This work was assisted by a grant from the Medical Research Council, to whom my thanks are due. I wish to express my thanks to Professor Mellanby for permission to publish these cases, which were under his care at the Royal Infirmary, Sheffield.

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REPORT ON THE RESULTS OF EXAMINATION OF NINE CASES AFTER THE ORAL INGESTION OF 1,000 GRAMS OF GLUCOSE.

BY

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It has been stated by different authorities that it is impossible to make a normal person pass sugar in the urine after the oral ingestion of glucose.

The leak point of the kidney for glucose is now generally recognized as being between 0.16 and 0.18 per cent. MacLean¹ states that the hyperglycaemia resulting from the ingestion of carbohydrates appears, in the normal individual, to be limited to about this level, the threshold level for glucose, and cannot easily, if at all, be forced above it. He also goes on to state that in this fact lies the explanation of the difficulty in provoking glycosuria in the normal individual by giving glucose, a difficulty referred to in several recent publications. Later on in the same book² he quotes Taylor, who, as the result of experimental work,³ stated that "in the majority of healthy males there is no limit of assimilation of glucose; glycosuria does not occur following the largest possible ingestion of pure glucose." These observers in five instances gave doses of 500 grams of glucose, with the production of glycosuria in one case only.

Shapland,⁴ commenting on this subject, states that—

A striking phenomenon in the curve of the healthy subject is the intervention of the storage mechanism, directly the blood sugar concentration approaches the normal renal threshold for sugar. This storage mechanism is so efficient that even if sugar ingestion is pushed to the limit of digestive tolerance, it is rarely possible to produce a demonstrable glycosuria in a normal subject. It is indeed doubtful if alimentary glycosuria can occur in perfect health. Should it occur in a subject with a normal renal threshold for sugar, it indicates a defect in dealing with excess of carbohydrate, and, therefore, the patient should be regarded as a potential diabetic.

Up to the present all attempts at giving doses of more than 500 grams of glucose have failed, owing to the nausea and vomiting which were induced. It occurred to me that, as the native races of Natal are fond of sugar, it might be possible to induce them to take larger doses than those previously recorded. Acting on this assumption nine natives were examined. In each case an ordinary glucose tolerance curve was first done in order to eliminate any cases in which there might be any disturbance of the glycogen-storing power of the liver. For this the usual dose of 50 grams of glucose was employed.

MacLean's method of estimating the blood sugar was employed throughout the investigation, and the urine tests were made with Benedict's solution. It will be seen from examination of the charts that, with the exception of Cases 3 and 5, a normal glucose tolerance was found. Cases 3 and 5 each showed a maximum blood sugar concentration of 200 mg. per 100 c.cm. of blood. I think that it may be assumed that these two readings are within the limits of experimental error. Each patient was then given a dose of 1,000 grams of glucose, and in each case this huge dose was swallowed without any nausea or vomiting. Cases 1, 5, 6, 7, and 9 show a distinct rise in the blood sugar, and a definite glycosuria. Examination of the charts will show that the glycosuria varied from a trace up to 2 per cent. The hyperglycaemia varied within rather wider limits.

This series of cases, though small, shows definitely that the ingestion of huge doses of glucose strains the glycogen-storing capacity of the liver to its fullest extent, and that there is then a certain degree of overflow.

During the course of this investigation I discussed these cases with Professor MacLean, who pointed out that in his opinion the interesting point was that some of the cases passed sugar in the urine with a blood sugar content which was lower than that which is ordinarily accepted as the normal excreting level. (See Cases 2, 3, 4, and 8.) It

In each of these charts the continuous curve shows blood sugar after 50 grams of glucose; the interrupted curve shows blood sugar after 1,000 grams of glucose.

Chart 1.

Chart 2.

Chart 3.

Chart 1 (Case 1).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil. After 1,000 grams of glucose: 1 hour, trace; 2 hours, 1½ per cent.

Chart 2 (Case 2).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil. After 1,000 grams of glucose: 1 hour, nil; 2 hours, 1 per cent.; 8 hours, 2 per cent.; 13 hours, 1 per cent.

Chart 3 (Case 3).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil. After 1,000 grams of glucose: 1 hour, nil; 2 hours, trace; 14 hours, trace.

Chart 4.

Chart 5.

Chart 6.

Chart 4 (Case 4).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil. After 1,000 grams of glucose: 1 hour, trace; 2 hours, 1 per cent.; 6 hours, 1½ per cent.; 18 hours, 1 per cent.

Chart 5 (Case 5).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil; 3 hours, nil. After 1,000 grams of glucose: 1 hour, nil; 2 hours, 1 per cent.; 3 hours, 2 per cent.; 4 hours, 2 per cent.

Chart 6 (Case 6).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil. After 1,000 grams of glucose: 1 hour, trace; 2 hours, 1 per cent.; 6 hours, 1½ per cent.; 18 hours, trace.

Chart 7.

Chart 8.

Chart 9.

Chart 7 (Case 7).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil; 3 hours, nil. After 1,000 grams of glucose: 1 hour, nil; 2 hours, trace; 3 hours, 1 per cent.

Chart 8 (Case 8).—Urine after 50 grams of glucose: 0 hour, nil; 1 hour, nil; 2 hours, nil. After 1,000 grams of glucose: 3 hours, trace; 16 hours, 1 per cent.

Chart 9 (Case 9).—Urine after 50 grams of glucose: 1 hour, nil; 2 hours, nil; 3 hours, nil. After 1,000 grams of glucose: 1 hour, nil; 2 hours, 1 per cent.; 7 hours, trace.

was interesting also to note that in some cases the glycosuria persisted for periods up to eighteen hours after the ingestion of the glucose.

In view of the information derived from these experiments it is interesting to review again the current views on alimentary glycosuria and renal glycosuria. Cammidge⁵ admits that if the glycogenetic powers of the liver are exceeded a portion of the carbohydrate derived from the food may enter the peripheral circulation, and so produce hyperglycaemia and glycosuria. In this way, he states, it

is possible to account for the glycosuria produced by large doses of sugar, even in healthy people.

Graham⁶ states that a study of the blood sugar in cases of so-called alimentary glycosuria and severe diabetes does not suggest that there is any difference between the two types. In both the machine which regulates the taking up of the sugar from the blood is only out of action to a greater or less extent, the tissues are unable to burn sugar, which therefore floods the blood and is excreted in the urine.

Commenting on this series of investigations, Professor MacLean suggested that in the cases where the normal renal threshold was not exceeded, but where glycosuria was found, there might be some mechanism which lowered the normal threshold in order to eliminate the excessive quantity of sugar ingested. Cases 2, 3, and 4, and possibly 8, show that it is not necessary to have hyperglycaemia before glucose is passed in the urine, while in Cases 1, 5, 6, 7, and 9 a hyperglycaemia as well as a glycosuria was demonstrated.

The investigation was carried out on natives in the Mental Hospital, Pietermaritzburg. It might be contended that these subjects were not normal. I maintain, however, that the normal glucose tolerance, after 50 grams, shown by the cases eliminates any possibility of there being any defective power of glucose storage due to their mental condition. I have come to the tentative conclusion that in normal persons there is present in the kidney a hypothetical mechanism which is brought into play when huge doses of glucose are given. By this mechanism the kidney can eliminate the excess of sugar in the urine without increasing the blood sugar content. If this is so, then it would be possible to explain renal glycosuria as either an absence of this hypothetical mechanism or else as an impairment of it.

SUMMARY.

Nine cases showing a normal glucose tolerance were examined after the administration of 1,000 grams of glucose.

Five of these cases showed a hyperglycaemia with a corresponding glycosuria. Four of the cases showed no hyperglycaemia, but showed a glycosuria varying from a trace to 2 per cent. Therefore, these cases passed sugar in the urine at a leak point which is below what is considered to be the leak point of the normal person. Seven of the cases continued to pass sugar in the urine for varying periods up to eighteen hours after the blood sugar had returned to normal limits.

I wish to thank Dr. Egerton Brown, superintendent of the Mental Hospital, Pietermaritzburg, for his courtesy and consideration during the investigation, and also Dr. J. D. Montgomery for her help in the blood sugar estimations.

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¹ MacLean: *Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes*, p. 21. ² *Ibid.*, p. 54. ³ *Journ. Biol. Chem.*, 1916, 25, 173. ⁴ *Lancet*, September 18th, 1925, 591. ⁵ Cammidge: *New Views on Diabetes Mellitus*, p. 83. ⁶ Graham: *The Pathology and Treatment of Diabetes Mellitus*, p. 66.

A NOTE ON ETHER CONVULSIONS.

BY

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IN view of the interest aroused recently in convulsions occurring during ether anaesthesia, the following case is recorded as one in which impurities in the ether were a causative factor in the condition.

A girl, aged 8 years, was admitted to the Children's Hospital, Birmingham, on April 28th as a case of acute abdominal crisis. Careful inquiry failed to elicit any previous history of epilepsy either in the child or in the parents. On admission she presented a very toxic appearance and marked pyrexia, although the symptoms were only of a few hours' duration. Immediate laparotomy was performed at 11.30 p.m. No morphine was given before operation, but atropine sulphate 1/100 grain was administered according to routine half an hour previous to it.

Operation.—Anaesthesia was induced by a mixture containing two parts of ether to one of chloroform, and open ether sequence. The child passed quietly through the opening stages, and all

was proceeding comfortably until the intestines were handled. Although deeply anaesthetized she began to show distress, indicated by jerky respiration and a slightly greyish tinge. Various measures were tried at this stage to combat the difficulty—namely, air breathing alone, deeper anaesthesia, and oxygen administration together with ether. As a result her colour improved, and gradually the breathing became more regular, so ether alone was resumed. In a short while twitching of both eyebrows occurred, and the facial muscles next became involved; the eyeballs remained stationary with the pupils fixed and widely dilated. These myoclonic movements were rapid and continuous, at the rate of, approximately, seven per second. In turn the left arm, abdominal muscles, trunk muscles, leg and right arm muscles were involved. The rate of twitching became less and the amplitude of movement increased. Until the skin sutures were inserted periods of generalized convulsions alternated with briefer intervals of flaccidity. The jactitation of legs and abdomen was of sufficient magnitude to throw off instruments which were laid there, and to interfere with peritoneal and muscular suture. Continuous oxygen through an airway—which latter had been used throughout—had no effect on the convulsive movements. The ether-chloroform mixture was also tried for about ten minutes during the later part of the operation, and this coincided with the onset of intermittent but more powerful convulsions.

Condition Found at Operation.—No free pus was found, but there was hyperaemia of the lower abdominal peritoneum. The appendix was bound down to the posterior wall of the caecum, and therefore was not removed, since the caecum could not be mobilized. A tube was left to drain the pelvis, and later a sero-purulent discharge issued, from which pneumococci were isolated in culture. The operation took approximately forty-five minutes. Convulsions persisted for about thirty minutes. The optic fundi examined at the close of the operation revealed no abnormality. Before leaving the operating table the patient showed profound exhaustion as a result of the continued convulsions, the pulse rate having risen from 140 to 180 per minute, with a coincident marked fall in pulse volume.

Subsequent Progress.—After leaving the theatre at 12.15 a.m. the patient remained quiet for half an hour; a second series of convulsions then occurred. They were, as before, epileptiform, and generalized in distribution. This time they lasted for twenty minutes, being controlled by a small rectal dose of potassium bromide and chloral hydrate. After a free interval of twenty-five minutes she was again seized by an attack, lasting for twenty minutes, during which time a further dose of potassium bromide and chloral was given. At 2.15 a.m. a fourth and last series of convulsions occurred after a free interval of twenty-five minutes. This time the spasms were of mild degree and confined to the right side. Consciousness was not regained in the usual manner afterwards, but the patient had a restless night and was very dazed.

During the following twenty-four hours she only vomited twice. For forty-eight hours afterwards there was marked delirium and restlessness, but, judging from the high temperature and pulse rate, this might have been due to the virulence of the infecting organism. The patient has since made gradual but good progress towards recovery.

COMMENT.

By a coincidence a short article on tests for ether impurities appeared in the *Lancet* of the same date as the above-described case. E. B. Robinson¹ of Manchester University describes two tests as advocated by W. Wobbe.² One is for the detection of acetaldehyde by means of an alkaline-ammoniacal solution of silver nitrate; the second test is for the presence of peroxides by means of a reagent consisting of potassium iodide and phenolphthalein.

I am indebted to Dr. Hickmans, biochemist to the Children's Hospital, who investigated samples of the ether administered in the above case, and nine other sample bottles from the same batch. The ether employed in the present case was a new bottle, which was only opened shortly before use, and had been kept in dark storage since it was received from the makers in April, 1928.

The nine other bottles, taken at random from stock, failed to respond to either test, whereas the bottle of ether used at operation gave a strongly positive reaction to the presence of acetaldehyde and peroxides. Moreover, when a small sample of ether from the implicated bottle was poured into the palm of the hand and allowed to evaporate, a noticeably pungent acrid smell was noted; whereas the other samples merely left a clean, sweet, ether odour.

It is necessary, I think, to mention here that the first test solution is more unstable than hinted at by E. B. Robinson. When the reagent A (the alkaline solution of silver nitrate) and the tested ether mixed with it were poured away, on the day following the test, a violent explosion occurred in each case, a biochemist being temporarily disfigured by spots of black silver stain. If the solutions are poured away immediately after the conclusion of the test all is well.