THE EXCRETION OF XYLOSE AS AN INDEX OF DAMAGED RENAL FUNCTION

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The constancy of the rate of excretion of xylose by normal subjects suggested the possibility of its use as a delicate indicator of damage to renal function. Without entering into the controversy as to the fate of the sugar not accounted for in the urine, it may be stated that the uniformity of the amount excreted in unit time by normal persons following ingestion of a definite quantity of xylose under conditions of fixed fluid intake makes the relative values obtained in patients manifesting impaired kidney function of particular theoretical and clinical significance. The present availability of xylose due to its recently established low cost renders its use for this purpose feasible.

Five grams of purified recrystallized xylose were injected intravenously into a normal subject weighing 75 kilos. The urine was collected by catheter in one minute samples for the first thirteen minutes, and was then voided at intervals of two, four and sixteen hours. It can be seen from Table I that the excretion of xylose starts one minute

TABLE I

Urine by catheter after injection of 5 grams xylose in a normal subject

Time	Volume	Per cent	Xylose	Average output per minute
minutes	*cc.*		*grams*	*grams*
1	0.6	0.0	0.0	
2	1.8	0.05	0.0008	
3	3.8	0.1	0.004	
4	1.4	0.4	0.006	
5	1.5	0.4	0.006	
6	3.4	0.3	0.010	
7	1.2	0.5	0.006	
8	1.6	0.5	0.006	
9	2.0	0.4	0.008	
10	1.0	0.8	0.008	
11	1.2	0.7	0.008	
12	1.6	0.5	0.008	
13	3.4	0.27	0.008	
14–120	65.	0.8	0.5	0.0047
120–240	240.	0.14	0.3	0.0025
240–960	1500.	.03	.45	0.0006

Reducing substance determined by method of Hagedorn and Jensen (5).

after injection, to rise within the next three minutes to the rate of 10 mgm. per minute during the sixth minute and then fall to 8 mgm. per minute for the next 7 minutes. Up to the second hour the rate averages 4.7 mgm. per minute, 2.5 during the next two hours and 0.6 mgm. for the next twelve hours. Approximately 25 per cent of the amount injected can be accounted for in the first sixteen hours. After five minutes we may assume that the entire amount is circulating in the blood stream because the blood volume calculated on this basis, 5.75 liters for a man weighing 75 kilos agrees well with that determined by the congo red method, 5.48 liters. This method of determining blood volume may prove of some clinical use.

It was found by one of the authors (1) that xylose injected into the marginal vein of a rabbit disappears at a rate proportional to the concentration of the nonfermentable reducing substance present in the blood at any moment or that

$$\frac{dC}{dt} = -aC$$

where C is the concentration of nonfermentable reducing substance in the blood as determined by the method of Somogyi (2). On integration we get $C = Ae^{-at}$ where a is a constant dependent on the unit of time employed and A must be equal to the initial value when t is 0. This is the equation governing the velocity of a monomolecular chemical reaction. It is thus possible to determine the concentration of the nonfermentable reducing substance in the blood at any time when its concentration at any particular moment is known, since the logarithm

TABLE II

Disappearance of nonfermentable reducing substance from blood after injection of xylose in a normal subject

Time	Nonfermentable reducing substance in blood	A $a = 4.6 \times 10^{-3}$
	mgm. per cent	
0	28	
2	54	
5	115	118
60	89	117
120	71	123
180	56	126
240	40.4	119

of the concentration of the foreign sugar is proportional to the time after injection. Using any two values of C we can eliminate a and get a numerical value for A. Thus from Table II

$$\frac{C_2}{C_1} = \frac{115}{89} = \frac{e^{-at_1}}{e^{-at_2}} = e^{a(t_2-t_1)}$$

$$a(t_2-t_1) = \log_e 1.29$$

$$a = .0046$$

$$A = 123$$

The constancy of A, as seen in Table II, is then proof both of the constancy of a and the correctness of form of the equation used. On plotting the values found as percentages of the initial value on semilogarithmic paper it is found that a straight line is obtained (Figure 1).

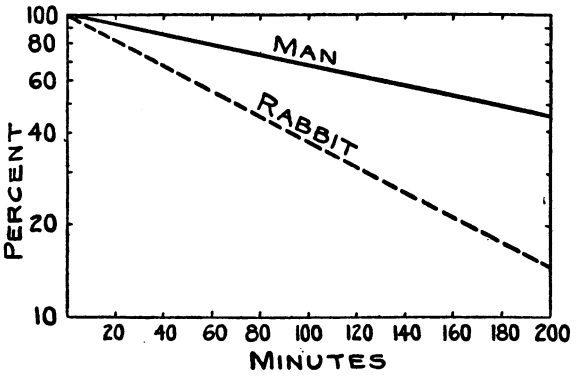

FIG. 1. DISAPPEARANCE OF NONFERMENTABLE REDUCING SUBSTANCE FROM BLOOD

After the ingestion of 50 grams of xylose on limited fluid intake and a fasting stomach we found that the blood nonfermentable reducing substance rose to a maximum of approximately 80 within three hours to return to a value of 40 or below within five hours. The return to the original fasting figure is of necessity slow because of the logarithmic nature of the function governing the disappearance of the xylose from the blood. 25 ± 5 per cent of the xylose is excreted within twenty-four hours with the majority of normal findings tending to group around 12 to 13 grams. The normal kidney has the power of concentrating xylose to 2.5 per cent within two hours, a point of paramount importance in distinguishing damage to renal function. It can be seen from Figure 3 that the normal kidney excretes 25 per cent of the amount given irrespective of the amount of fluid ingested, since the same quantity was excreted within 24 hours in 554 cc. of urine as in 3450 cc. The balance was so finely adjusted that the excretion in grams per hour was fairly constant whatever the amount of fluid given.

Ten mgm. of uranium acetate were injected into a rabbit and the following morning the animal was given 10 grams of xylose by mouth. As can be seen from Figure 4, within five hours the added nonfermentable reducing substance had disappeared from the control rabbit, while the animal treated with uranium retained a high concentration of xylose in the blood for many hours afterward. An animal treated with phosphorus in which the ingestion of 10 grams of galactose produced a prolonged galactose hyperglycemia, was given 10 grams of xylose by mouth. The curve of nonfermentable reducing substance in the blood showed no

deviation from the control. At autopsy the animal showed definite hepatic injury, so it would seem as if damage to liver function does not impair the elimination of xylose.

From a study of Figure 2 it is evident that in patients manifesting kidney lesions the blood curve of nonfermentable reducing substance, instead of approaching the normal fasting value after five hours, continues upward, so that values of 100 mgm. per cent or more are encountered. In cases of uremia accompanied by vomiting where some of the xylose

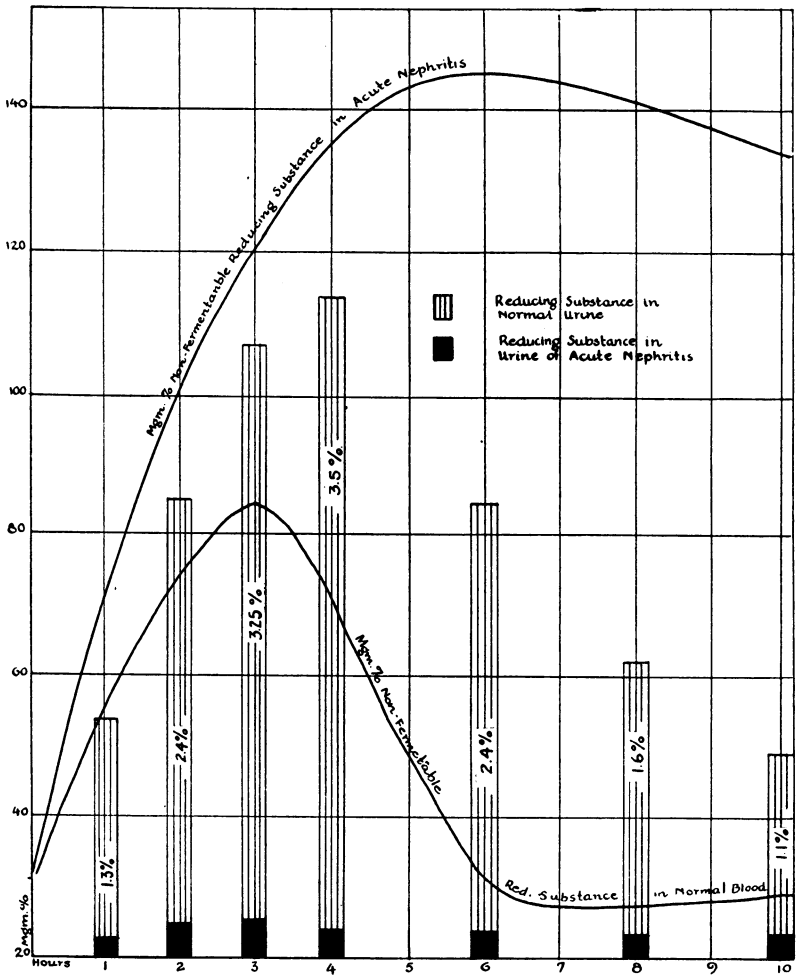

FIG. 2. INGESTION OF 50 GRAMS OF XYLOSE BY NORMAL SUBJECT AND BY NEPHRITIC PATIENT

The curves indicate the concentration of nonfermentable reducing substance in the blood; the bars indicate the percentage concentration of reducing substance in the urine.

is lost by the vomiting, it can be seen from Figure 5 that the curve maintains the characteristic shape of poor renal function, though the absolute values reached are never as high. This graph is made from data taken from a case where we were able to recover 22 grams of xylose from the vomitus. For purposes of comparison, a normal subject was given 25 grams of xylose by mouth. It can be seen that the patient with kidney

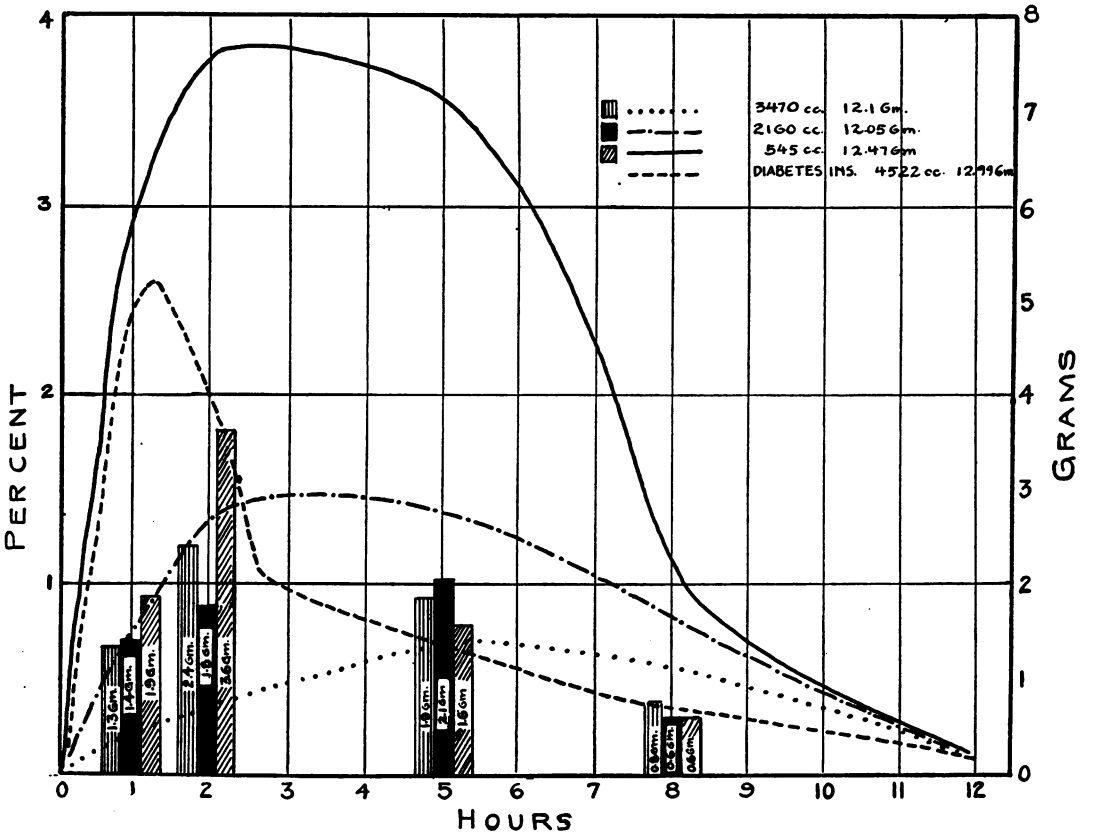

FIG. 3. INGESTION OF 50 GRAMS XYLOSE IN NORMAL SUBJECT ON DIET WITH VARYING AMOUNT OF FLUID

The curves indicate the percentage concentration of reducing substance in the urine; the bars show the output of reducing substance in the urine in grams per hour. For purposes of comparison, the broken line curve indicates the percentage concentration of reducing substance in the urine of a case of diabetes insipidus.

damage shows an entirely different curve. It will be observed in Figure 6 that in a case of acute nephritis which was studied over a period of four months the nonfermentable reducing substance curve of the blood gradually turns down as recovery proceeds, to reach the normal form when kidney function returns to normal. This characteristic shape of the

curve is of special value in incontinent patients where the phenolsulfonphthalein elimination or the urea clearance cannot be obtained.

It has become apparent of recent years that the fundamental manifestation of impairment of renal function is the diminution in the ability of the kidney to eliminate the urinary constituents in high concentration. This is very delicately exemplified in the case of xylose where the normal

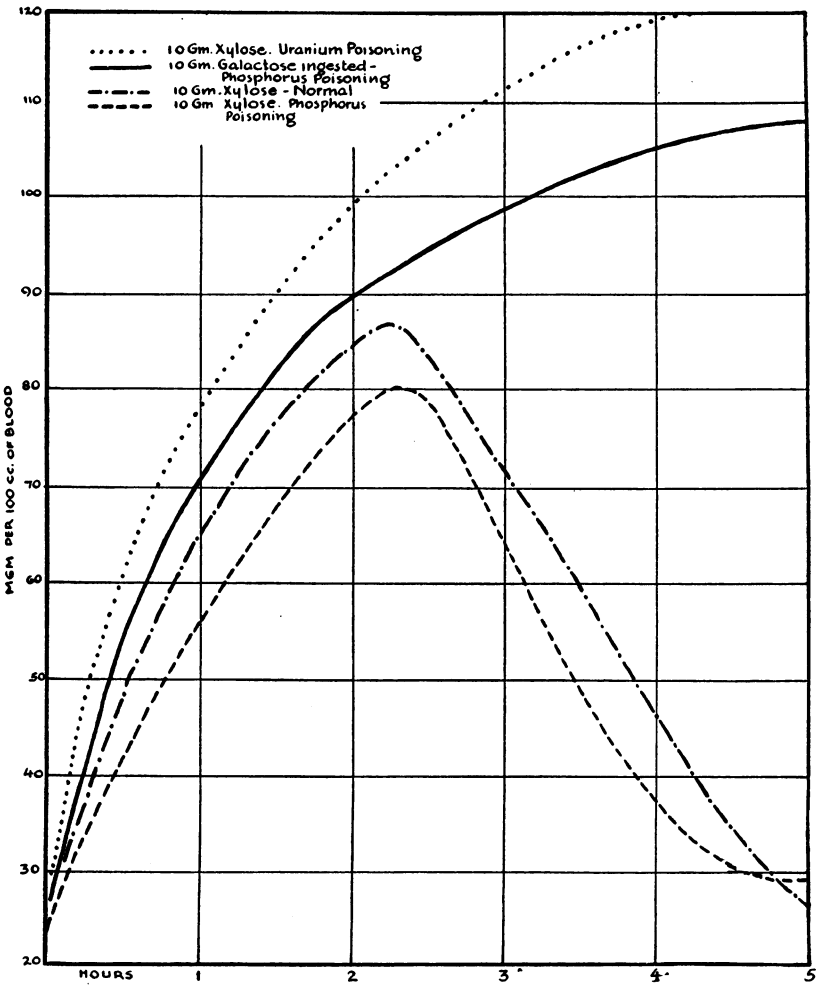

FIG. 4. INGESTION OF 10 GRAMS OF NONFERMENTABLE SUGAR IN RABBIT

(— · — ·) indicates the nonfermentable reducing substance in the blood of a normal rabbit after ingestion of xylose, which does not essentially deviate from that of a rabbit in which experimental acute liver damage has been caused by phosphorus (— — — —). The solid line indicates the curve of the latter animal on ingestion of galactose. (· · · · · ·) indicates the concentration of the nonfermentable reducing substance in the blood of an animal manifesting experimental acute kidney damage caused by uranium.

person concentrates to 2.5 per cent or more within two hours after ingestion of 50 grams on limited fluid intake. It is evident from Figure 2 that the subject with damaged kidney function cannot concentrate to this extent. In cases of severe impairment of renal function the concentrating power of the kidney is almost entirely gone; a quantitative Benedict reaction carried out on the urine two hours after ingestion of the xylose shows a concentration of nonfermentable reducing substance of 0.1 — 0.2 per cent instead of at least twelve times as much in individuals with healthy kidneys. It can be calculated from Figure 2 that the normal

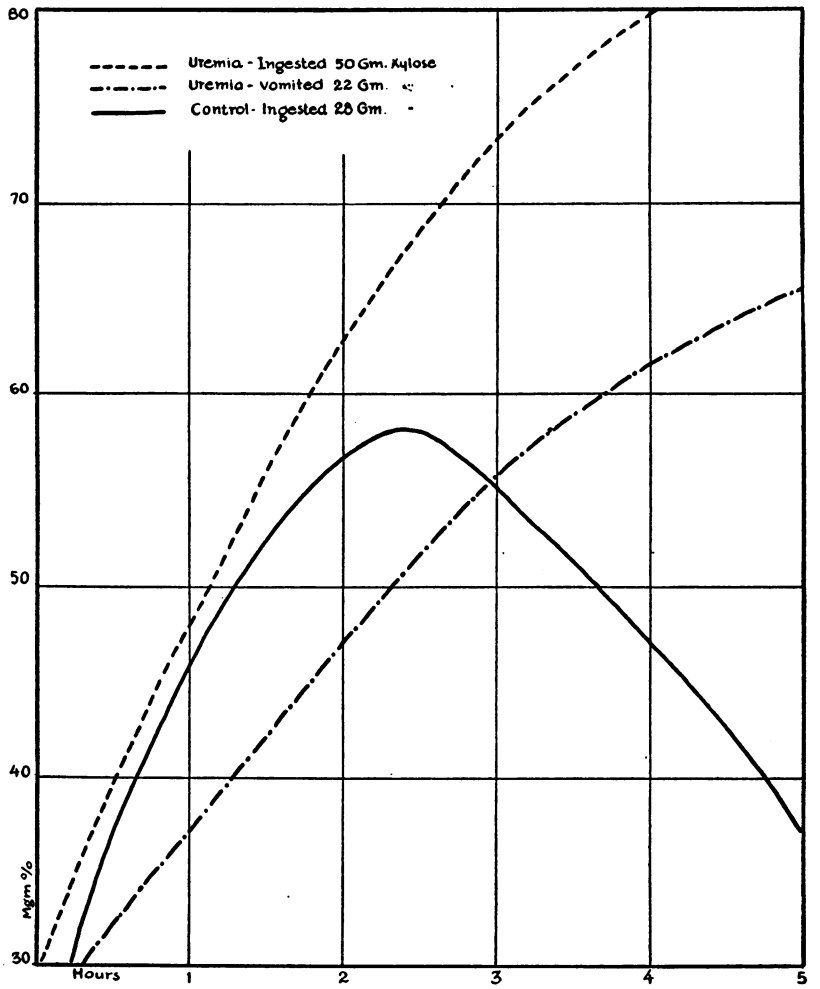

FIG. 5. INGESTION OF 50 GRAMS OF XYLOSE BY PATIENT SHOWING MARKED KIDNEY DAMAGE (— — — —)

Same patient after vomiting 22 grams (— · — · — ·). Control, normal subject, after ingestion of 28 grams xylose (————).

kidney has the power of concentrating xylose from thirty to sixty times while the urine elaborated by the damaged kidney shows a concentration of xylose which is practically equal to that in the blood. This loss in concentrating ability is seemingly correlated with a diminution of the

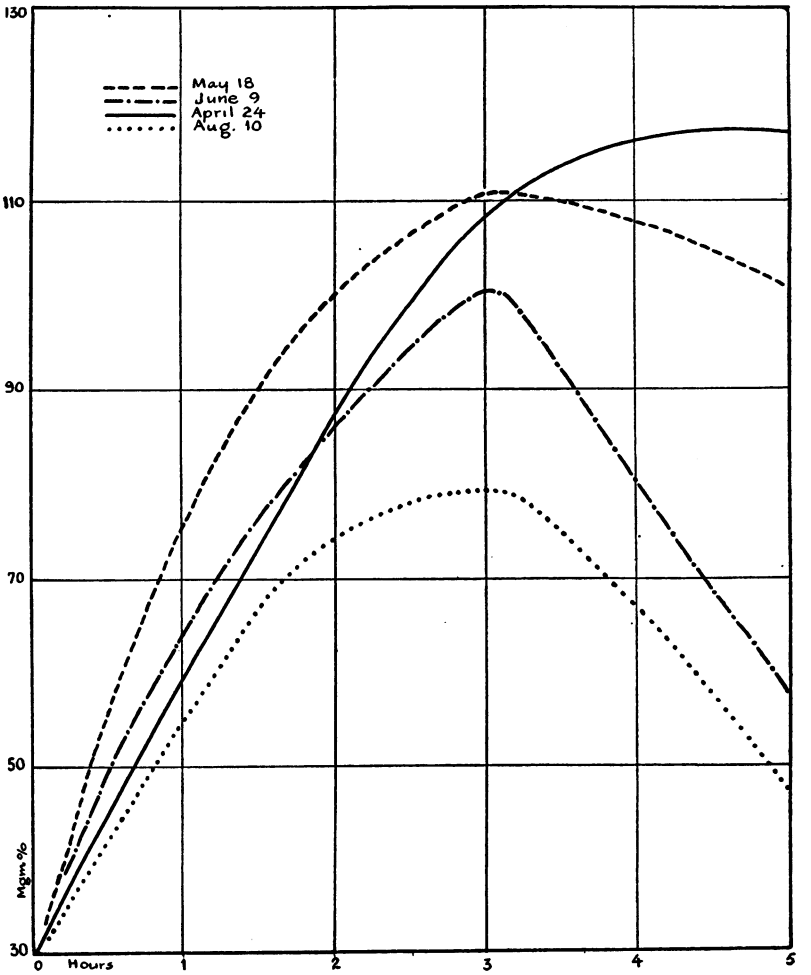

FIG. 6. INGESTION OF 50 GRAMS OF XYLOSE AT SUCCESSIVE INTERVALS BY A PATIENT RECOVERING FROM ACUTE NEPHRITIS

The return of kidney function is shown by the change in the form of the curve of the nonfermentable reducing substance in the blood on these successive dates.

number of functioning renal units (a renal unit is a glomerulus with its appertaining tubule), but further investigation is necessary to determine in how far this relation can be said to be quantitative, i.e., that the intermediate values between the two extremes mentioned above are proportional to the extent of kidney tissue damage.

The damaged kidney is not alone unable to concentrate the xylose, but if the amount excreted in twenty-four hours is determined, it is found that this is radically decreased, so that in severe cases of renal disease excretion of one gram or even less is encountered. It is seen that the amount excreted by the normal kidney is a constant independent of the amount of water ingested, so that extrarenal factors may not be of such paramount importance in governing the amount excreted as is the case in other kidney function tests; and the amount of xylose excreted may more closely measure the exact functional permeability of the kidney membrane.

Figure 7 shows a case of acute nephritis in a young girl, which was studied over a period of four months. The comparative renal function tests are represented. It is seen that the ability to concentrate xylose is early and severely impaired, as is the urea clearance. The amount of xylose excreted during 24 hours is also low. The excretion of phenolsulfonphthalein is not so low. This may be an early sign of recovery, since phthalein excretion of the improving patient shows a definite rise sooner, and thereafter rises very quickly toward normal. In the recovery phase it is found in accordance with the work of Peters and Van Slyke (3) that the urea clearance lags behind, so that it is only 50 per cent at a time when the phenolsulfonphthalein excretion is 75 per cent, the xylose concentration is nearly 3 per cent and the patient is able to excrete 11 grams of the fifty grams of xylose ingested.

In Table III the disposition of the xylose in the blood and urine of patients manifesting various types of kidney lesions can be seen.

In the case of J. A. the ability to concentrate to 2.6 per cent within 2 hours and the excretion of 10.81 grams of xylose within 24 hours, as well as the normal xylose curve in the blood, showed intact kidney function. At autopsy, the only kidney lesions found were those of chronic passive congestion. However, in this case, owing to sluggish circulation, the phenolsulfonphthalein excretion was definitely lowered, as was the urea clearance. The specific gravity test was on the border line. In the case of R. A., with valvular cardiac disease, kidney function was intact, as the xylose excretion was 12.24 grams per day and the concentration 3.3 per cent within 2 hours. All the other kidney function tests were in accord with this view.

In a case of diabetes insipidus we found that the patient excreted xylose very quickly, so that if the curve of the concentration of xylose in the urine is compared with those of a normal patient excreting approximately the same volume of urine (see Figure 3) it is seen that the curves are entirely dissimilar. Whether this is characteristic of diabetes insipidus cannot be determined from the one case at our disposal.

In cases of diabetes mellitus it is of course necessary to employ yeast fermentation of the urine to destroy the fermentable reducing substance.

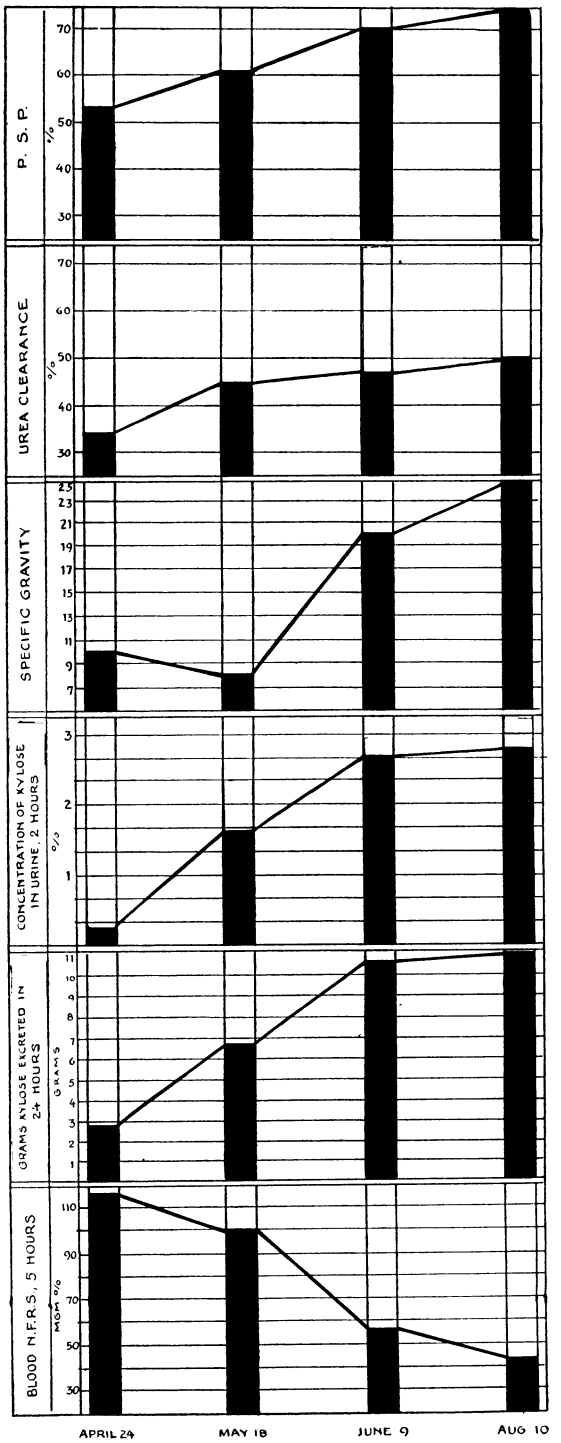

FIG. 7. THE UREA CLEARANCE; SPECIFIC GRAVITY OF THE URINE; PHENOLSULFONPHTHALEIN EXCRETION

Also after ingestion of 50 grams of xylose the output in grams in 24 hours, the concentration of the nonfermentable reducing substance in the blood after 5 hours, the percentage concentration of xylose in the urine after 2 hours are indicated at varying periods in a patient recovering from acute nephritis.

TABLE III

Xylose in blood and urine in patients with kidney lesions

Name and age	Diagnosis	Blood							Urine										
					Xylose									Xylose					
		Systolic pressure	Red blood cells	Non-protein nitrogen	0 hour	1 hour	3 hours	5 hours	Volume in 24 hours	Urea clearance	Phenolsulfonphthalein	Specific gravity	Protein	1 hour	2 hours	3 hours	8 hours	Max. conc.	Output in 24 hours
			millions	*mgm. per cent*	*mgm. per cent*	*mgm. per cent*	*mgm. per cent*	*mgm. per cent*	*cc.*	*per cent*	*per cent*		*grams*	*grams*	*grams*	*grams*	*grams*	*per cent*	*grams*
M. B. 50	Amyloid contracted kidney	85	2.2	120	31	69	100	110	777	37	3	1.010	f.t.	.1	.1	.1	.2	.3	1.6
H. G. 63	Essential hypertension	200	4.1	28	28	46	75	42	1034	47	65	1.010	f.t.	.2	.4	1.3	4.4	2.4	8.5
M. S. 43	Essential hypertension, secondary contracted kidney	260	2.0	100	28	84	100	130	791	72	25	1.012	f.t.	2.2	(for first 5 hours)			1.9	4.2
B. A. 55	Chronic glomerulonephritis. Pyelitic contracted kidney	180	3.0	300	37	40	56	64	787	21	19	1.008	f.t.	0	0	0	0.3	0.3	1.0
					Vomited 22 grams														
B. B. 62	Arteriolosclerosis of kidney with superimposed acute inflammation	160	2.0	75	31	80	138	131	Incontinent										
H. G. 39	Arteriolosclerosis of kidney	232	2.7	150	28	81	100	116	872				f.t.	0	0	.1	.1	0	.29
S. C. 18	Acute nephritis	168	3.6	50	30	73	109	117	806	34	53	1.010	3.6	.1	.2	.3	.6	.5	2.4
E. R. 13	Valvular cardiac disease. Subacute glomerulonephritis	300	4.1	33	27	56	90	60	1016	64	80	1.020	f.t.	1.0	2.3	2.5	3.2	3.3	12.2
Y. F. 36	Postpartum hypertension	160	4.3	27	28	57	74	42	679	67	73	1.022	f.t.	.3	1.6	6.5	2.5	2.7	11.8
J. O. 58	Diabetes insipidus	142	3.7	37	27	40	48	36	4522	80		1.003	f.t.	2.5	1.4	5.3	.9	2.6	13
S. G. 24	Diabetes mellitus	124	4.2	28	27	80	83	41	845				Neg.	.9 .4*	1.2 .7*	5.2 1.5*		3.2	11.4
J. S. 43	Essential hypertension (cardiac) stasis in kidney	248	4.1		29	52	70	54	985	51	32	1.018	Neg.	1.1	1.9	3.5	3.4	2.6	10.8
M. B. 16	Acute glomerulonephritis	131	3.2	58	28	72	90	94	739	41	61	1.008	1.2	.4	.6	1.3	1.6	1.3	6.6
N. H. 23	Acute glomerulonephritis	110	4.1	24	28	63	81	42	800	39	62	1.024	4.1	.6	1.4	2.3	2.3	2.1	10.8

* Fermentable reducing substance.

When this is done it is found that these subjects have a normal ability to excrete xylose as long as kidney function is intact. It is of interest that Ebstein (4), working on the metabolism of the pentose sugars, reports the case of a diabetic patient who was given 25 grams of xylose by mouth and after nine days was still excreting nonfermentable reducing substance in the urine. He cites this as a proof of some disturbance in the tolerance of pentose sugars in diabetics. In the protocol it is recorded that the patient shows a large quantity of albumin in the urine and we may therefore assume that the subject was retaining the xylose because of some damage to the kidney.

Since nonfermentable reducing substance appears in the urine of catheterized patients with normal kidneys one minute after injection of xylose intravenously, this pentose may find some application in surgical conditions where a quick decision as to the functional integrity of one or the other kidney is often of vital importance.

SUMMARY

The excretion of xylose is used as an index of renal function. On ingestion of 50 grams of xylose with limited fluid intake the intact kidney is able to concentrate the xylose to 2.5 per cent within 2 hours and excretes 25 per cent of the total given within 24 hours. Damaged renal function is manifested by concentrations as low as 0.1 per cent and total excretions as low as 1 gram. The curve of nonfermentable reducing substance in the blood approaches its normal value after 5 hours with intact kidney function, while in patients with impaired renal function the curve of the nonfermentable reducing substance continues upward so that values of 100 mgm. per 100 cc. and more are encountered. The possibility of the use of xylose for the determination of blood volume and in the quick diagnosis of the functional integrity of single kidneys for surgical purposes is also indicated.

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