CHRONIC DIARRHOEAS IN INFANCY AND CHILDHOOD

I: D-XYLOSE TOLERANCE TEST

BY

C. J. INGOMAR, S. MÜLLERTZ and E. TERSLEV

From the Dronning Louise Children's Hospital and the Department of Clinical Chemistry, Blegdamshospitalet, Copenhagen, Denmark

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Chronic diarrhoeas constitute a major part of the diseases of childhood. In recent years separate entities with known aetiology and pathogenesis have been demonstrated. Among these, that of cystic fibrosis of the pancreas is an inborn error with pancreatic insufficiency (Andersen, 1938), while coeliac disease is caused by intolerance to gluten (Dicke, 1950; Kamer, Weijers and Dicke, 1953), producing an absorptive defect in the small intestine. Some cases are caused by intolerance to mono- or disaccharoses (Froesch, Prader, Labhart, Stuber and Wolf, 1957; Holzel, Schwarz and Sutcliffe, 1959; Jeune, Charrat, Cotte, Fournier and Hermier, 1960; Prader, Auricchio and Mürset, 1961; Weijers, Van de Kamer, Dicke and Ijsseling, 1961; Weijers and Van de Kamer, 1962). In many cases, however, the aetiology or pathogenesis or both are unknown.

D-xylose is not affected by digestive enzymes or intestinal bacteria (Cori, 1925). It is not absorbed against a concentration gradient, although it is taken up slightly faster than L-xylose (Wilson and Vincent, 1955). D-xylose is not normally present in blood. The distribution phase is 20% of the body weight, i.e. a little more than the extracellular body volume. The distribution phase is increased by insulin, but only slightly (Segal, Wyngaarden and Foley, 1957; Wyngaarden, Segal and Foley, 1957).

Studies with D-xylose-1-C¹⁴ indicate that a certain part of administered D-xylose is rapidly metabolized in the organism (Wyngaarden *et al.*, 1957). After intravenous administration, 40% is excreted in urine at a blood concentration corresponding to that obtained during tolerance tests in healthy subjects (Segal *et al.*, 1957; Wyngaarden *et al.*, 1957). Generally renal excretion is roughly proportional to plasma concentration.

During later years the D-xylose tolerance test has been preferred for absorption studies and the results obtained have so far been encouraging

(Benson, Culver, Ragland, Jones, Drummey and Bougas, 1957; Gardner and Santiago, 1956; Kalser, 1957; Thaysen and Müllertz, 1962). In adults the test usually consists of an oral ingestion of 25 g. of D-xylose followed by the determination of the blood concentration and the urinary excretion. The test has been used in children by Wolfish, Hildick-Smith, Ebbs, Connell and Sass-Kortsak (1955), Heiner and Lahey (1962), Polonovski and Gombault (1962) and Jones and di Sant' Agnese (1963). These authors found abnormally low values in coeliac disease and normal values in cystic fibrosis of the pancreas.

It is the aim of the present work to establish normal values for the D-xylose tolerance test in infants and children and to present the results of the test in children with chronic diarrhoeas of known as well as unknown aetiology and pathogenesis.

Methods and Material

Estimation of D-xylose in blood and urine was performed according to the photometric method described by Roe and Rice (1948). The development of the colour is influenced by small changes in temperature and by exposure to light, and is consequently poorly reproducible. Therefore, in each series, five solutions containing known concentrations of D-xylose were analysed and the calculations were based on the values obtained with these solutions.

Recovery experiments performed by addition of known amounts of D-xylose to normal blood were satisfactory. The analytical error was calculated from 20 duplicate determinations performed on blood samples with concentrations of D-xylose ranging from 35 to 40 mg. per 100 ml. In this range the coefficient of variation was 1.75%.

Samples of blood and urine containing D-xylose can be stored at 5° C. for at least one week without any decrease in the xylose content.

The D-xylose tolerance test was performed as follows: After an overnight fast 15 g. D-xylose per m.² body

TABLE 1
AGE AND SEX DISTRIBUTION OF THE MATERIAL

Group No.	Diagnosis	Age (yrs.)								Total
		Boys				Girls				
		<1	1-2	3-5	>6	<1	1-2	3-5	>6	
1	Controls	3		5	3	1	1	4	5	22
2	Secondary diarrhoeas		5	4	1	2	1	2	1	16
3	Idiopathic diarrhoeas	2	10	4	2	2	3	1	1	25
4	Coeliac disease	1	5			1			3	10
5	Diseases of the colon		1	2	3			1		9
6	Carbohydrate intolerance		1		2		1			4
7	Cystic fibrosis of the pancreas			2					1	2
8	Miscellaneous				1			1		2
Total number of patients with diarrhoeas		3	22	12	9	6	5	5	6	68
Total number of patients		6	22	17	12	7	6	9	11	90

surface area were administered orally as a 10% solution in water followed by the same volume of water. Urine was voided and discarded. Samples of capillary blood were drawn one, two and three hours later. Urine was collected during the 24 hours following the ingestion of xylose. The results of the test were expressed as the maximal concentration of xylose in blood ('blood values') and as the urinary excretion in 24 hours as a percentage of the given amount ('urinary values'). During the test the child was kept on a normal diet.

The material comprised 22 control subjects and 68 patients with various types of chronic diarrhoea, a total of 90 subjects. They were admitted to the children's hospital in the years 1961 and 1962 (Table 1). The 22 controls (11 boys and 11 girls) had no gastro-intestinal disease, but were in hospital for non-somatic causes. The 68 patients were grouped according to the clinical picture, effect of treatment and course of the disease, faecal fat output on a standardized diet, tolerance tests with glucose and other carbohydrates, radiological evidence and a series of laboratory tests (examination of the stools for bacteria, skin tests for allergy, examination of the sweat for electrolytes, etc.).

The fat tolerance test was abnormal only in cystic fibrosis of the pancreas and coeliac disease; the glucose tolerance test was abnormal in coeliac disease, but normal in all the other groups, and the pathological sweat test was only found in cystic fibrosis of the pancreas.

The results of the D-xylose tolerance tests performed here have not been used in distinguishing between the different groups.

(1) Controls. (2) Secondary diarrhoeas (16 patients): The diarrhoeas were closely correlated to parenteral infections, primarily in the upper respiratory tract and the routine tests failed to demonstrate any local cause for the condition. (3) Idiopathic diarrhoeas (25 patients): this group comprised children who, on a diet normal for the age and controlled in the hospital, still suffered from diarrhoeas. Furthermore, neither the applied routine tests nor examinations concerning allergic or psychological origin of the diarrhoeas could demonstrate the cause of the disease. Parenteral infections were excluded too. (4) Coeliac disease (10 patients): the

diagnosis was established from the clinical picture, a flat glucose tolerance curve, steatorrhoea, and clinical improvement on a gluten-free diet. (5) Diseases of the colon (nine patients): five patients had constipation complicated with diarrhoeas, and four patients suffered from ulcerative colitis. (6) Diarrhoeas caused by intolerance to carbohydrates (four patients): in these patients the reducing capacity of the blood showed abnormally little increase after loading with the carbohydrate in question. Furthermore, loading or elimination of the substance in question produced a typical clinical response. (7) Cystic fibrosis of the pancreas (two patients): the diagnosis was established from the clinical picture including pulmonary complications, steatorrhoea and an abnormal electrolyte content of the sweat. (8) A miscellaneous group consisting of two patients, one suffering from a helminthic infection and one with diarrhoea caused by an extensive resection of the distal part of the small intestine.

Results

Distribution of Populations. An analysis of the distribution of the registered values was performed for the control group and for the whole material except Group 4. In both cases the blood values (mg./100 ml.) showed a normal distribution, while the urinary values (%) showed a positively skew distribution which was normalized by logarithmic conversion. Consequently, the logarithms of the urinary values were used in the statistical significance tests (Tables 2 and 3). Group 4 (coeliac disease) was excepted because it differed obviously in range and distribution characteristics from the other groups.

Co-variation of Blood Values and Urinary Values. The urinary values (y) and their logarithms ($\log y$) were both correlated to the blood values (x) (Figs. 1 and 2). The correlation coefficient was 0.6845 ($p < 0.001$) for y and x and 0.7540 ($p < 0.001$) for $\log y$ and x . Figs. 1 and 2 show diagrams of the

TABLE 2

PARAMETERS AND SIGNIFICANCE TESTS FOR CONTROL AND PATIENT GROUPS: MAXIMAL CONCENTRATION OF D-XYLOSE IN BLOOD (mg./100 ml.)

Group	Diagnosis	Number (n) Mean (M) and Variance (s ²)			Variance Ratio		Standard Deviation (s) Standard Error of Mean (s/√n) and Ranges				Difference of Mean From Control Mean	
		n	M	s ²	F	p	s	M ± 2s	s/√n	M ± 2s/√n	t	p
1	Controls	22	48	125			11.2	26-70	2	43-53		
2	Secondary diarrhoeas	16	47	81.6	1.53	n.s.	9.03	29-65	2	42-52	0.29	n.s.
3	Idiopathic diarrhoeas	25	36	152	1.22	n.s.	12.3	11-61	2	31-41	3.48	<0.002
4	Coeliac disease	10	16	68.2	1.83	n.s.	8.26	0-33	3	11-21	8.08	<0.001
5	Diseases of the colon	9	46	279	2.23	n.s.	16.7	13-79	6	35-57	0.39	n.s.
6	Carbohydrate intolerance	4	41	19.7	6.34	n.s.	4.44	32-50	2	37-45	1.22	n.s.
7	Cystic fibrosis of the pancreas	2	52	60.0	2.08	n.s.	7.75	37-67	5	41-63	0.49	n.s.
8	Miscellaneous	2	32	8.00	15.6	n.s.	2.83	26-38	2	28-36	1.98	n.s.

F = ratio of the variance of each patient group to the variance of the control group, the greater variance being placed as the numerator. $t = M_c - M_x / \sqrt{s^2 \left(\frac{1}{n_c} + \frac{1}{n_x} \right)}$ where c = control group, x = any patient group and s^2 = the mutual variance.
p = probability. n.s. = not significant.

correlation between y and x and $\log y$ and x and the regression of y on x and $\log y$ on x . The standard error of the estimate of $y = 9.78$, of $\log y = 0.1645$.

The corresponding regression equations were:

$$\begin{aligned} y &= 0.6229 x + 2.3650, \\ x &= 0.7522 y + 19.5671, \\ \log y &= 0.0128 x + 0.8633, \\ x &= 44.4162 (\log y) - 21.0139. \end{aligned}$$

Theoretically, the urinary excretion should give an expression of the integrated concentrations of d-xylose in the blood during the test, and thus be a better expression of the absorptive capacity of the intestine than the maximal of three blood values obtained during a test.

Generally, however, the latter constituted a better means of discrimination between normal and pathological values (see below).

Parameters of Populations. The mean (M), variance (s^2) and standard deviation (s) and standard error of the mean ($s/\sqrt{n}$) for the various groups are shown in Table 2 and Fig. 3 (blood values) and in Table 3 and Fig. 4 (log (urinary values)). Table 4 contains mean values and upper and lower limits for the control group, calculated as $M \pm 2s$. The lower normal limit was 26 mg./100 ml. and 16 mg./100 ml. for blood and urinary values respectively.

The variances of the control group were compared with the variances of any of the other groups by

TABLE 3

PARAMETERS AND SIGNIFICANCE TESTS FOR CONTROL AND PATIENT GROUPS: LOGARITHM OF THE URINARY EXCRETION OF D-XYLOSE AS PERCENTAGE OF INGESTED DOSE

Group	Diagnosis	Number (n), Mean (M) and Variance (s ²)			Variance Ratio		Standard Deviation (s), Standard Error of Mean (s/√n) and Ranges				Difference of Mean From Control Mean	
		n	M	10 ⁴ · s ²	F	p	s	M ± 2s	s/√n	M ± 2s/√n	t	p
1	Controls	22	1.490	201.8			0.142	1.774-1.206	0.030	1.550-1.430		
2	Secondary diarrhoeas	16	1.428	397.3	1.47	n.s.	0.199	1.826-1.030	0.050	1.528-1.328	1.12	n.s.
3	Idiopathic diarrhoeas	25	1.329	327.3	1.62	n.s.	0.181	1.691-0.967	0.036	1.401-1.257	3.35	<0.002
4	Coeliac disease	10	0.970	984.2	4.88	<0.01	0.314	1.598-0.342	0.099	1.168-0.772	5.01	<0.001
5	Diseases of the colon	9	1.527	437.3	2.17	n.s.	0.209	1.945-1.109	0.070	1.667-1.387	0.58	n.s.
6	Carbohydrate intolerance	4	1.467	659.6	3.27	<0.05	0.257	2.181-0.953	0.128	1.723-1.211	0.26	n.s.
7	Cystic fibrosis of the pancreas	2	1.552	66.6	3.03	>0.025	0.082	1.716-1.388	0.058	1.668-1.436	0.60	n.s.
8	Miscellaneous	2	1.360	7.9	25.5	n.s.	0.028	1.416-1.304	0.020	1.400-1.320	1.26	n.s.

Symbols: See Table 2. t was calculated as in Table 2, except for Group 4, where $t = M_c - M_x / \sqrt{e^2 + e_x^2}$, where $e^2 = \frac{s^2}{n}$.

FIG. 1.—Correlation of urinary excretion of D-xylose as percentage of ingested dose (y), and maximal concentration of D-xylose in blood (x). The lines show the regression of y on x (M) and the limits placed at 1 and 2 standard errors (se) of the estimate of y on either side of the regression line.

means of a variance ratio test (Tables 2 and 3). A highly significant difference was observed only for the logarithm of the urinary values of the group with coeliac disease. With the latter possible exception, this indicated that all variances were estimates of the same population variance.

A χ^2 test showed no significant correlation of the blood values to age and sex.

FIG. 3.—The maximal concentration of D-xylose in blood obtained in the Groups 1-8 (see text). The horizontal lines indicate the mean for each group. The upper and lower limits of the framing indicate $M \pm 2s$, while the upper and lower limits of the expansion of the framing indicate $M \pm 2(s/\sqrt{n})$.

FIG. 2.—Correlation of $\log y$ and x . See Fig. 1.

Control Group and Groups of Children with Diarrhoeas. The existence of any significant difference between the mean of the blood and urinary values for the control group and the corresponding

FIG. 4.—The urinary excretion of D-xylose as percentage of the ingested dose (y) obtained in the Groups 1-8 (see text). The left ordinate shows $\log y$, the right ordinate y (on a logarithmic scale). Further, see Fig. 3.

means of any other group was investigated by means of 'Student's *t* test'. The values of *t* and the probability (*p*) of the differences occurring by chance are given in Tables 2 and 3. No significant difference was observed for Groups 5 to 8. In these cases the pathogenesis of the diarrhoeas was known and no affection of the absorptive capacity of the small intestine was expected. A highly significant difference was established both for the blood and urinary values of Group 4 (coeliac disease). In this group, nine out of 10 blood values, and six out of 10 urinary values were below the normal lower limit, the remaining values being above, but rather near this limit. The reduced absorptive function of the intestine is well known in these patients.

The pathogenesis of the diarrhoeas in Groups 2 and 3 is unknown. No significant difference was observed for Group 2 (secondary diarrhoeas), in which no blood values and only two urinary values were below the lower normal limit.

However, the mean of Group 3 (idiopathic diarrhoeas) differed significantly ($0.002 > p > 0.001$) from the control mean. Among the 25 patients of this group, seven had blood values and six urinary values equal to or below the lower normal limit, while 19 blood values and 19 urinary values were below the control mean.

TABLE 4
MEAN VALUES (*M*) AND UPPER AND LOWER LIMITS, CALCULATED AS $M \pm 2s$, FOR CONTROL GROUP

	Blood Values (mg./100 ml.)	Urinary Values (%)
<i>M</i> + 2 <i>s</i>	70	50.4
<i>M</i> + <i>s</i>	59	42.8
<i>M</i>	48	30.9
<i>M</i> - <i>s</i>	37	22.3
<i>M</i> - 2 <i>s</i>	26	16.0

The figures for the urinary excretion are calculated as the anti-logarithms of the normally distributed logarithmic values.

Discussion

In some previous studies (Benson *et al.*, 1957; Gardner and Santiago, 1956) the urinary excretion of D-xylose was found to be a better expression of the absorptive capacity of the intestine than was the maximal blood concentration.

However, the latter was found by Thaysen and Müllertz (1962) and by us to constitute a better means of discrimination between normal and pathological values.

The greater scattering of the urinary values may be due to variations in the renal excretion and to a more or less complete collection of the urine.

The lower normal limit of the maximal blood

concentration of the D-xylose and of the excreted amount of D-xylose in the urine (as a percentage of ingested dose) has been found a little lower than reported (Wolfish *et al.*, 1955; Heiner and Lahey, 1962; Jones and Sant' Agnese, 1963) in children. However, Polonovski and Gombault (1962) have found nearly the same values. Thaysen and Müllertz (1962) applied the same technique in adults, as used in the present work. Their results were similar to those of other adult series, but the lower limit was estimated to be somewhat higher than that found in the present work.

The present paper describes few of the more severe well-known forms of chronic diarrhoeas. The distinction between these types by means of the routine tests (fat tolerance test, glucose- and disaccharose tolerance tests and examinations of the electrolyte content of the sweat, etc.) has not caused difficulties, and the results have not differed from those published before. Our interest has therefore been focused on the less severe forms of chronic diarrhoea.

If the normal values are compared with the values found in infants and children suffering from different types of chronic diarrhoeas, it is seen that most values are within the normal range. Thus normal values are found in cystic fibrosis of the pancreas, diseases of the colon, diarrhoea caused by intolerance to mono- or disaccharoses and in secondary diarrhoeas.

The earlier observations of very low values in patients with coeliac disease were confirmed by us.

The group with idiopathic diarrhoea attracts interest. The only common feature of the patients in this group was the lack of any obvious cause of the diarrhoea, and the normal results of the various routine tests. Therefore, the group may be heterogeneous, and include cases of coeliac disease too slight to be demonstrable by the other tests applied. Thus, in six out of 25 patients the values were below the lower normal limit. On the other hand, as a whole, the results of the test in this group were lower than those of the control group and the variances of the two groups were of similar magnitude.

This shows that most of these patients have a reduced capacity to absorb D-xylose. It may suggest that the pathogenesis of these diarrhoeas is an absorptive defect of the small intestine.

Further studies are needed to establish the aetiology of the idiopathic diarrhoeas. These should include exclusion and provocation experiments with gluten, and repeated tolerance tests with D-xylose and possibly other relevant substances.

Summary

The D-xylose absorption tolerance test was carried out by the oral administration of 15 g. D-xylose per m.² body surface to 90 infants and children, 22 controls and 68 with chronic diarrhoeas. The evaluation of the test was based on the maximal concentration obtained in the blood (after one, two and three hours) and on the urinary excretion during the first 24 hours expressed as a percentage of the ingested amount. The former constituted a better means of discrimination between normal and pathological values.

In the control group the mean values and the upper and lower limits (mean $\pm$ 2 standard deviations) were 48 (26-70) mg./100 ml. blood and 31 (16-59)% urinary excretion.

In 10 patients with coeliac disease nine blood values and six urinary values were below the lower normal limit. In 25 patients with idiopathic diarrhoeas blood and urinary values were below the lower normal limit in seven and six cases respectively.

For both groups the mean values were significantly lower than the control mean.

This may suggest that the pathogenesis of idiopathic diarrhoeas is an absorption defect in the small intestine.

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