmatic patients.

### Introduction

In asthmatics heavy exercise over several minutes may be followed by an increase in airways resistance (Pearson, 1952; McNeill *et al.*, 1966; Sly *et al.*, 1967; Sly, 1970), which is inhibited by sympathomimetics but usually not by atropine or

cortisone (Jones *et al.*, 1962; McNeill *et al.*, 1966; Sly *et al.*, 1967). The mechanism of the reaction has not been explained, though several suggestions and hypotheses have been presented (Seaton *et al.*, 1969; Ward *et al.*, 1969; Kerr *et al.*, 1970).

Inhalation of disodium cromoglycate may inhibit the bronchoconstriction after inhalation provocation tests in patients with extrinsic asthma (Altounyan, 1967; Pepys *et al.*, 1968; Muittari, 1969). Disodium cromoglycate is thought to block the mechanism by which bronchoconstrictive substances are released from mast cells after antigen-antibody reaction (Cox, 1967) or to inhibit the effect of pharmacologically active amines on bronchial smooth muscle or both (Kerr *et al.*, 1970). Uncontrolled studies (Davies, 1968; Muittari and Kreis, 1969; Palmer and Legge, 1969; Ward *et al.*, 1969) suggest that disodium cromoglycate may inhibit exercise-induced asthma. To our knowledge, however, no double-blind trials have been reported.

The purpose of the present study is (1) to estimate the prevalence, severity, and repeatability of exercise-induced asthma in inpatients with uncomplicated asthma and (2) to evaluate the effect of disodium cromoglycate on exercise-induced asthma by using a double-blind cross-over technique.

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