CLXXXIV. ON OSCILLATIONS OF BLOOD-SUGAR VALUES WITHIN BRIEF PERIODS, AND THE BLOOD-SUGAR CURVE ON UNIFORM INGESTION OF GLUCOSE.

BY OTTO JUL NIELSEN.

From Medical Clinic A, University of Copenhagen.

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IN late years a number of investigations on the blood-sugar have demonstrated not only that the daily fasting blood-sugar has no constant value, but also that, if instead of one single determination being made, the fasting blood-sugar is determined repeatedly through a certain period—with blood withdrawn at intervals of $\frac{1}{4}$ to $\frac{1}{2}$ hour—the blood-sugar curve obtained will show wide and long, more or less regular waves, which are supposed to be due to “sugar waves” issuing from the liver. Undoubtedly these waves are one of the reasons why the fasting blood-sugar value is found to change from day to day.

In addition to these rather regular curve waves Hansen [1923] has reported other oscillations in the blood-sugar, which were found on determining the blood-sugar at very frequent intervals for some time. Hansen found these oscillations, as distinct from the regular curve waves,

- (1) in normal individuals during fasting;
- (2) in diabetics during fasting, apart from the well-known steady fall in blood-sugar which is usually associated with fasting in hyperglycaemia;
- (3) after ingestion of carbohydrate, as the rise in blood-sugar does not proceed in a smooth curve but in connection with oscillations of the main grade. These oscillations are particularly brisk and relatively large when the blood-sugar level is fairly settled, that is, at the top of a rise which forms a plateau before the fall sets in, or at an unchanged high level.

Later similar results after ingestion of glucose have been reported by Klein [1925]. Gilbert, Schneider and Bock [1926] found similar results, but the blood was withdrawn only at intervals of 10–20 minutes.

Hansen thinks that these oscillations “represent the manner in which the blood-sugar regulation takes place.” Various observations in other work of mine have necessitated a further investigation into the occurrence of these oscillations. In particular, it was important to ascertain whether they really occur as a fairly constant phenomenon, which would seem most likely if they were a part of the intermediate sugar metabolism, or whether their appearance to some extent might be due to external factors resulting more or less from the experimental conditions under which the patients were examined. To get

some light on this question the experimental conditions were standardised as far as practicable and the technique was made as sensitive as possible.

In addition to the investigation on the oscillations of the blood-sugar values, this report also gives the result of experiments which were made in order to find out whether uniform blood-sugar curves might be obtained on different days after administration of the same amount of glucose. Bang [1914] has shown that in rabbits the administration of glucose causes a higher and more enduring rise of the blood-sugar in animals which have been starved for several days than it does in animals kept on ordinary diet. Later Traugott, Staub, Sakagushi [see v. Noorden and Isaac, 1927], Malmros [1928], Stenström [1928], Hagedorn [1921], Hansen [1923], Holst [1924], and others have shown that hyperglycaemia from the same doses of glucose or other carbohydrate does not always give the same curve, and that the course of the curve depends on the diet on the preceding days. The latter point is particularly emphasised by Stenström, who shows that the hyperglycaemia after glucose administration (the blood-sugar was determined only every $\frac{1}{2}$ hour) is higher and more persistent after a period of fat and vegetable diet than it is after a period of normal diet.

TECHNIQUE.

The blood-sugar is determined by the Hagedorn-Jensen method. In order to make the analytical errors as small as possible the determinations were made in a particular way, which does not, however, differ from the original method in any essential point. With this exact method, the bleeding time and the pipette constitute the chief source of error. All samples of blood are taken in about the same length of time and in such a way that the blood enters the pipette freely, and the pipette is filled a little above the mark within 10–12 seconds and exactly adjusted within a few seconds more. The contents of the pipette are emptied carefully into the colloidal zinc solution in the usual way, after which the pipette is at once carefully cleaned.

The width of the lumen of the pipette may also be of some importance in measuring the content exactly, and I have therefore tried both tubular and oval pipettes of varying length. The same pipette has been used in most of the determinations here reported, namely, a capillary pipette measuring 22 cm. from point to mark. Otherwise the method has been carried out exactly as indicated by the authors. In most instances the precipitation of protein is done in direct connection with the withdrawal of blood. The sodium thiosulphate titration is done with a 2 cc. burette divided into 1/100 cc., and all titrations are made in 50–60 seconds and every analysis is completed within a few hours.

The patients had been lying perfectly quietly in bed for 10–15 minutes before the first sample of blood was taken (usually after 12–14 hours' fasting), and throughout the entire period of blood-taking, so that the curves have been in no way influenced by muscular work [Hagedorn, 1921; Hromadko, 1928; Weiland [see v. Noorden and Isaac, 1927], Hatlehol, 1924].

The experimental error of the method was determined on freshly drawn blood without anticoagulants and immediately after the withdrawal. A large number of tests, too voluminous to be reported here, showed a mean error of ± 0.002 .

For glucose administration 1 g. of pure anhydrous glucose per kg. of body-weight was used in 10 % aqueous solution.

Urinary sugar was determined qualitatively by Fehling's and Almén's tests, and quantitatively in some experiments by fermentation and in others by the Benedict-Osterberg [1918, 1921] method for total sugar determination.

EXPERIMENTS.

The experiments fall into the following groups:

- (1) blood-sugar in fasting non-diabetic patients;
- (2) blood-sugar in fasting diabetics;
- (3) blood-sugar after ingestion of glucose in non-diabetic patients;
- (4) blood-sugar during food absorption in diabetics;
- (5) blood-sugar curves on different days in non-diabetics on uniform diet.

(1) *Blood-sugar in fasting non-diabetic patients.*

This group comprises five patients with perfectly normal carbohydrate metabolism. The first blood was taken after 13 hours' fasting.

Fig. 1 *a* is typical of the blood-sugar findings in these five patients. In every instance the curve was quite smooth, without any "oscillation," as the variations in blood-sugar values do not exceed the limits of experimental error.

(2) *Blood-sugar in fasting diabetics.*

This group comprises 11 cases which fall into the following subdivisions:

- (a) six diabetics, not treated with insulin;
- (b) one diabetic with kidney lesion, not treated with insulin;
- (c) four insulin-treated diabetics.

The first blood was taken after 13 hours' fasting.

(a) *Diet-treated diabetics.* Fig. 1 *b* is typical of the blood-sugar findings in these six cases. In every instance it was found that, at perfect rest, the high fasting blood-sugar value decreases gradually and smoothly, without any "oscillations" in the curve during the 2 hours' observation.

(b) *Non-insulin-treated diabetes combined with nephritis.* There was practically no fall in the increased blood-sugar during 70 minutes of observation (initial value 0.285 %, final value 0.281 %), and there was no "oscillation" in the curve.

(c) *Insulin-treated diabetics.* Here are found two different forms of fasting blood-sugar curve: one, the most frequent (Fig. 1 *c*), in which the blood-sugar rises during fasting; and the other, more rare (Fig. 1 *d*), in which the blood-sugar falls during fasting. (The possible effect of a late insulin injection is excluded in this instance.) No "oscillation" was noticed in any of the cases examined.

In fasting diabetics, examination of the blood-sugar that has increased during the night [Hatllehol, 1924]—due to “physiological” conditions in diabetics during sleep—bears out the difference observed between insulin-treated diabetics and diabetics treated by dietary measures only, namely, that the blood-sugar in insulin-treated diabetics in most instances rises during 1–2 hours’ observation, whereas the blood-sugar in diet-treated diabetics falls in the same period.

Fig. 1.

- a Blood-sugar in fasting non-diabetic.
 b " " diet-treated diabetic.
 c " " insulin-treated diabetic.
 d " " " "
 e " after ingestion of glucose in non-diabetic.

(3) *Blood-sugar after ingestion of glucose in non-diabetic patients.*

This group covers five patients with perfectly normal carbohydrate metabolism. The experimental conditions are exactly as already described. Fig. 1 *e* is typical of the blood-sugar curve in these patients. The rise itself, the fall and the waves of the individual curves cannot be discussed in detail in this paper, but no “oscillation” has been detected.

(4) *Diabetics. Blood-sugar during food absorption in 24 hours.*

This group consists of two insulin-treated diabetics. One is examined at various times throughout the 24 hours; the other is examined only in connection with administration of insulin and intake of food. The blood-sugar findings in the first case are given in detail; the second patient shows a perfectly analogous course of blood-sugar curve. I was not able to find any “oscillation” of the blood-sugar curve in either of these two diabetics by determining the blood-sugar at various intervals throughout the 24 hours; there were only the well-known rises and falls and waves in connection with the insulin and the food intake.

J., male, 27 years. Patient has been treated with insulin for 12-14 months and is now getting 20 + 15 units of insulin "Leo." Patient was resting perfectly quietly in bed throughout the entire experimental period. The examination was made on 15. ix. 1927.

Time	Blood-sugar	Time	Blood-sugar	Time	Blood-sugar
hr. min.	%	hr. min.	%	hr. min.	%
Fasting		15.38	0-104	22.27	0-273
7.38	0-239	15.42	0-107	22.30	0-257
7.40	0-239	15.45	0-108	22.35	0-238
7.43	0-241	15.48	0-109	22.40	0-229
7.46	0-241	15.52	0-109	22.41	0-227
		15.56	0-111	22.42	0-226
20 units of insulin and 1 rusk		15.58	0-110	22.45	0-221
+ 1 cup of tea.		16.00	0-112	22.50	0-215
7.49	0-243	16.04	0-113	22.53	0-209
7.52	0-245	16.08	0-116	22.55	0-205
7.55	0-248	16.12	0-115	22.56	0-203
7.59	0-240	16.16	0-115	23.00	0-192
8.02	0-236	16.20	0-117		
8.06	0-228	16.24	0-118	The patient slept during the following hours.	
8.09	0-224	16.27	0-117		
8.12	0-220	16.30	0-118	Next morning	
8.16	0-209	16.32	0-120	5.00	0-098
8.20	0-201	16.34	0-121	5.02	0-101
Pause till 10.00, during which		16.36	0-121	5.04	0-103
the patient gets breakfast.		16.40	0-122	5.08	0-109
10.00	0-150	Pause for 3½ hours in which the patient eats supper (at 18.30).		5.09	0-111
10.03	0-148			5.10	0-113
10.06	0-143	20.00	0-237	5.11	0-115
10.10	0-139	20.02	0-237	5.12	0-115
10.14	0-134	20.03	0-239	5.16	0-119
10.18	0-129	20.04	0-239	5.18	0-122
10.22	0-125	20.06	0-240	5.20	0-126
10.26	0-121	20.08	0-241	5.21	0-128
10.30	0-115	20.12	0-245	5.22	0-131
10.34	0-113	20.16	0-249	5.24	0-134
10.38	0-110	20.20	0-258	5.28	0-140
10.42	0-108	20.24	0-262	5.30	0-144
10.46	0-104	20.29	0-264	5.32	0-148
10.50	0-094	20.32	0-260	5.34	0-154
10.55	0-089	20.36	0-258	5.36	0-168
11.00	0-086	20.38	0-257	5.38	0-176
11.04	0-084	20.40	0-256	5.40	0-184
11.08	0-082	20.44	0-252	5.44	0-187
11.16	0-080	20.48	0-250	5.45	0-187
11.17	0-078	20.52	0-247	5.46	0-189
11.18	0-077	20.56	0-244	5.48	0-191
11.19	0-077	20.58	0-242	5.52	0-190
11.20	0-076	21.00	0-243	5.56	0-196
11.24	0-073	21.04	0-244	6.00	0-199
11.28	0-067	21.07	0-242	6.04	0-203
11.30	0-064	21.08	0-244	6.06	0-206
11.32	0-062	21.11	0-246	6.10	0-212
11.36	0-058	21.14	0-252	6.12	0-215
11.40	0-057	21.18	0-263	6.14	0-219
11.44	0-053	21.20	0-266	6.18	0-223
11.48	0-048	21.24	0-270	6.20	0-222
11.52	0-044	21.27	0-273	6.24	0-226
11.53	0-044	21.31	0-275	6.28	0-231
11.56	0-042	21.36	0-277	6.32	0-234
11.59	0-040	21.38	0-278	6.36	0-233
12.00	0-041	21.40	0-276	6.41	0-238
Pause for 3 hours, during which		21.44	0-279	6.44	0-241
the patient gets dinner (at		21.48	0-281	6.48	0-246
13.00).		21.53	0-283	6.52	0-248
15.00	0-094	21.57	0-285	6.56	0-252
15.04	0-096	22.00	0-288	7.00	0-254
15.08	0-097	22.02	0-289	7.03	0-252
15.12	0-099	15 units of insulin "Leo."		7.06	0-256
15.16	0-097			7.10	0-258
15.20	0-099	22.04	0-291	7.14	0-256
15.22	0-098	22.10	0-293	7.18	0-256
15.24	0-099	22.14	0-289	7.22	0-258
15.28	0-101	22.18	0-283	7.26	0-260
15.32	0-102	22.23	0-278	7.28	0-261
		22.24	0-276	7.29	0-262
				7.30	0-262

(5) *Blood-sugar curves on various days in non-diabetics on uniform diet.*

This last group gives the results of some experiments made in consequence of an investigation into the factors which regulate the carbohydrate metabolism. The object of the experiments was to find out whether it were possible with definite experimental conditions and uniform ingestion of glucose to obtain uniform blood-sugar curves on different days—uniform with regard to the rise of the curve as well as to its fall. It would take too much space to report the preliminary experiments which consisted in the daily intake of a definite amount of glucose irrespective of dietary balance, etc.; but the experiments showed that it was impossible in that way to obtain even approximately uniform curves. At once it was evident that the only possible way of obtaining uniform blood-sugar curves would be first to bring the organism into a stable equilibrium and then to proceed with the administration of glucose. I therefore tried whether I could obtain uniform curves in non-diabetic patients on ordinary mixed diet (without particular regard to its content of carbohydrates, proteins, fats, salts, etc.) by giving the same amount of glucose every fourth day; thinking that in the interval the individuals might return to the same equilibrium, but the following experiments proved this to be impossible.

In every experiment of this group the patients got a 10 % watery solution of 1 g. of glucose per kg. of body-weight after fasting 12 hours, and they had been resting perfectly quietly in bed throughout the experiment.

This group comprises altogether eight patients—with three to four uniform administrations of glucose in each case; but, as the findings are similar in all the cases, only two of them will be reported in detail.

In comparing the curves for each individual patient we find that, although they are on the whole fairly uniform with regard to approximately the same numerical rise, the curves differ rather markedly in the time of rise and in the waves on different days. As to the elimination of sugar by way of the urine, however, we find about the same total amount of glucose eliminated on each experimental day (the total amount of glucose determined by Benedict-Osterberg's method).

From these experiments it was evident that the pre-requisite for obtaining perfectly uniform curves on different days is that the patient is first balanced at an absolute equilibrium with regard to diet and all other factors and is then kept on exactly the same food every day as long as the experiment lasts. I have not yet had an opportunity of carrying out such experiments, but Fig. 2 supports this view. Throughout the entire experimental period this patient daily received practically the same amounts of carbohydrate, fat, protein, liquid and salts (his carbohydrate metabolism was not quite normal). Fig. 2 illustrates the blood-sugar findings in this case.

The three curves for this patient are very similar.

E. N., fem., 25 years. Neurasthenia.
Ewald: 105 cc., 55/75. No objective
signs apart from constipation

N. L., male, 39 years. Cardialgia and
constipation. Ewald: 100 cc. 30/60.
B.P. 125/90. Sahli 95 %

Date Min.	Blood-sugar			Blood-sugar		
	... 16. ii.	19. ii.	24. ii.	27. i.	31. i.	4. ii.
-5	0-078	0-080	0-080	0-086	0-085	0-081
-2	0-078	0-080	0-079	0-085	0-084	0-082
0	0-078	0-081	0-079	0-086	0-084	0-082
	Ingestion of 60 g. glucose in 600 cc. water			Ingestion of 60 g. glucose in 600 cc. water		
2	0-078	0-082	0-082	—	0-086	0-084
4	0-083	0-080	—	0-090	0-088	0-088
5	—	—	0-097	—	—	—
6	0-096	0-087	0-100	0-101	0-087	0-098
8	0-117	0-092	0-111	0-111	0-089	0-107
10	0-120	0-106	—	—	0-094	0-114
12	0-136	0-120	0-121	0-120	0-102	0-126
14	0-147	0-131	0-135	—	0-115	0-130
16	0-151	0-142	0-146	0-134	0-122	0-135
18	0-154	0-149	0-157	0-137	0-133	0-139
20	0-156	0-154	0-168	0-139	0-138	0-153
22	0-155	0-154	0-175	0-143	0-144	0-159
24	0-158	0-154	0-176	0-155	—	0-160
26	0-158	0-156	0-180	0-159	0-158	0-162
28	0-154	0-153	0-186	0-161	0-169	0-170
30	0-155	0-151	0-164	0-170	0-172	0-169
32	0-148	0-146	0-160	0-173	0-178	0-170
34	0-146	0-144	0-159	—	0-180	0-172
36	0-140	0-135	0-146	0-180	0-181	0-174
38	0-138	0-129	0-141	0-187	0-179	0-179
40	0-135	—	0-139	0-190	0-181	0-180
42	—	0-127	—	0-193	0-183	0-178
43	0-128	—	0-132	0-192	—	—
44	0-126	0-126	0-130	—	0-185	0-175
46	0-128	0-126	0-123	0-193	0-187	0-174
48	0-133	0-120	0-121	0-190	—	0-170
50	—	0-117	—	0-187	0-184	0-171
52	0-138	0-115	0-121	0-186	0-181	0-169
54	—	0-113	0-118	0-176	0-176	0-165
56	0-140	0-111	0-115	0-173	0-174	0-155
58	0-142	0-113	0-113	0-171	0-170	0-151
60	0-138	0-115	0-109	0-165	0-166	0-149
63	—	0-117	0-111	0-160	0-162	0-147
65	0-135	0-115	0-113	0-155	0-159	0-145
67	0-130	0-110	0-109	—	—	—
69	—	—	0-102	0-148	0-154	0-143
72	0-131	0-101	—	0-135	0-150	0-138
75	—	—	0-098	0-129	0-146	0-128
76	0-126	0-101	0-096	—	—	—
78	0-124	0-100	—	—	0-144	0-124
80	0-123	0-098	0-094	0-117	—	—
82	—	—	0-092	—	0-137	0-115
84	0-121	0-094	—	0-110	0-135	0-103
87	0-119	0-092	0-092	—	0-131	0-099
90	0-117	0-094	0-090	0-102	0-118	0-098
93	0-116	0-092	0-094	0-096	0-110	0-092
94	—	—	—	0-097	0-107	—
96	0-114	0-092	—	—	—	0-084
99	0-110	0-091	0-092	0-094	0-102	0-078
102	0-107	0-092	0-085	0-094	0-098	0-072
105	0-098	0-091	0-081	—	0-095	0-070
108	0-095	0-089	0-080	0-091	0-091	0-066
111	0-091	0-088	—	—	0-087	0-063
113	0-089	0-084	0-080	0-083	—	0-062
115	—	—	—	0-078	0-082	—
117	0-087	0-080	0-078	0-077	0-078	0-059
120	0-086	0-078	0-076	0-071	0-073	0-057

Urine tests during these experiments.

Date	...	16. ii.		19. ii.		24. ii.		27. i.		31. i.		4. ii.
Time (min.)		50 120		50 120		50 120		50 120		50 120		50 120
Diuresis (cc.)		320 475		400 400		580 280		230 265		300 350		330 300
Albumin		—		—		—		—		—		—
Glucose (mg.)		213 60		194 63		230 30		195 65		208 72		205 70
Total glucose eliminated (mg.)		273		257		260		260		280		275

Fig. 2.

a 14. ii. 1927.

b 18. ii. 1927.

c 22. ii. 1927.

SUMMARY.

1. In a number of determinations of the blood-sugar in fasting individuals at complete rest—made at intervals of 1–5 minutes for a period of $\frac{1}{2}$ –2 hours—I have failed to find the previously described oscillations of the blood-sugar curve, either in normal individuals, in whom I found an almost horizontal curve, in insulin- and diet-treated diabetics, in whom I generally found a rising curve, or in diabetics merely treated with diet, in whom I found a falling curve, and in a diet-treated diabetic with advanced kidney insufficiency, in whom I found an almost horizontal blood-sugar curve.

2. In no instance did I find any “oscillations” in non-diabetics after ingestion of glucose or in diabetics at different times of the day after ingestion of food or administration of insulin.

3. I did not succeed in obtaining uniform blood-sugar curves on different days after ingestion of the same amount of glucose, although the experiments

were carried on for some time during which the individuals had plenty of fairly uniform mixed food. On the other hand, the amount of glucose eliminated in the urine in 2 hours was found to be about the same each day.

4. In a single instance I succeeded in obtaining uniform blood-sugar curves after ingestion of glucose on three different days. This was in a patient who on each day had about the same amounts of food, salts, liquid, etc.

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