LXXXVIII. THE COMPARATIVE RATES OF ABSORPTION OF SUGARS FROM THE HUMAN INTESTINE.

By ROBERT ALEXANDER McCANCE[1] and KATE MADDERS.

From the Biochemical Laboratory, King's College Hospital, London, S.E. 5.

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Hoppe-Seyler [1881] and Heidenhein [1894] first drew attention to the fact that simple physical laws could not explain the absorptive phenomena in the intestine. Höber [1899] compared the rates of absorption of several sugars and salts and found that dogs absorbed galactose slightly faster than glucose. Hédon [1900] compared the rates of absorption of glucose, fructose, galactose and arabinose from a loop of rabbit's gut. He found that from a 25 % solution arabinose was absorbed most quickly and then in order galactose, glucose and fructose. From isotonic solutions glucose was absorbed most rapidly. Working with "Vella" fistulae on a series of four dogs Nagano [1902] found that the monoses showed characteristic relative rates of absorption. Galactose was most rapidly absorbed and then in order glucose, fructose, mannose, xylose and arabinose. Solutions over 10 % were not used. Hewitt [1924] compared the rates of absorption of dilute solutions of glucose, fructose and galactose from loops of gut. In rabbits no very conclusive results were obtained, but in cats glucose was absorbed much more rapidly than fructose, while galactose occupied an intermediate position. All were absorbed at equal rates after killing the intestinal mucosa by hot liquids or sodium fluoride. Cori [1925], using standard rats, administered by stomach-tube a strong solution of the sugar to be tested and subsequently killed the animals after varying intervals, and the sugar still left in the whole of the alimentary tract was estimated. This method was an improvement on the older ones in that intact animals could be employed. Large numbers of rats moreover could be used and the results averaged. Cori placed the sugars in the same order as Nagano and found their relative rates (glucose = 100) to be: galactose 110, glucose 100, fructose 43, mannose 19, xylose 15, and arabinose 9. Macleod [1929] has recently criticised one or two points in Cori's technique, and Magee and Macleod [1929] have determined the rates of diffusion of sugars through isolated oxygenated loops of rabbits' intestine. No more definite conclusions were drawn than that hexoses were absorbed more rapidly than pentoses.

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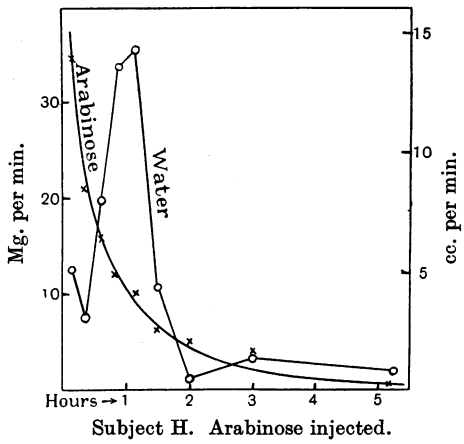
Clearly none of the methods so far described is applicable to man, but we have devised a method by which the rates of absorption of rhamnose, arabinose and xylose have been compared. These three sugars are all excreted readily by the kidney and are only comparatively slowly destroyed in the tissues. We have therefore compared the rate and amount of each sugar excreted (*a*) when injected intravenously, (*b*) when taken by the mouth.

The sugars used were naturally occurring ones and were obtained from The British Drug Houses, Ltd. The xylose and arabinose each contained 0·2 % ash and 0·2 % moisture and were at least 98 % pure. The rhamnose contained 0·3 % ash and 15·8 % moisture which was allowed for in making the weighings. Dried, it melted at 121–125°. The estimations were all carried out by McCance's methods [1926, 1929]. Three normal adult men have been the subjects, H. age 23, wt. 64·5 kg.; H.L.S. age 25, wt. 57·2 kg.; R.A.M. age 30, wt. 66 kg. The procedure on each has been identical.



Subject H. Arabinose injected.

Fig. 1. Each point is plotted in the centre of the period during which that particular specimen of urine was secreted. It indicates in mg. per min. and cc. per min. the average rate of excretion of arabinose or water over that period of time.

Experimental.

The effect of diuresis upon excretion.

Our experiments early established the fact that a moderate diuresis made little or no difference to the rate or amount of the sugar excreted. Fig. 1 illustrates this by comparing the rates of excretion of water and arabinose by subject H. The pentose was injected. Assuming the pentoses to be non-threshold bodies and that they are filtered off in the glomeruli we take this to mean that a diuresis of this degree does not involve the opening up of fresh glomerulo-tubular units to the circulating blood, but merely re-absorption of less water in the tubules [Rehberg, 1926]. Sometimes with small frequent samples of urine we have observed an increased output of sugar to accompany a small increase in urinary volume. This we have only observed when the

rate of excretion was falling, and we regard it as being technical in origin. It is not always easy to empty the bladder completely at short intervals and a small amount of urine left behind would be voided with the next specimen and explain the experimental finding.

Injection experiments.

5 g. of the sugar to be tested were dissolved in 15 cc. of distilled water and sterilised at 100°. The whole of this solution was then injected slowly into the antecubital vein, the time taken for the actual injection being 4 mins. Zero time for the experiment was taken to be 2 mins. after the injection had begun. No tourniquet was applied. The bladder was emptied just before the

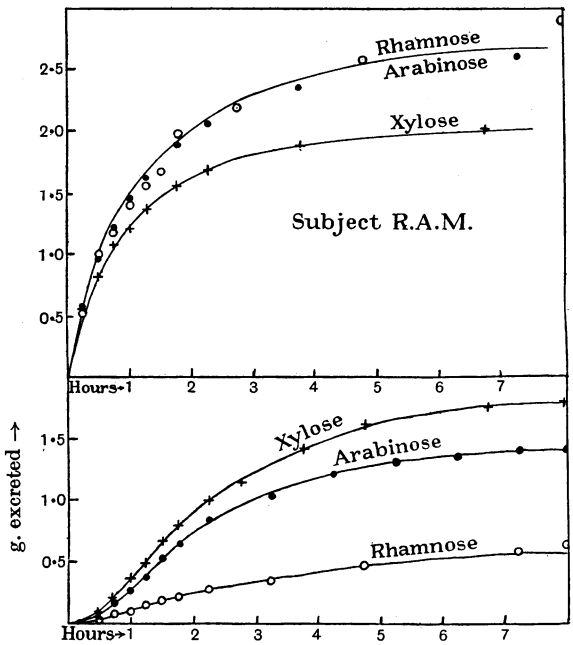


Fig. 2.

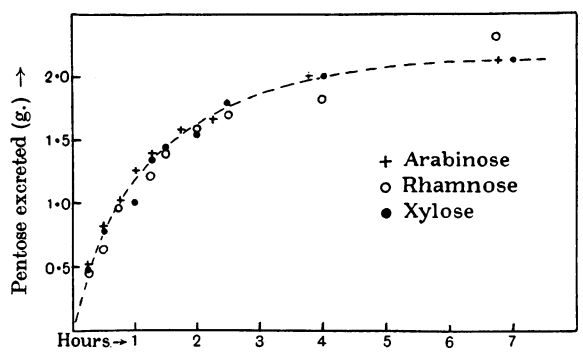
injection and again every 15 mins. for $1\frac{1}{4}$ hours: later at extending intervals up to 7 or 8 hours when the experiment terminated. These experiments always began at about 10 a.m. and the subject had had a light breakfast. Small amounts of water were drunk at intervals. A moderate lunch of cheese and bread was taken about 1.30 p.m. at which water only was drunk. Fig. 2 (upper half) shows the detailed results from one subject (R.A.M.). The excretion curves of rhamnose and arabinose are almost identical. The rate is slower and the amount of xylose excreted less than that of the other two, but the shape of the curve is the same. In the case of subject H. the excretion curves of all three sugars were superimposable and are reproduced in Fig. 3. Differences in the rate and amounts of excretion (as in the case of xylose above)

are presumably due to differences in the rate of utilisation by the tissues (see later).

There is no evidence that pentoses are stored as such in the animal body, and therefore these injected sugars can only be destroyed or excreted. The amount destroyed (or used) in any experiment can therefore be found by deducting the total amount excreted from the amount injected, *i.e.* 5 g.

Ingestion experiments.

Each subject took 5 g. of sugar by mouth and the excretion was again followed as before. After an overnight fast the subject emptied his bladder and drank 100 cc. water in which the sugar was dissolved. Urine was collected at the end of the first half hour and then for 1½ hours at 15 minute intervals. Thereafter collections were made at longer intervals up to 7 or 8 hours. Small amounts of water were taken from time to time. Fig. 2 (lower half) shows the actual results obtained from one subject (R.A.M.). These curves should be compared with those obtained from the same subject after the sugars had been injected. The initial delay in excretion shown by all three sugars is not due to the temporary delay of the solution in the stomach as will be apparent later. It should be noted that, whereas xylose is here excreted in greater amount than either of the others, less was excreted on injection.



Subject H. 5 g. injected intravenously.

Fig. 3.

Rhamnose is very poorly excreted when taken by the mouth, though readily after injection, which confirms injection experiments of Voit [1897]. On the other hand the relative amounts of these three sugars excreted by our subjects do not correspond to those of Von Jaksch [1899].

From these curves we obtain for each sugar the total amount excreted after ingestion. From the injection experiments we have obtained the characteristic ratio $\frac{\text{sugar used}}{\text{sugar excreted}}$ for each sugar. By applying it we obtain the amount used in these ingestion experiments. The amount used + the amount excreted = the amount absorbed. In this way we can calculate the amount of each sugar which has reached the tissues in the time of the experiment.

Results.

By applying this method we have obtained the following results which may be put into tabular form.

Table I.

Injection experiments.

Subject	Total amount excreted after injection of 5 g.			Total amount used			Ratio $\frac{\text{sugar used}}{\text{sugar excreted}}$		
	Rhamnose	Arabinose	Xylose	Rhamnose	Arabinose	Xylose	Rhamnose	Arabinose	Xylose
R.A.M.	2·8	2·65	2·1	2·2	2·35	2·9	0·79	0·9	1·38
H.L.S.	2·3	2·7	2·3	2·7	2·3	2·7	1·17	0·79	1·17
H.	2·3	2·2	2·2	2·7	2·8	2·8	1·17	1·27	1·27
Average	2·5	2·5	2·2	2·5	2·5	2·8	1·0	1·0	1·27

Ingestion experiments.

	Total excreted			Total used			Amount absorbed		
	Rhamnose	Arabinose	Xylose	Rhamnose	Arabinose	Xylose	Rhamnose	Arabinose	Xylose
R.A.M.	0·62	1·6	1·8	0·49	1·4	2·5	1·1	3·0	4·3
H.L.S.	0·40	1·2	1·65	0·47	0·95	1·9	0·87	2·15	3·55
H.	0·82	1·5	2·2	0·96	1·9	2·8	1·78	3·4	5·0
Average	0·60	1·4	1·9	0·6	1·4	2·4	1·2	2·8	4·3

The consistency of these results is very satisfactory. It will be noted that subject H. absorbed more of all the sugars than the others and H.L.S. less. R.A.M. absorbed intermediate amounts of each sugar. If the rate of absorption of rhamnose is taken to be 1 the comparative rates become rhamnose: arabinose : xylose, 1 : 2·33 : 3·6. We may note in passing that the very small amounts of rhamnose absorbed explain the high coefficients of utilisation found by many of the pioneers on this subject [Lindeman and May, 1896].

Experiments with rats.

We decided to repeat some of Cori's experiments on xylose and arabinose and extend them to rhamnose. The rats used were obtained from Vitamins, Ltd. and were all adult males of an inbred strain weighing between 230 and 300 g. each. Four rats were used for each sugar in two lots of two each and the procedure was as follows. 2 g. sugar were dissolved in a small quantity of distilled water and the volume was made up to 5 cc. $3\frac{1}{2}$ ins. of a No. 3 flexible rubber catheter was attached to the nozzle of a 2 cc. "Record" syringe and the whole was filled with sugar solution up to the 2 cc. mark. A rat was then lightly anaesthetised with ether, the catheter passed quickly into the stomach and 2 cc. discharged from the syringe. In this way each rat received 0·8 g. After 3 hours the rats were killed by coal gas and the whole alimentary canal was at once dissected out and placed in a beaker, covered with a little water and boiled. The intestines were then cut up into small fragments

with scissors and extracted repeatedly with boiling water. The washings were made up to 200 cc. and the sugar was estimated. The amount so found deducted from 0·8 g. gives the amount absorbed.

Note. Both Cori and Macleod have considered the possibility that the intestinal flora may utilise the sugars sufficiently fast to invalidate this method of obtaining the amount of sugar absorbed. Cori's controls show that the bacterial action is negligible.

Table II.

Sugar	Amount absorbed (g.)				Average (g.)	Comparative rates rhamnose = 1	
						Rats	Man
Rhamnose	0·04	0·20	0·07	0·15	0·12	1	1
Arabinose	0·23	0·30	0·23	0·25	0·25	2·1	2·33
Xylose	0·45	0·47	0·44	0·40	0·44	3·67	3·6

The relative rates in man have been added to the table for comparison and it is unnecessary to emphasise the agreement. The relative rates of absorption of arabinose and xylose found by Cori, when reduced to our scale become 2·1 : 3·5, results almost identical with our own.

There can be little doubt that the epithelium of the human intestine reacts to sugars in the same way as that of the rat. The relative rates of absorption of rhamnose, arabinose and xylose have been shown experimentally to be the same in both. We may assume with considerable confidence that the comparative rates of absorption of glucose, galactose and fructose found in rats will also hold in man. It is probable also that the same relative rates hold for the dog [Nagano, 1902], but our knowledge of this very fundamental relationship between sugars on the one hand and intestinal epithelium on the other is regrettably incomplete. The limited experiments on rabbits have not been consistent. We do no even know, therefore, whether this peculiar relationship holds throughout the mammalia, much less at what stage in evolutionary history it appeared.

The kinetics of sugar absorption.

1. So far we have dealt only with the total amounts of sugar excreted or absorbed. Fig. 4 now shows the varying rates of excretion of all three sugars following their ingestion by H.L.S. It is at once evident that the peak of excretion occurs about 1 hour after they have been swallowed, whatever the sugar taken and whatever percentage of that sugar is ultimately to be excreted. This we interpret to mean that these sugars are all absorbed best at the same level in the intestine and that this level is high up near the pylorus.

2. *The actual absorption curves.* It is evident that the curves of excretion shown in Figs. 2 and 4 in no way resemble the actual curves of absorption. Sugar continues to be excreted long after it has ceased to be absorbed because the amounts temporarily stored in the fluids of the body are only slowly utilised or excreted. The fact that excretion is not yet quite finished

8 or 9 hours after 5 g. have been injected is proof of this. The curves of absorption can however be constructed from the following considerations. The amount absorbed up to any given moment is equal to the sum of:

(1) the amount excreted up to that moment;
(2) the amount used up to that moment;
(3) the amount still in the "tissues" at that moment.

The first is obtained by direct estimation. The second is obtained as follows. Assuming that the rate of excretion and the rate of destruction (or utilisation) are both proportional to the amount in the body at any given time, then the ratio $\frac{\text{sugar used}}{\text{sugar excreted}}$ is a constant whatever the time. We have already made use of this ratio to calculate the total amount of each sugar used. It can be employed in the same way to calculate the amount used at any given time. The third, *i.e.* the amount in the tissues at any moment, is proportional to the rate of excretion at that moment and can be calculated from it.

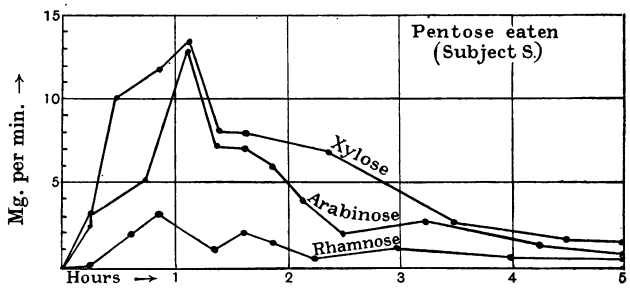
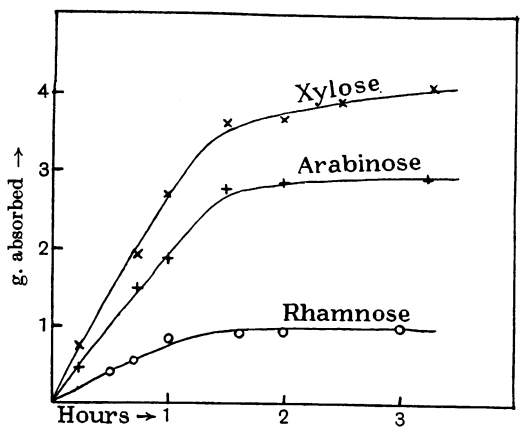


Fig. 4. Each point is plotted in the centre of the period during which that particular specimen of urine was secreted. It indicates in mg. per min. the average rate of excretion of sugar over that period of time.



Subject R.A.M.
Fig. 5.

The actual curves of absorption of subject R.A.M. are shown in Fig. 5, and should be contrasted with the curves of excretion of the same subject (Fig. 2, lower half). The exact determination of one of the points is given for

the sake of clarity. The characteristic ratio $\frac{\text{sugar used}}{\text{sugar excreted}}$ for each sugar has been determined from the smoothed experimental curves and is for xylose 1·38 and for arabinose and rhamnose 0·82.

To calculate the amount of arabinose absorbed 1 hour after ingestion, proceed as follows:

(1) The amount excreted up to 1 hr. (by direct estimation) = 0·25 g.
(2) The amount used up to 1 hr. = 0·25 × 0·82 = 0·19 g.
(3) The amount in the tissues.

The amount excreted between ¾ hr. and 1 hr. after ingestion = 0·1 g. (by direct estimation); the amount similarly excreted between 1 and 1¼ hrs. = 0·09 g. Assuming the rate of excretion to be constant for this half hour, the rate of excretion per hour at 1 hr. after ingestion = 0·38 g. From the smoothed curve of excretion after injection this rate of excretion is found 2·05 hrs. from the start and at this time 1·95 g. have been excreted and therefore 1·95 × 0·82 = 1·6 have been used.

Therefore 5 − (1·95 + 1·6) = the amount in the tissues corresponding to a rate of excretion of 0·38 g. = 1·45.

Therefore the amount in the tissues 1 hr. after ingestion = 1·45 g.

Total amount absorbed = 1·905 g.

Great accuracy cannot be expected from these curves. In the first place they are based upon the assumption that the sugars distribute themselves equally throughout the body as soon as they are absorbed. This cannot be strictly true, but they certainly leave the blood stream and diffuse into the organs with great rapidity, for after 5 g. have been injected intravenously the curve of excretion is smooth and regular from the start. There is no excess of excretion in the first 10 mins. No serious error therefore, is involved in this assumption. Secondly, the determination of rates in this manner is not strictly accurate, particularly over parts of the curve where the rate is changing fast, *e.g.* between ½ and ¾ hour after ingestion. At the same time the samples of urine were collected over short periods (15 mins.), and the curves are extremely regular, so that there can be no doubt of the general truth of the results.

It is striking that the absorption of all these sugars should proceed rapidly (at a linear rate) for about 1½ hours and then almost or entirely cease when large amounts of arabinose and rhamnose presumably still remain in the gut. It is clear that absorption must commence as soon as the sugar is ingested and—as has already been pointed out—the upper part of the small intestine is the site of absorption. The lag in excretion is due to the time taken for the concentration in the tissues to rise.

Cori found that the rate of absorption in rats proceeded at a linear rate for 3 hours if enough sugar was given [Cori, Cori and Goltz, 1929; Pierce, Osgood and Polanski, 1929]. This Cori appears to consider a function of the epithelium. Cori's published results are very convincing and there can be little doubt that they are correct. Our own calculated absorption curves also show this tendency to a linear rate of absorption, at any rate at first, and it is to be recalled that we gave relatively very small amounts of sugar.

We would attribute the steady linear rate of absorption in Cori's cases (and in our own) not to a function of the epithelium, but to a slow steady

emptying of the stomach. With rhamnose in our subjects absorption ceased while four-fifths of what was taken still remained in the intestine, and a steady linear rate of absorption could only have been obtained by a slow steady supply of fresh sugar to the absorbing areas in the upper part of the small intestine. The sudden cessation of absorption at $1\frac{1}{2}$ hours in our experiments we take to mean that after this time the stomach was empty and no fresh sugar was being passed down the intestine. It is significant that there was always sugar left in the stomach of Cori's rats.

Note. By making certain assumptions it is possible to calculate the rate of filtration through the glomeruli directly from the curves of sugar excretion following injection. Thus in Fig. 2 the rate of excretion after 2 hrs. = 0·38 g. per hr. Assuming this rate to be constant for 15 mins. this would lead to the excretion of $\frac{0{\cdot}38}{4} = 0{\cdot}095$ g.

1·95 g. have been excreted at this time. Therefore, $1{\cdot}95 \times 0{\cdot}82$ have been used = 1·6 and so $5 - (1{\cdot}95 + 1{\cdot}6)$ g. remain in the body = 1·45. Assuming the fluid content of the body to be 60 % of the weight, this subject contains about 40 litres, and assuming further the pentose not excreted to be uniformly distributed, the concentration of pentose in body fluids is 3·6 mg. per 100 cc., so that 2660 cc. must have been filtered off to give the 0·095 g. excreted, *i.e.* 178 cc. per minute.

Similar calculations from other curves give amounts of filtration varying between 100 and 170. The example given in detail is an exceptionally high one.

It is perhaps not quite legitimate to assume that the pentose sugars distribute themselves equally throughout the cells of the body, for Kozawa [1914] found that human red blood-corpuscles were impermeable to rhamnose although permeable to xylose and arabinose. Cori and Goltz [1925], however, have found that pentoses penetrate the tissues as readily and freely as hexoses, and the similarity of our excretion curves for the three sugars also indicates that this is true of the three pentoses. Accurate work on this subject would necessarily require estimations of pentose in the plasma.

These figures for glomerular filtration agree with those obtained by Rehberg [1926].

Summary.

1. Rhamnose, arabinose and xylose are excreted equally readily when injected intravenously in man. Their curves of excretion are of identical shape and may all be superimposable.

2. The relative rates of absorption of rhamnose, arabinose, and xylose are the same both in rats and men. If the rate of absorption of rhamnose = 1, those of arabinose and xylose are 2·33 and 3·6 respectively.

3. These sugars are all absorbed at the same level in the intestine and this level is high up in the small intestine. Lower down little or no absorption takes place.

4. In normal man absorption of these sugars proceeds rapidly and at a linear rate for 1½ hours and then almost ceases, even when large excess still remains in the intestine.

5. We may assume with reasonable confidence that the relative rates of absorption of glucose, galactose and fructose found in rats also hold in man, *i.e.* galactose is absorbed slightly faster than glucose, and the latter twice as fast as fructose.

We wish to express our thanks to Mr J. B. S. Haldane for some very valuable criticism.

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