CI. OBSERVATIONS ON THE RENAL THRESHOLD FOR GLUCOSE.

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IN the course of a recent investigation on the blood-glucose changes in general anaesthesia, certain observations were made which have a direct bearing on the question of the so-called renal threshold for glucose.

The renal threshold may be defined as being that level or concentration of sugar in the blood which has to be reached or exceeded before any easily recognisable quantity of sugar will appear in the urine. The idea of a renal threshold for a substance presupposes that until a certain concentration shall have been reached in the blood none will appear in the urine.

The prevailing opinions on this subject may be briefly summarised as follows: Macleod [1926] considers the renal threshold for sugar to lie between 0.160 % and 0.180 %; Todd [1923] from 0.170 % to 0.180 %; MacLean [1925] from 0.160 % to 0.170 %; de Wesselow [1925] regards the normal as 0.180 %, but he recognises considerable variations above and below this figure. Host [1925], in an interesting study on carbohydrate tolerance in pregnancy, has shown that, while early in pregnancy the renal threshold is normal, later on the threshold falls and permits glycosuria to occur independently of hyperglycaemia. Goto and Kuno [1921] placed the upper level of the renal threshold at 0.170 %, but they were unable to state the lower level. Benedict, Osterberg and Neuwirth [1918] deny the significance of a renal threshold, stating that their results (on two normal men) indicate that the threshold doctrine should be abandoned. Most of the foregoing workers have based their conclusions generally on studies of carbohydrate tolerance, or on the giving of standard doses of glucose; in other words, their studies are based on the behaviour of exogenous glucose.

Certain difficulties stand in the way of a correct estimation of the renal threshold: (a) even when blood and urine are removed as nearly at the same time as possible they cannot be considered as simultaneous specimens, (b) while a blood-sugar curve is falling the relationship between the sugar concentration in the blood and in the urine may be quite different from what it is while the curve is ascending, (c) the rate of urine formation is an unknown and variable but important factor, (d) it is difficult (unless blood is removed very often, e.g. at 2-minute intervals) to make quite certain about the highest point of a curve, e.g. after a glucose meal, or during or after anaesthesia.

METHOD OF INVESTIGATION.

It was decided to approach this subject from a different view-point, and to study the behaviour of endogenous, as opposed to exogenous, sugar in the blood. For some time it has been generally known that a marked hyperglycaemia may be caused by the administration of a general anaesthetic, such as chloroform or ether, the hyperglycaemia being presumably a manifestation of the glycogenolytic action of the anaesthetic which causes a "mobilisation" in the sugar depôts of the body. The source of the hyperglycaemia is thus endogenous, unlike that caused by a glucose meal.

The method of investigation chosen was as follows. Forty-four successive subjects, for operation under general anaesthesia by ether or chloroform-ether mixture, had their blood-sugar estimated at intervals of 15–20 minutes, before, during and after anaesthesia. The cases were not selected in any way, and none of them was known to suffer from diabetes or from renal trouble. The variety of the lesions for which operation was performed was characteristic of that found on the surgical side of any large general hospital. In the case of each patient a blood-sugar curve was drawn up, and the curve in Fig. 1

Fig. 1.

(A) Blood-sugar curve of case No. 3.

A. W., *aet.* 35 years. Hydatids in liver.

Open ether anaesthesia for 70 minutes.

Sugar absent from urine both before and after operation.

This curve, which is quite typical of the blood-sugar alterations in anaesthesia, may be compared on the same scale with

(B) Blood-sugar curve after 50 g. glucose meal as carried out by MacLean [1925].

(case 3) is characteristic of the curves in the 44 cases under consideration. On this graph there is also shown, for comparison, the curve of the blood-sugar after a 50 g. glucose test meal in normal individuals as carried out by MacLean [1925]. All the essential details, such as nature of the anaesthetic chosen (mainly ether), period of administration, nature of disease and of operation,

age of patient, etc., were noted and tabulated. In addition, the first urine passed after recovery from the anaesthetic was collected and examined for sugar by (1) the fermentation test, and (2) Bertrand's modification of Fehling's test. The pre-operative urine was also examined for sugar and in each case was found to be negative. The initial and maximum blood-sugar percentages were noted, and, in addition, an approximate estimate was made of the length of time during which the blood-sugar might reasonably be considered to be at a hyperglycaemic level. This level was fixed arbitrarily at 0.180 %.

The essential results are shown in Table I.

Table I. *To show increase in blood-sugar due to anaesthesia, the period in minutes during which the blood-sugar was above 0.180 %, and the presence or absence of post-operative glycosuria.*

Number in series	% B.S. before opera- tion	Maxi- mum % B.S.	Minutes above 0.180 %	Sugar in urine	Number in series	% B.S. before opera- tion	Maxi- mum % B.S.	Minutes above 0.180 %	Sugar in urine
1	0.177	0.297	100	+	23	0.109	0.187	5	+
2	0.122	0.241	10	+	24	0.143	0.253	200	+
3	0.083	0.222	220	-	25	0.160	0.181	.	+
4	0.115	0.196	.	+	26	0.095	0.187	15	+
5	0.146	0.386	250	-	27	0.090	0.184	.	-
6	0.160	0.216	45	+	28	0.100	0.211	35	-
7	0.146	0.181	.	+	29	0.106	0.156	.	+
8	0.137	0.206	60	-	30	0.100	0.287	50	+
9	0.184	0.227	30 +	+	31	0.050	0.143	.	+
10	0.100	0.216	5	+	32	0.118	0.156	.	+
11	0.150	0.184	5	+	33	0.075	0.181	.	-
12	0.120	0.181	.	-	34	0.118	0.175	.	+
13	0.093	0.243	140	-	35	0.098	0.133	.	+
14	0.118	0.156	.	+	36	0.165	0.206	25	-
15	0.175	0.320	200	+	37	0.110	0.175	.	+
16	0.141	0.156	.	+	38	0.143	0.193	15	-
17	0.162	0.266	50	-	39	0.118	0.137	.	+
18	0.088	0.214	10	-	40	0.112	0.150	.	+
19	0.099	0.137	.	+	41	0.106	0.237	60	+
20	0.109	0.225	200	+	42	0.037	0.193	5	+
21	0.109	0.227	45	+	43	0.110	0.175	.	-
22	0.106	0.147	.	-	44	0.191	0.291	180	+

DISCUSSION.

It is necessary now to examine this table in detail. Of the 44 cases 30 showed glycosuria and 14 did not.

(A) Of the 30 glycosuric cases, in 11 the blood-sugar never reached 0.180 %, *i.e.* in 37 % of cases sugar was excreted by the kidney at a level below the normal threshold value. Of the 14 cases where no sugar was excreted, in 12 cases (*i.e.* in 86 %) the blood-sugar had risen above the normal threshold of 0.180 %. Thus 37 % in the first case and 86 % in the second do not seem to accord with the doctrine of the renal threshold. It may be objected, however, that in a number of cases the blood-sugar may have been above 0.180 % for such a short period that practically no sugar would be excreted in that time. To overcome this legitimate objection a further analysis has been made.

(B) Taking those cases where the blood-sugar as shown on the curves

lay above 0.180 % for over 20 minutes one finds that of 17 such cases in 7 (*i.e.* 41 %) there was no glycosuria—still too high a percentage to permit the wholehearted acceptance of this theory. Further, of the 13 cases where the blood-sugar was continuously under 0.180 %, 11 were found to excrete sugar, *i.e.* 87 %.

Therefore, when an arbitrary average figure of 0.180 % is taken as the renal threshold for sugar, and when the results are considered with relation to that figure, one fails to get any weighty evidence in favour of the theory and finds much to gainsay its validity.

(C) If, instead of taking the renal threshold as 0.180 %—a fixed level—one considers only those cases outside the average range of renal thresholds as given by the workers quoted earlier—say 0.160 % to 0.190 %—then the findings are as follows. Of 30 cases of glycosuria, in 14 the blood-sugar was above 0.190 % and in 7 it was below 0.160 %, *i.e.* 14 are in conformity with the theory and 7 are against. Of the 14 sugar-negative cases 9 had a blood-sugar above 0.190 %, and 4 below 0.160 %. This gives 4 cases in consonance with the theory compared with 9 against it.

In other words, no matter how the foregoing table is analysed, whether the renal threshold is taken as a fixed level of 0.180 %, or as a fixed range of from 0.160 % to 0.190 %, and whether the time factor is included or omitted, no positive substantial evidence can be given to support the theory. Rather may it be said that the weight of the evidence is all against it. Case No. 5, for example, had a blood-sugar curve which rose from 0.146 % to 0.386 %, received an anaesthetic for 85 minutes and then a rectal saline with 5 % glucose, and had a blood-sugar concentration over 0.200 % for over 4 hours, and yet the first urine passed when consciousness was regained neither reduced Fehling's solution nor fermented with yeast.

The deduction made therefore from this analysis is that the results in half of the cases examined do not accord with the doctrine of a renal threshold for sugar of about 0.180 %. When, in addition, it is recollected that traces of sugar or related carbohydrates can be demonstrated in normal urine, a further doubt is thrown upon the validity of the theory, so far as sugar is concerned. The nature of the evidence here adduced, while not consistent with the present idea of a sugar threshold, is not sufficiently strong to enable one to submit another theory as attractive, but it demonstrates the need for some re-statement. For the moment, then, it is suggested that the present position should be summarised thus. The renal threshold for sugar, if there is one, is a much more variable factor than is generally supposed. Under the influence of an anaesthetic, it varies greatly between one normal person and another. It even appears to change during the course of a pregnancy [Host, 1925]. For all the evidence to the contrary, it may even vary frequently to slight degrees in the normal person at different times and in different circumstances. No physiological fluids in the body have an absolutely constant composition, but appear to be influenced, if only slightly, by various physical and metabolic

processes and influences in the attempt to maintain a condition of equilibrium. The renal threshold for sugar is not unlikely to be one such varying factor.

SUMMARY.

An investigation is described carried out with the object of determining the relationship between post-anaesthetic glycosuria and the blood-sugar changes due to the anaesthetic. The explanation of the results obtained in terms of the doctrine of the renal threshold for sugar at about 0.180 % proving unsatisfactory, it is suggested that this theory requires re-statement, if not, indeed, abandonment.

This investigation, which was suggested to me by Prof. E. P. Cathcart, F.R.S., was carried out in the biochemical laboratory of the Wolverhampton and Staffordshire General Hospital by kind permission of Dr S. C. Dyke, Pathologist to the Hospital, for whose friendly advice and criticism I am much indebted. Mr Deanesly, B.Sc., F.R.C.S., and Mr Cholmeley, F.R.C.S., Honorary Surgeons to the Hospital, kindly accorded me every facility in their theatres and wards, while all members of the anaesthetics staff gave me their cordial co-operation.

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