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On the Glucose Tolerance Test in Sprue.

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An important finding in sprue (S.) is the flat curve produced by the peroral glucose tolerance test. The cause of this has not been made clear, although most observations point towards insufficient absorption.

Himsworth has shown that carbohydrate is the sole dietary factor affecting the curve in the glucose tolerance test. High supply of carbohydrate results in an increased glucose tolerance with a flat curve, and vice versa (8). He originally held the view that the flat curve in S. was due to the patient's living mainly on carbohydrate, because of the poor absorption of fat (9), but he later abandoned this theory (10), as Thaysen's result, a low curve in the intravenous glucose tolerance test (17), has not been reproduced by others (5, 15, 16). Himsworth's theory however has been thoroughly discussed (11).

The S. patient could equally well show a decreased carbohydrate tolerance caused by reduced absorption of glucose. The RQ on a regular diet is normal (17), however, and Rothera's test is usually found negative.

Of importance to this problem is the intravenous glucose tolerance test. The curve has been found to be high and broad by some (5, 15, 16), and in one case it became more normal after glucose had been given intravenously for 43 hours (15). The combination, a flat peroral and a high intravenous curve, suggests a deficiency in carbohydrate (5, 15). Others have found the curve normal (4, 6, 7), also in the »blood glucose clearance test» (7). (McKean claims that this test is uninfluenced by previous diet (12)). Finally, some have found the curve flat (1, 13, 14, 17). Investigations resulting in a normal or a high curve, seem to be the more convincing.

The aim of this work has been to contribute to the solution of the problem by

examining whether the amount of carbohydrate in the diet is of importance to the glucose tolerance test in S.

Method.

After one week on a normal diet consisting of 80 g of protein, 85 g of fat and 225 g of carbohydrate, a glucose tolerance test was performed. Thereafter the patient had for one week a diet consisting of 117 g of protein, 85 g of fat and 42 g of carbohydrate. Rothera's test was then found to be positive. The glucose tolerance test was then repeated.

The test was performed in the morning, on fasting patients. In the peroral test the patient drank 50 g of glucose in 500 cc of water in 5 minutes. For the intravenous test a 20 per cent glucose solution was used, 0.5 g per kg of body-weight. It was given as a drip for 30 minutes (3). The intravenous test was always performed one day after the peroral. The blood sugar was determined by Hagedorn-Jensen's method, taking blood from the earlobe. The interval between the tests can be read from the curves.

1st patient. M. O. (female b. 23. 4. 1920.)

Pleurisy in 1942. In 1945 duodenal ulcer, and later moderate acid dyspepsia. Her main troubles since 1945 were periods of diarrhea with fatty stools, sore tongue, weakness, often anemia, amenorrhea for long periods and unstable weight.

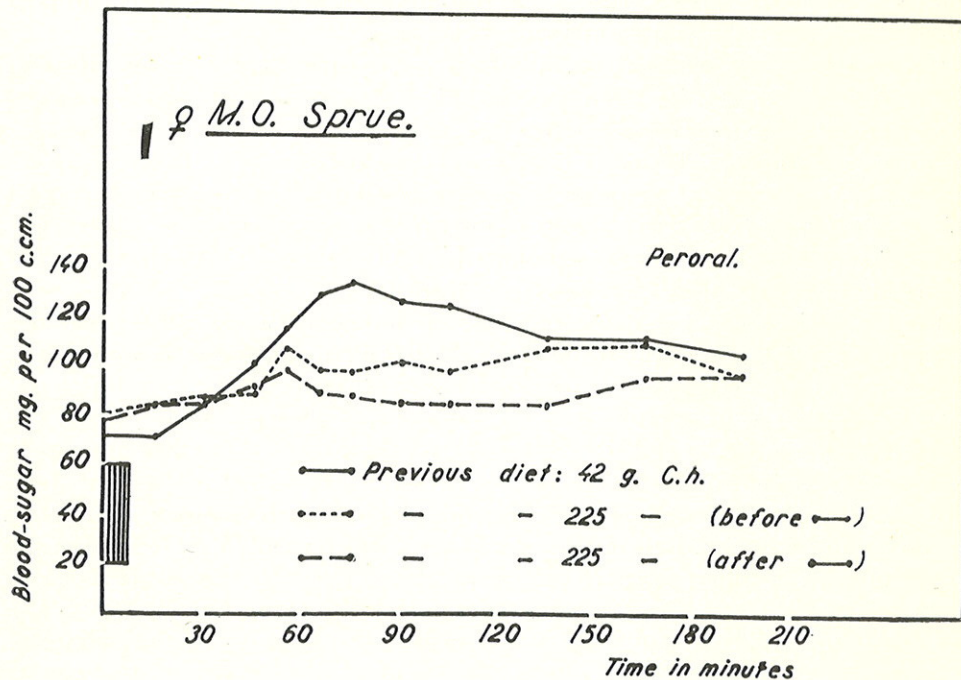


Fig. 1.

She was admitted to the hospital in January 1953. In appearance she was small and lean (H. 152 cm. W. 45 kg.) Pigmentation of the face, and smooth tongue. Blood pressure 105/75—95/55. Wassermann reaction negative. Pirquet test positive. Urine normal. Sedimentation rate 10—15 mm per hour. Hemoglobin 88 per cent, (Haldane's standard) red cells 4,910,000 per cu.mm. Red cell diameter 7.9 μ . The stools were abundant, about 250 g per day, and greasy. Microscopically split fat was found. On Schmidt's diet she excreted 19.8 g fat (87 per cent as fatty acids). Ewald's test showed acidity within normal limits. Blood chemistry: iron 0.030 mg per cent, calcium 8.8 mg per cent, phosphorus 4.2 mg per cent, albumin 4.3 g per cent, globulin 2.6 g per cent, ascorbic acid 0.39 mg per cent, prothrombin 60 per cent (Owren's P-P method) with no increase after vitamin K. X-rays of pelvis, stomach, colon and lungs were normal. X-rays of the small intestines showed changes similar to those in S.

She improved on diet, folic acid and liver extracts.

Peroral glucose tolerance test (see fig. 1) on a normal diet showed an increase of 27 mg per cent, and after a low-carbohydrate diet an increase to 62 mg per cent. After a regular diet for 9 days, the increase was reduced to 20 mg per cent.

2nd patient. M. H. (female b. 25. 5. 1894.)

Since 1945 intermittent diarrhea, worse after spring 1950, with watery diarrhea, weakness and tetanic fits reacting well to injections of calcium. The diarrhea disappeared after medication with hydrochloric acid in summer 1952, but abundant, greyish stools, swollen feet, pains in the legs and difficulty in walking were still present.

Registered at the hospital in May 1953. In appearance she was thin (H. 155 cm. W. 48 kg) and pale, with oedema of the lower legs, red tongue, large stomach, and her movements were stiff. Blood pressure 115/70. Trousseau's and Chvostek's signs negative. Wassermann reaction negative. Pirquet test positive. Urine normal, apart from *E. coli*. Sedimentation rate 14—37 mm per hour. Hemoglobin 92 per cent, red cells 4,300,000 per cu.mm. Smears showed anisocytosis. Red cell diameter 8.3 μ . The stools were plentiful, yellow-brown. Microscopically split fat was found. On Schmidt's diet she excreted 22.7 g fat (76 per cent as fatty acids) and 2.2 g N. in 24 hours. Ewald's test showed achlorhydria. Blood chemistry: iron 0.026 mg per cent, calcium 7.8 mg per cent, phosphorus 2.4 mg per cent, alkaline phosphatase 11.2—18 Bodansky units, albumin 3.4 g per cent, globulin 2.4 g per cent, prothrombin 70 per cent with no increase after vitamin K. X-rays of the stomach, duodenum, small and large intestines were negative. X-rays of the pelvis showed osteoporosis.

Quick recovery when treated with diet, folic acid and liver extract.

Peroral glucose tolerance test (see fig. 2) showed an increase of 29 mg per cent after a normal diet and 30 mg per cent after a low-carbohydrate diet. Following an intravenous test the curve was, as in normals, higher and broader after a low-carbohydrate diet.

3rd patient. J. N. (man b. 3. 6. 1903.)

Pleurisy in 1924. In January 1944 bronchopneumonia, later felt weak, cough, loss of weight. Admitted for observation in July 1944. In appearance patient was lean (H. 175 cm. W. 65 kg). Blood pressure 120/80. Wassermann reaction negative. Pirquet test positive, but TB was not demonstrated, nor at later examinations. Sedimentation rate 59 mm per hour. Urine normal. Stools normal. Blood normal. X-rays of lungs and spinal column negative. Discharged undiagnosed.

Conditions unchanged, he was readmitted in October 1944. Proteinuria, urine otherwise normal. Test for Bence-Jones' protein negative. Urea clearance 112 per cent. Intra-

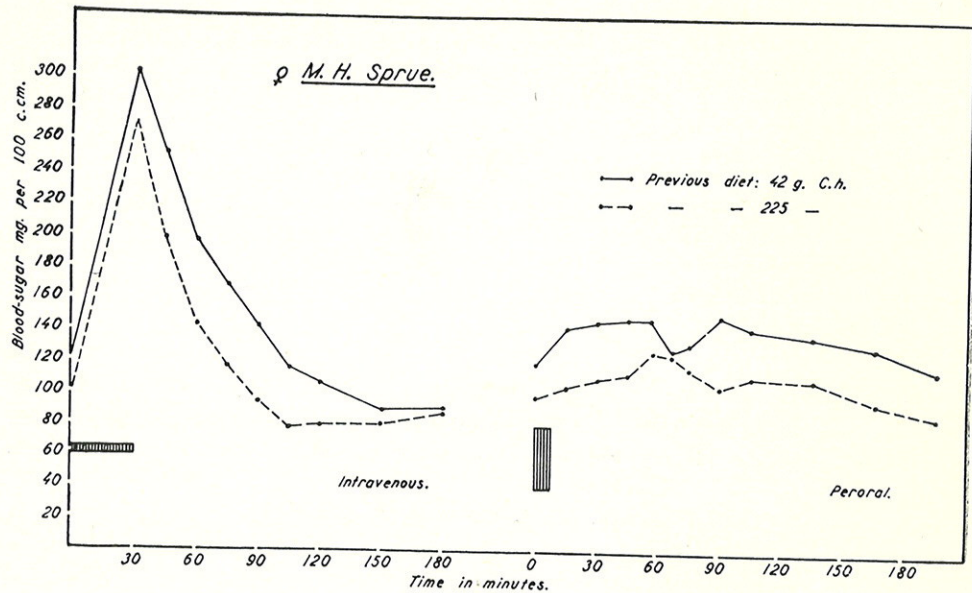


Fig. 2

venous pyelography normal. BP 90/50. (These findings remained unchanged at later examinations.) Sedimentation rate 56 mm per hour. Blood and sternal marrow normal. Complained of periods of diarrhea, but stools negative. Ewald's test within normal limits. Blood chemistry: Albumin 3.6 g per cent, globulin 3.0 g per cent. Peroral glucose tolerance test showed an increase from 90 to 117 mg per cent. Discharged undiagnosed (Addison's disease?).

Later on patient was engaged in heavy work, but complained of weakness with long periods of diarrhea. Admitted December 1949. Weight 66 kg. Distended stomach, rhagades in the corners of the mouth. Stools bulky and greasy, up to 1 kg per 24 hours. On Schmidt's diet daily excretion was 47 g fat (75 per cent as fatty acids) and 3.15 g N. (these values were practically the same at later examinations). Hemoglobin 80 per cent, red cells 4,100,000 per cu.mm. Smear showed aniso- and poikilocytosis. Sternal marrow normal. Sedimentation rate 63 mm per hour. Blood chemistry: iron 0.080 mg per cent, albumin 3.7 g per cent, globulin 2.9 g per cent, calcium 8.9 mg per cent, phosphorus 2.6 mg per cent. Peroral glucose tolerance test showed an increase from 89 to 143 mg per cent, the fasting value was reached after 80 min. X-rays of the small intestines showed changes as found in S. Treated by diet, folic acid, liver extract and calcium.

Later on became less capable of work, severe diarrhea and muscle cramps, weak, brittle nails, diminished dark vision. On admission in spring 1953, skin dry, scanty pubic and axillary hair, red tongue. Chvostek's sign positive. Hemoglobin 82 per cent, red cells 4,500,000 per cu.mm. Red cell diameter 8.1 μ . Sedimentation rate 100 mm per hour. Blood chemistry: iron 0.044 mg per cent, albumin 3.4 g per cent, globulin 4.0 g per cent, calcium 7.2 mg per cent, phosphorus 1.8 mg per cent, alkaline phosphatase 3.7-10 Bodansky units, prothrombin 65 per cent with no increase after vitamin K.

Peroral glucose tolerance test (see fig. 3) showed an increase of 39 mg per cent after a regular diet and 78 mg per cent after a low-carbohydrate diet. The intravenous test gave the same result as in previous patient.

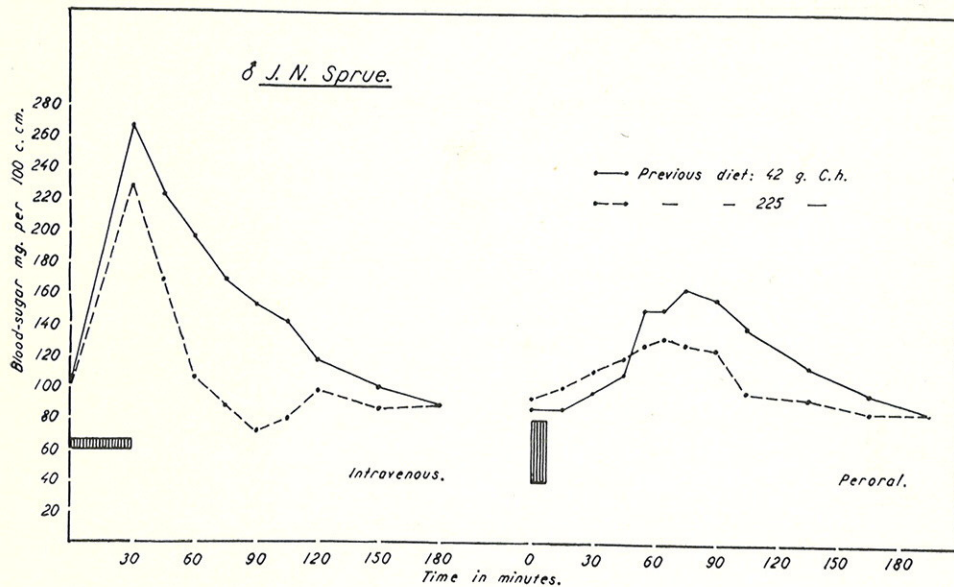


Fig. 3.

4th patient. T. H. (female b. 24. 7. 1919.)

In poor health as a child. In 1935 an epileptic seizure at the time of menarche. In the following 2 years 8—10 seizures. In 1937 a hemangioma of the occipital lobes was found (Sturge-Weber?). Face and retinae showed no hemangiomas, but in later years she developed changes in the skin on both calves. After X-ray treatment she had few symptoms, when given anticonvulsive drugs in small doses.

In 1936 diabetes was diagnosed, remaining moderate in spite of carelessness, acetonuria was never demonstrated. The quantity of insulin necessary for control varied from 0 to 28 units (Protamine Insulin). Without insulin she became thirsty, with increasing blood-sugar, up to 200 mg per cent in the morning. On the other hand patient was very sensitive to insulin, with hypoglycemia after 4—12 units.

From childhood had had periodic diarrhea, worse since April 1943. In June 1943 admitted to the hospital. She was thin (H. 161 cm. W. 43 kg). Wassermann reaction negative. Pirquet test negative. Blood pressure 95/70. Stools normal, apart from small amounts of fat on microscopic examination. Ewald's test: within normal limits. Urine: a trace of albumin, otherwise normal. Sedimentation rate 10—50 mm per hour. Hemoglobin decreased from 90 to 70 per cent and red cells from 5,700,000 to 3,600,000 per cu.mm. Blood chemistry: iron 0.015 mg per cent, ascorbic acid less than 10 mg per cent, calcium and phosphorus normal. Peroral glucose tolerance test: an increase of from 137 to 230 mg per cent, the fasting value was reached after 3 hours. X-rays of the intestines showed enterocolitis. Improved on diet, but many relapses in the following years.

In April 1949 admitted for persistent diarrhea. Weight 53 kg. Stools bulky, up to 400 g daily. On Schmidt's diet she excreted daily 25.1 g fat (78 per cent as fatty acids) and 1.3 g N. Hemoglobin 74 per cent, red cells 4,090,000 per cu.mm. Sedimentation rate 26 mm per hour. Blood chemistry: iron 0.038 mg per cent, albumin 3.8 g per cent, globulin 3.8 per cent, calcium 7.8—9.8 mg per cent, phosphorus 3.6—4.5 mg per cent, alkaline phosphatase normal, ascorbic acid 0 mg per cent, prothrombin 70 per cent. Peroral glucose tolerance test: increase from 190 to 270 mg per cent, the fasting value was reached

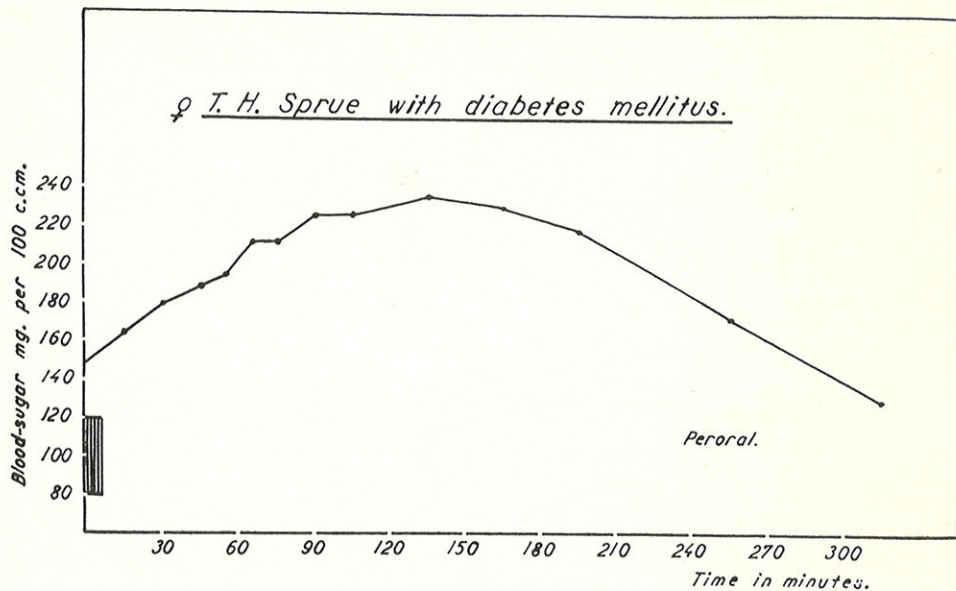


Fig. 4.

after 3 hours. BMR 110 per cent. X-rays of pelvis showed osteoporosis and of small intestines, changes as seen in S. Treated by diet, iron, calcium and vitamin D₂, but deteriorated in the following few years.

In May 1953 her weight was 49 kg. Severe periods of diarrhea, weak, unable to work. On Schmidt's diet she excreted 91 g fat daily (75 per cent as fatty acids) and 4.4 g N. Hemoglobin 78 per cent, red cells 4,180,000 per cu.mm. Prothrombin 30 per cent, with no increase after vitamin K. X-rays of the small intestines were unchanged. Improved under usual treatment.

Peroral glucose tolerance test (see fig. 4) showed an increase of 87 mg per cent the curve being of the diabetic type. (The test was done 12 days after discontinuation of insulin. Diet: 60 g of protein, 60 g of fat, 120 g of carbohydrate).

Conclusions and Summary.

1. After a low-carbohydrate diet the peroral glucose tolerance test showed in patient 1 and 3 a higher and broader curve, surpassing the borderline of 40 mg per cent. In patient 1 the curve flattened again on a normal diet. In patient 2 the curve was flat even on a low-carbohydrate diet.

After a low-carbohydrate diet the curves did not change in the direction of normal, but more in the direction of »diabetic» curves with increased breadth (cf. the curve for patient 4, who has S. as well as diabetes). The same is seen in normals (8). The results therefore seem to be in opposition to the view that the flat curves in S. are due to increased carbohydrate tolerance, caused by high supply of carbohydrate.

2. The intravenous glucose tolerance test is probably normal after a regular

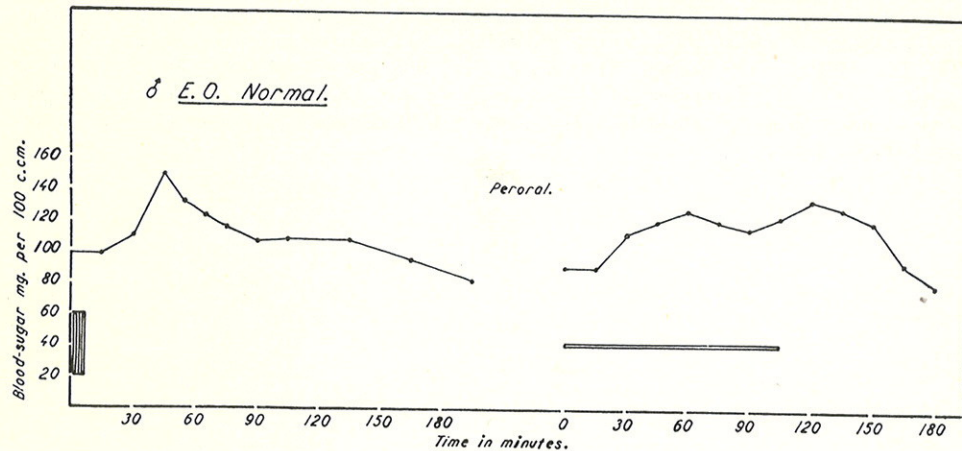


Fig. 5.

diet, and the curve higher and broader after a low-carbohydrate diet, as in normals. The results, therefore, do not point towards any abnormality in the blood sugar regulation, and are consistent with the theory of reduced absorption as a cause of the flat curves.

There is no doubt that in *S.* glucose *can* be resorbed. What is abnormal in *S.* seems to be a reduced speed of absorption, possibly resulting in a decrease in the absorbed amount. As an illustration (but evidently no proof) of this view is presented a curve from a normal man (on a normal diet) having had 50 g of glucose in 500 ml of water, 25 ml given per os every 5 min. for 100 min. Such a slow supply produces a somewhat flat curve (in this case an increase of 44 mg per cent), and the *S.* curve can in this way, therefore, probably be imitated in normal people. (The conditions will not be identical, as the *S.* patient presumably is losing some glucose due to the slow absorption).

3. In cases where a flat curve is *not* found in *S.*, this may be due to carbohydrate intolerance caused by reduced supply or absorption of carbohydrate. In these cases it may therefore be justified to repeat the test after some days of high supply of carbohydrate, if necessary intravenously.

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