DIODRAST AND INULIN CLEARANCES IN NEPHROTIC CHILDREN WITH SUPERNORMAL UREA CLEARANCES

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Elevation of the urea clearance above the calculated normal value has been frequently observed in our clinic in children with the nephrotic syndrome. Previous studies of this phenomenon have shown it to be related to the intake of protein, but not induced by the oral administration of urea (1). Glomerular filtration, measured by inulin clearance, has been found by Emerson, Futcher, and Farr (2) to be elevated as much or more than the urea clearance. The present study is an attempt to answer the question raised in the last report (2) as to whether renal blood flow is elevated proportionately to the glomerular filtration rate. Evidence presented by Goldring, Chasis, Ranges, and Smith (3) and by White and Heinbecker (4) indicates that the diodrast clearance approximates the renal blood flow in man. In order to obtain some indication as to whether the high urea and inulin clearances observed in nephrosis are probably due to filtration of an increased fraction of plasma water or to an increased renal blood flow, we have therefore, in 4 cases, made a series of simultaneous determinations of the clearances of urea, inulin, and diodrast.

MATERIAL

Four nephrotic children, aged 3, 5, 5, and 10 years, were selected for study, the oldest of whom (R.Q.) had also been included in the previous group (2). All had been maintained during at least the preceding 4 months on diets high in protein (over 3 grams per kgm. per day), and low in salt (less than 1.6 grams per day). Routine urea clearances during this period showed values around 140 per cent of normal or higher.

METHODS

Urea was determined by the hypobromite method (5), diodrast by colorimetric estimation of liberated iodine (6), and inulin by measurement of the color developed with diphenylamine reagent (7, 8). For colorimetric measurements, a Klett-Summerson colorimeter was used.

As in previous work, clearance values are corrected for differences in size of the subjects by applying the surface area factor of Møller, McIntosh, and Van Slyke (9) to the urine flow figures. In the instances of corrected urine flows lower than 2 cc. per minute, maximal plasma clearances of urea were calculated by the formula:

$$\text{Maximal clearance} = \frac{U\sqrt{2V_c}}{P},$$

where U is urine urea concentration, P is plasma urea concentration, and V_c is the corrected urine volume in cc. per minute (see (2) p. 364). Normal maximum plasma clearance is taken as 72 cc. per minute per 1.73 sq. M. for the purpose of calculating percentages. This figure is derived from the usual standard of 75 cc. per minute per 1.73 sq. M. for whole blood urea clearance (9) by assuming that plasma urea concentration is 4 per cent higher than whole blood concentration.

PROCEDURE

Five experiments were performed on the 4 subjects. In each experiment, continuous urea clearances were measured during the preceding 2 to 5 hours in order to observe any variations that might be induced by subsequent manipulations. Water was given hourly in 100 cc. portions, beginning 3 hours before the test. Priming doses of 2 to 4 grams of inulin and 1 to 2 cc. of a 35 per cent diodrast solution, depending on the size of the subject, were given in 100 cc. of saline, intravenously, over a period of about 10 minutes, followed by continuous infusion of a solution which contained 1 to 2.5 per cent inulin and 0.6 to 2.0 per cent of 35 per cent diodrast. This was given at a rate of approximately 3 cc. per minute throughout the experiment. No measurements of inulin or diodrast clearances during the initial 10 to 30 minutes of equilibration are included, although urea clearances were continued during this time.

DISCUSSION

The distribution of observed clearance values in relation to normal adult standards is shown on a log-log graph (Figure 1), with urea clearance values as abscissae, and clearances of diodrast and inulin as ordinates. This type of graph is used because, if the clearance ratios,

$$r_1 = \frac{\text{urea clearance}}{\text{diodrast clearance}}$$

and

$$r_2 = \frac{\text{urea clearance}}{\text{inulin clearance}},$$

are constant, the values of their denominators fall on straight lines with slopes of 45°; it is thus possible to make a visual estimate of the variability of clearance ratios as well as of the deviation of the clearance values themselves from normal standards. The areas indicating the normal ranges of the ratios are plotted from data

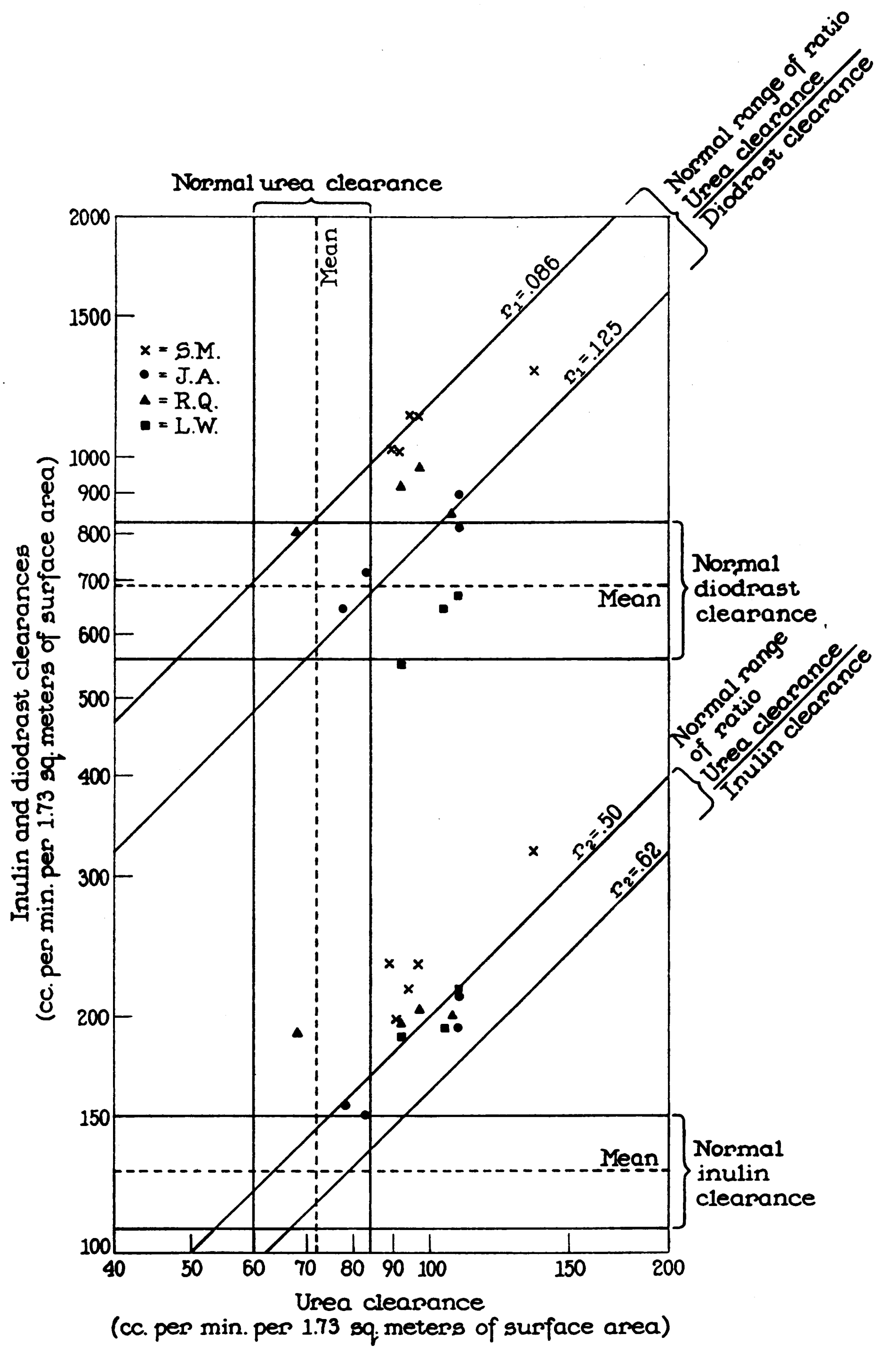

FIG. 1. LOG-LOG GRAPH OF THE INULIN AND DIODRAST CLEARANCES, PLOTTED AGAINST THE UREA CLEARANCE OF 4 CHILDREN WITH NEPHROSIS

TABLE I

Summary of clearance data

Subject	Period	Duration	V_c	Plasma U	Plasma I	Plasma D	Urine U	Urine I	Urine D	Clearances U $\frac{UV_c}{P}$	Clearances U Per cent normal	Clearances I $\frac{UV_c}{P}$	Clearances D $\frac{UV_c}{P}$	Ratios U/I	Ratios I/D
		minutes	*cc.*	*mgm. per 100 cc.*			*mgm. per 100 cc.*			*cc. per minute*					
March 22, 1942	1	96	6.19	8.1			102			78	108				
J. A. ♀ 5 years	2	25	7.16				111			99	136				
factor = 2.52	3	31	3.62		81	2.23	185	3000	440	83	115	150	714	0.57	0.21
	4	29	8.08		51	2.19	109	1280	220	109	151	194	812	0.57	0.24
	5	31	3.90		51	2.13	161	1940	350	78	108	154	641	0.52	0.24
	6	20	5.29		38	1.68	165	1610	285	108	149	213	898	0.52	0.24
Average										92	128	178	766	0.55	0.23
March 12, 1942	1	45	3.47	10.5			337			115	159				
L. W. ♀ 3 years	2	58	4.11				162			63	88				
factor = 2.64	3	61	1.98				472			89	123				
	4	33	7.50		34	2.90	146	872	250	104	145	194	647	0.56	0.30
	5	32	4.35		35	3.23	223	1506	408	92	128	188	550	0.51	0.34
	6	26	5.75		28	2.80	196	1059	326	108	149	217	670	0.52	0.32
Average										95	132	200	622	0.53	0.32
March 16, 1942	1	53	3.34	8.3			235			94	131				
S. M. ♂ 5 years	2	50	3.10				255			95	132				
factor = 2.35	3	30	3.83		23	1.27	194	1400	352	89	124	233	1006	0.40	0.22
	4	27	2.61		23	1.20	290	1738	468	91	126	197	1002	0.48	0.16
	5	31	6.00		24	1.38	130	869	260	94	130	217	1130	0.45	0.19
Average										93	129	216	1046	0.44	0.19
March 30, 1942	1	250	0.99	7.1			760			109	210				
S. M.	2	58	1.17				572			94	172				
	3	37	0.93		21	0.72	736	5240	880	97	197	232	1136	0.44	0.20
	4	38	2.35		17	0.71	406	2330	386	135	187	322	1277	0.44	0.25
	5	29	6.50		20	0.80		778	158			253	1284		0.20
Average										109	192	270	1232	0.44	0.22
R. Q. ♀ 10 years	1	84	6.58	8.5			117			90	125				
factor = 1.76	2	65	9.20	8.3			92			102	141				
	3	29	10.36	8.1	41	0.98	83	820	80	106	142	200	846	0.55	0.24
	4	33	5.40	7.9	37	1.12	100	1300	166	68	95	190	800	0.37	0.24
	5	28	10.66	7.8	39	1.32	71	740	120	97	135	202	970	0.50	0.21
	6	31	6.43	7.6	38	1.22	109	1160	174	92	128	196	918	0.49	0.21
Average										92	128	197	884	0.48	0.23

V_c gives values of urine flow corrected to a surface area of 1.73 sq. M.; to obtain observed flows, divide by the factor given in the first column. U, I, and D represent urea, inulin, and diodrast, respectively.

obtained from adults (3), since the necessary data from normal children are lacking. This use of adult standards for comparison with results from children is partially justified by the fact that urea clearance values in children, when corrected to a surface area of 1.73 sq. M., fall into the same range as adult values, similarly corrected (10). There is a fair degree of presumption, therefore, that diodrast and inulin clearances per sq. M. body surface may be the same for children as for adults, but this presumption remains to be verified by observations on normal children.

The mean normal plasma clearances, in cc. per minute per 1.73 sq. M. of body surface, have been found to be 72 for urea (with urine flows above 2 cc. per minute per 1.73 sq. M. surface), 125 for inulin (3), and 690 for diodrast (3). Compared with these, in our 4 nephrotic cases, the urea clearances were 128 to 192 per cent, the inulin 140 to 220 per cent, and the diodrast 95 to 185 per cent as great as the mean normal values. Since in our 4 high urea clearance nephrotic children, the elevation of the urea clearance was found to be associated with an elevation of both the inulin and diodrast clearances, we conclude that the elevation of the urea clearance is due principally to an increase in renal blood flow (Table I).

SUMMARY

The elevated urea clearance in 4 nephrotic children was found to be associated with increase of both inulin and diodrast clearances.

BIBLIOGRAPHY

1. Farr, L. E., The effect of dietary protein on the urea clearance of children with nephrosis. J. Clin. Invest., 1936, **15**, 703.
2. Emerson, K., Jr., Futcher, P. H., and Farr, L. E., The relation of high and low urea clearances to the inulin and creatinine clearances in children with the nephrotic syndrome. J. Clin. Invest., 1941, **20**, 361.
3. Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W., Relations of effective renal blood flow and glomerular filtration to tubular excretory mass in normal man. J. Clin. Invest., 1940, **19**, 739.
4. White, H. L., and Heinbecker, P., Observations on inulin and diodrast clearances and on renal plasma flow in normal and hypophysectomized dogs. Am. J. Physiol., 1940, **130**, 464.
5. Van Slyke, D. D., and Kugel, V. H., Improvements in manometric micro-kjeldahl and blood urea methods. J. Biol. Chem., 1933, **102**, 489.
6. Flox, J., Pitesky, I., and Alving, A. S., A direct photoelectric colorimetric method for the determination of diodrast and iodides in blood and urine. J. Biol. Chem., 1942, **142**, 147.
7. Alving, A. S., Rubin, J., and Miller, B. F., A direct colorimetric method for the determination of inulin in blood and urine. J. Biol. Chem., 1939, **127**, 609.
8. Harrison, H. E., A modification of the diphenylamine method for determination of inulin. Proc. Soc. Exper. Biol. and Med., 1942, **49**, 111.
9. Møller, E., McIntosh, J. F., and Van Slyke, D. D., Studies of urea excretion. II. Relationship between urine volume and the rate of urea excretion by normal adults. J. Clin. Invest., 1928, **6**, 427.
10. McIntosh, J. F., Møller, E., and Van Slyke, D. D., Studies of urea excretion. III. The influence of body size on urea output. J. Clin. Invest., 1928, **6**, 467.