CHANGES IN BLOOD PHOSPHATE AFTER INGESTION OF GLUCOSE AND FRUCTOSE IN SPRUE

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When normal subjects are given glucose by mouth there is a fall in the plasma inorganic phosphate. This fall is related to the metabolism of glucose and not to its actual absorption, for it is also observed when glucose is given intravenously and after the injection of adrenaline or insulin (Peters and Van Slyke, 1931). Moreover, the absorption of glucose without utilization, as in severe diabetes (Hartman and Bolliger, 1925), does not lead to a fall in inorganic phosphate. The changes in serum inorganic phosphate during glucose absorption in sprue have been investigated by Hanes and Reiser (1940), who found that there was an abnormally small drop in the serum inorganic phosphate in sprue patients when glucose was given by mouth but that the normal drop occurred when the glucose was given intravenously. These findings seemed to reflect the poor absorption of glucose known to occur in sprue. Hanes and Reiser also found that the urinary excretion of phosphate after glucose ingestion is greater in sprue patients than in normals. The object of the work described below was to investigate the cell as well as the plasma changes in phosphate with both glucose and fructose; if the changes with fructose were to parallel those with glucose in normals, the relative changes after glucose and fructose ingestion in sprue patients could be used in comparing the absorption of glucose and fructose in sprue. This oblique method of approach is made necessary by the fact that blood-fructose curves after a fructose meal are an unsatisfactory measure of absorption, in that the increment in blood fructose even in normal people is of the order of only 10 mg. per 100 ml. and depends very largely on the efficiency of the liver in converting fructose to glucose rather than on the speed of absorption. These considerations make it difficult to accept the claim of Maegraith *et al.* (1945), based on blood-fructose curves, that fructose absorption is normal in sprue.

Method of Investigation

Five normals and four sprue patients were studied. All the patients had steatorrhoea and had recently lost weight, but none of them had watery diarrhoea. In each subject observations were made after the ingestion of glucose (50 g.) and of fructose (50 g.) respectively. Specimens of blood were taken into oxalate tubes, one before the meal and four at half-hourly intervals for two hours after the meal. Trichloroacetic acid filtrates of the whole blood were made immediately, and for observations on the plasma the oxalated blood was centrifuged without delay. The estimations were done together at the end of the two-hour period. The following data were obtained for each experiment: (1) Plasma inorganic phosphate and (2) whole-blood inorganic phosphate, using the Bodansky (1933) method; (3) fasting and hourly urinary excretion of inorganic phosphate up to two hours, using the Briggs (1922) method; and (4) the packed cell volume. In addition data were obtained in three of the sprue patients and three of the normals on the "ester" phosphate changes, using Briggs's method.

Fasting blood values were usually determined from the mean of duplicate observations. The estimated error of

a single determination was 2% for the inorganic phosphate, using a visual colorimeter, and 1% for the "ester" phosphate, using a Klett-Summerson photoelectric colorimeter. The inorganic phosphate content per 100 ml. of red cells was calculated from the figures for the plasma and whole

Graphs showing results of colorimetric estimations of (A) glucose and (B) phosphorus in the blood of a normal subject (N5) after oral administration of 50 g. of glucose.

blood and the haematocrit reading. The whole-blood "ester" phosphate content was calculated as the difference between the whole-blood acid-soluble phosphate and the inorganic phosphate content. Each curve consisted of one fasting value and four half-hourly observations after the meal. To compare the changes in the different curves we used the mean decrement (M.D.) of each curve defined as the difference in mg. per 100 ml. between the fasting value and the mean of the lowest three consecutive values after the meal. When the mean value rises above the fasting level the mean decrement is negative.

Fasting Values

The fasting values from the curves were analysed together with additional data obtained in another investigation. The mean values for inorganic phosphate in plasma, cells, and whole blood in normals and sprue patients are shown in Table I. The inorganic phosphate

TABLE I.—Fasting Inorganic Phosphate Content of Plasma, Cells, and Whole Blood in Sprue Patients and Normal Subjects (Mean values, mg. per 100 ml.)

	Plasma	Cell	Whole Blood
Normals	3.74 ± 0.59	2.85 ± 0.44	3.31 ± 0.34
Sprue patients	3.36 ± 0.65	3.17 ± 0.50	3.20 ± 0.47

The means for plasma and cell values are derived from 5 normals and 5 sprue patients, those for the whole-blood values from 8 normals and 10 sprue patients. Determinations were made on each subject twice, on different days.

level is normally higher in the plasma than in the cells, and this difference is found in the present small series. On the other hand, no significant difference was found between the plasma and the cell levels in the sprue patients. Comparing the sprue values with the normals, the whole-blood levels are virtually the same; the mean plasma level is

lower, and the cell level higher, than the corresponding mean normal levels, but these differences are not significant.

Fasting "ester" phosphate values were determined in altogether 12 cases of sprue and 7 normals. None of the patients had diarrhoea. They were often anaemic; their mean haematocrit value was 41.1% (range 27-49%). Since about 98% of the blood "ester" phosphate is in the cells, for comparing the fasting "ester" phosphate values in sprue patients and normals they are given in terms of the cell content:

Mean Cell "Ester" Phosphate Content (mg./per 100 ml.)

Normal	..	..	..	47.56 $\pm$ 5.27%
Sprue	..	..	..	53.25 $\pm$ 5.63%
Difference of means				5.69 $\pm$ 2.74%
(P* less than 0.05 by "t" test)				

The average red-cell content of "ester" phosphate was significantly raised in the sprue patients. This finding may be due to the inclusion of cases with anaemia, for in anaemia the red-cell "ester" phosphate is often high (Guest and Rapoport, 1941). The whole-blood "ester" phosphate values did not differ significantly in the sprue patients and the normals.

Changes after Ingestion of Glucose and Fructose

1. Inorganic Phosphate Changes in the Blood

The changes in the whole-blood, plasma, and cell phosphate after the ingestion of the two sugars are shown in Table II.

cell-plasma inorganic phosphate distribution after taking the sugar than in the fasting state.

In one of the normals, N5, simultaneous observations were made on the inorganic phosphate changes in the venous and capillary blood during the absorption of glucose, to see whether the arteriovenous difference in glucose normally observed during glucose absorption is associated with the disappearance of inorganic phosphate as the blood flows through the muscles. A photoelectric colorimeter was used for the estimations, which were carried out on 0.2 ml. of blood by means of the stannous chloride reduction method. The findings (see Graphs) suggest that at least part of the fall in inorganic phosphate occurs in the peripheral circulation and is related to the disappearance of glucose from the blood into the muscles.

Sprue Patients.—In the sprue patients most of the whole-blood inorganic phosphate curves did not differ significantly from the normals. One curve with glucose (S1) and two with fructose (S1 and S4) were definitely abnormal in that they showed a rise instead of a fall in inorganic phosphate. In patient S2 the changes were relatively slight with both glucose and fructose. The cell changes were variable. The plasma changes were consistent, and for both glucose and fructose differed significantly from those found in normals. With glucose there was a slight fall in the inorganic phosphate (average M.D. +0.087), while with fructose there was no change or a rise (average M.D. -0.137). In the case of the glucose curves S3 and S4 and the fructose curve S3 the slight fall or the rise in plasma inorganic phosphate corresponded to a relatively low fasting level and not to a significantly small whole-blood inorganic phosphate fall.

TABLE II.—*Plasma, Cell, and Whole-blood Inorganic Phosphate Mean Decrements (M.D.) in Normals and Sprue Patients after Glucose and Fructose Ingestion*

	After Glucose						After Fructose					
	Plasma		Cells		Whole Blood		Plasma		Cells		Whole Blood	
	F	M.D.	F	M.D.	F	M.D.	F	M.D.	F	M.D.	F	M.D.
Normals:												
N1	3.87	0.473	2.37	0.403	3.18	0.387	4.63	0.653	2.18	-0.350	3.43	0.143
N2	3.44	0.673	2.67	0.217	3.06	0.447	4.57	0.190	3.51	-0.290	4.05	0.233
N3	3.02	0.037	3.61	0.573	3.29	0.269	2.99	-0.200	2.74	0.333	2.87	0.057
N4	3.58	0.190	2.83	0.310	3.23	0.243	3.37	0.290	2.96	0.167	3.18	0.187
N5	3.60	0.793	2.66	0.087	3.18	0.380	4.32	1.037	2.82	-0.107	3.64	0.532
Sprue patients:												
S1	4.1	0.067	2.5	-0.100	3.4	-0.033	4.09	-0.287	2.97	0.350	3.61	-0.147
S2	3.04	0.100	2.78	0.380	2.97	0.153	3.45	-0.257	3.37	0.883	3.43	0.090
S3	3.55	0.070	3.19	0.500	3.40	0.252	3.33	-0.003	3.83	0.563	3.54	0.217
S4	3.15	0.110	3.74	0.857	3.42	0.467	3.88	0	3.22	-0.007	3.53	-0.007
Mean of M.D.:												
Normals		0.443		0.283		0.345		0.394		0.067		0.230
Sprue patients		0.087		0.409		0.210		-0.137		0.447		0.041
Difference of means of M.D.		0.346		-0.126		0.135		0.531		-0.380		0.189
(normal - sprue)												
P		0.04		>0.1		>0.1		0.04		0.06		0.07

F = Fasting values.

P = The probability that the given positive or negative values respectively could have arisen by chance.

Normals.—In normals there was a consistent fall in the whole-blood inorganic phosphate with both glucose and fructose. The fall was apparently greater with glucose than with fructose, but not significantly so. The cell and plasma changes were not simply related, and the cell change might be greater or smaller than the plasma change, or even in the opposite direction, so that the changes were much more variable in the plasma and cells than in the whole blood. The direction of the cell and plasma changes appeared to depend on the relative fasting cell and plasma values. Thus in the fructose curve on subject N1 the fasting cell inorganic phosphate content was very low compared with the plasma level, and rose after taking the sugar; subject N3 had in both curves a relatively high fasting cell inorganic phosphate content, and after taking the sugar the cell content fell markedly while the plasma content changed very little with the glucose and actually rose with the fructose. In general there was much less variability in the

From the changes shown in Table II one may conclude that after the ingestion of glucose and fructose the whole-blood inorganic phosphate normally falls. There was usually a corresponding fall in the cell and plasma levels, but when either of these levels was initially low in comparison with the other the corresponding inorganic phosphate fall was reduced or absent. In sprue, with fructose as well as with glucose, the fall in the whole-blood inorganic phosphate does not always happen. A consistently diminished fall in the plasma levels was observed, but this may in some cases have been due to the plasma inorganic phosphate content being initially low relative to the cell content.

2. "Ester" Phosphate Changes in the Blood

Two glucose and two fructose curves were done on normals, and three of each on sprue patients, to estimate any changes that may occur in the blood "ester" phosphate

*P=the probability that the difference could have arisen by chance.

levels (Table III). In the normals there was a slight but consistent fall, the M.D. being about 4–5% of the fasting value. Though more difficult to detect than the 10–15% fall which occurs in the whole-blood inorganic phosphate,

TABLE III.—“Ester” Phosphate Changes after Glucose and Fructose in Normals and Sprue Patients (mg. per 100 ml. Blood)

	After Glucose			After Fructose		
	Fasting	Mean Decrement	Cell Vol. (% of Whole Blood)	Fasting	Mean Decrement	Cell Vol. (% of Whole Blood)
Normals:						
N3 ..	18.9	0.30	46	—	—	—
N4 ..	22.4	0.93	47	21.7	0.77	47
N5 ..	—	—	—	21.5	1.83	45
Sprue patients:						
S2 ..	14.9*	−0.12*	26*	18.4	−0.50	27
S3 ..	20.8	1.53	41	18.0	1.57	42
S4 ..	22.0	0.40	46	20.4	0.10	46

* These estimations were not made at the same time as the corresponding inorganic phosphate estimations.

the absolute reduction in “ester” phosphate is greater than that in inorganic phosphate, so that the inorganic phosphate fall cannot be ascribed to a change into blood “ester” phosphate.

In three sprue patients the changes were variable from case to case but similar for the two sugars: a slight rise in “ester” phosphate occurred in one patient; in the other two there was a fall, slight in one, marked in the other. The changes parallel those in the corresponding inorganic phosphate curves for whole blood.

3. Changes in the Urinary Excretion of Phosphate

Phosphorus excretion in the urine is often diminished immediately after glucose absorption (Peters and Van Slyke, 1931), but this does not always occur (Reiser, 1940). Our own results on normals showed a diminished excretion of phosphate after the ingestion of both sugars (Table IV).

TABLE IV.—Change in Excretion of Phosphate after Glucose and Fructose Ingestion (Mean Hourly Phosphate Excretion (mg./hr.) during Two Hours after Meal, as compared with the Fasting Excretion)

	After Glucose		After Fructose	
Normals:				
N1 ..	..	−16.65	..	−15.7
N2 ..	..	−10.0	..	−5.4
N3 ..	..	−9.85	..	−11.1
N4 ..	..	−15.8	..	−1.2
N5 ..	..	−12.7	..	−8.7
Sprue patients:				
S1 ..	..	−8.9	..	+16.85
S2 ..	..	+4.7	..	+1.45
S3 ..	..	+8.6	..	+4.5
S4 ..	..	+8.2	..	+13.4

The series is very much smaller than that of Bachmann *et al.* (1938), who in 25 normals found no significant change in urinary phosphate excretion after glucose and fructose. In our sprue patients there was an increased excretion of phosphate during the two hours after taking the glucose and fructose; even on the assumption that there is normally no change in excretion, the rise is significant for the fructose though not for the glucose figures.

Discussion

The results in normal subjects show that fructose ingestion is followed by blood-phosphate changes similar to those observed after taking glucose. Using the fall in the whole-blood inorganic phosphate as evidence that the sugars have been absorbed, it was found that two sprue patients had some impairment in the absorption of both

glucose and fructose. Like glucose, fructose can form phosphate esters, and a defect in phosphorylation, which Stannus (1942) thinks may be present in sprue, would be expected to interfere with the absorption of both these sugars.

Summary

The plasma, cell, and whole-blood changes in inorganic phosphate after the ingestion of glucose and fructose were investigated in five normals and four patients with tropical sprue. Observations were also made on the changes in urinary phosphate excretion, and in some of the cases on the changes in the blood “ester” phosphate.

There is normally a fall in the whole-blood inorganic phosphate after the absorption of both glucose and fructose. It usually affects both plasma and blood cells, but may be limited to either. It is associated with a fall in the blood “ester” phosphate content and is partly due to a passage of phosphate into the tissues. The normal whole-blood inorganic phosphate changes after glucose and fructose were diminished or reversed in some sprue patients, indicating a defective absorption of both these sugars. The plasma inorganic phosphate fall was abnormally small; this may have been due partly to the initially low fasting plasma inorganic phosphate levels found in some of the patients. There was a rise in urinary phosphate excretion in the sprue patients, while normally there is either no change or a fall.

No difference could be demonstrated between the absorption of glucose and fructose in patients suffering from tropical sprue.

Thanks are due to the Director of Medical Services in India for permission to publish this work, which was carried out as part of the G.H.Q. (I.) Medical Research Organization investigation on sprue. I am grateful to Major D. A. K. Black, R.A.M.C., for much helpful advice and criticism, and to Pte P. Trinder, R.A.M.C., for his technical assistance.

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At the tenth anniversary celebrations of the Empire Rheumatism Council not long ago Sir Wilson Jameson, who was deputizing for the Minister of Health, said—in appreciation rather than in complaint—that the Council had been “sometimes a thorn in the side of the Ministry.” In the annual report of the Council, now published, Lord Horder, the chairman, says that this tribute to its “nuisance value” is accepted with gratitude. The position at the date of the foundation of the Council was that only about 10% of under-privileged rheumatic sufferers had hope of effective treatment, though such treatment could have saved the majority of them from crippling disability. The Council stressed the fact that it was quite unreasonable to await the full success of research before instituting measures for dealing with treatment, and it put forward a plan for national action, a challenge which has been met with the right answer.

Writing of the new National Health Service, Lord Horder says that much has yet to be settled before the Council can definitely plan its course so as to help in every way possible; but it is known that the system suggested by the Council will be followed in principle—namely, the provision of special treatment centres in each region, with peripheral local centres linked to them. These special centres will normally be sited in association with university medical teaching schools. On the recommendation of its Scientific Advisory Committee the Council has appointed two whole-time registrars whose duty it will be to estimate the factors concerned in the causation of rheumatoid arthritis.