MEASUREMENT OF GLOMERULAR FILTRATION RATE IN CHILDREN WITH KIDNEY DISEASE [1, 2]

By GUILHERME MATTAR,[3] HENRY L. BARNETT, HELEN McNAMARA, AND HENRY D. LAUSON

(From the Departments of Pediatrics and Physiology, The New York Hospital-Cornell Medical Center, New York, N. Y.)

(Submitted for publication July 7, 1952; accepted August 1, 1952)

The renal clearance of inulin is generally accepted as a measure of glomerular filtration rate (GFR) of water in normal subjects (1). If specific methods (2, 3) are used to determine endogenous creatinine in serum and urine, the creatinine: inulin clearance ratio is close to unity in normal infants, children (4) and adults (5). However, in patients with diminished kidney function, the creatinine [4] clearance is consistently higher than the clearance of inulin (4–7). This fact suggests that in patients with kidney disease, there may be either tubular secretion of creatinine, tubular reabsorption of inulin, or both. The present observations were designed to investigate more completely than had been done previously (8) the problem of whether the clearance of inulin or of creatinine provides a valid measure of glomerular filtration rate in children with kidney disease.

SUBJECTS AND METHODS

Clearances of inulin (C_{IN}) and creatinine (C_{CR}) were measured simultaneously in 57 children with kidney disease (40 patients with the nephrotic syndrome, 15 patients with glomerulonephritis, and two patients with congenital renal anomalies) whose ages ranged from 1½ to 15½ years and in 11 children without kidney disease whose ages ranged from 4 to 12½ years. In some of the observations, clearances of one or more of the following substances were also measured: *p*-aminohippurate (C_{PAH}),[5] urea (C_U), thiosulfate (C_{THIO}), and glucose (C_G). Clearances were measured before and after administration of Carinamide [5] (4′-carboxyphenylmethanesulfonanilide) in four children with kidney disease; before and after injection of desoxycorticosterone glucoside (DCG) [5] in two children with and one without kidney disease; at both low and high concentrations of serum PAH in five children with kidney disease; and at three different concentrations of serum inulin in two children with and one without kidney disease. In the latter observations, step-wise increases in serum inulin concentrations were achieved by increasing the concentration of inulin in the infusion fluid which was administered intravenously at a constant rate. The catheterization and infusion technique used for short-term simultaneous clearances has been described previously (6, 9). Inulin was measured in serum and urine using resorcinol as described by Schreiner (10); PAH by the method of Smith and his associates (11); thiosulfate as described by Newman, Gilman and Philips (12); urea by the method of Archibald (13); and glucose as described by Nelson (14). Carinamide was measured in serum as described by Brodie, Levy, and Bernstein (15). Pre-injection samples of serum and urine were used for blank determinations in all clearances; the urine blank excretions were calculated as milligrams per minute. Endogenous creatinine was determined as described by R. S. Hare (3) except that 5 per cent trichloracetic acid filtrates of serum and urine were used, as has since been advocated by Mandel and Jones (16).

[1] Presented in part before the Society for Pediatric Research at Old Point Comfort, Virginia, May 5, 1952.

[2] This investigation was supported in part by a research grant from the National Institutes of Health, Public Health Service.

[3] Mead Johnson—Society for Pediatric Research Fellow in Pediatrics, 1951.

[4] Here and throughout this paper, the term "creatinine" refers to endogenous creatinine measured by specific methods.

[5] We are indebted to Dr. William Boger, of Sharp and Dohme, Inc., for supplying PAH and Carinamide and to Dr. Ernst Oppenheimer, of Ciba Pharmaceutical Products, Inc., for the DCG.

RESULTS

Creatinine: inulin clearance ratios in children with and without kidney disease

Individual values for the ratio of C_{CR} : C_{IN} in 12 observations on 11 children without kidney disease and in 105 observations on 57 children with kidney disease are shown in Figure 1. The mean value and standard deviation for the ratio in children without kidney disease were 1.03 ± 0.11. Although data from the children with kidney disease show a wide scatter, the ratio tended to be markedly elevated in those children who had reduced C_{IN}.

Thiosulfate: inulin clearance ratios in children with kidney disease

Values for simultaneously determined ratios of C_{THIO} : C_{IN} and C_{CR} : C_{IN} in 36 observations on 25 children with kidney disease are shown in Figure 2. Although the scatter of the data is again large, it is apparent that in contrast to the ratio of C_{CR} : C_{IN} the range of values for C_{THIO} : C_{IN} is the same at all levels of C_{IN} and centers about unity.

Despite the evidence that there may be slight tubular secretion and reabsorption of thiosulfate (17–19), these data suggest that C_{IN} and C_{THIO}, rather than C_{CR}, are at the level of GFR. If C_{CR} measured GFR in the children with reduced kidney function, one would have to conclude that the net effect of tubular transfer of thiosulfate and inulin was approximately the same; this is unlikely for two substances of such different physical-chemical properties.

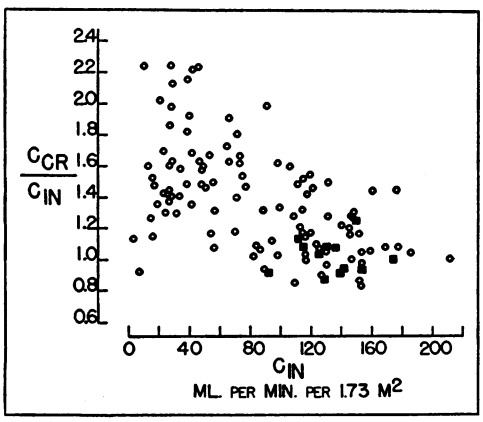

FIG. 1. CREATININE: INULIN CLEARANCE RATIOS (C_{CR}/C_{IN}) IN CHILDREN WITH (OPEN CIRCLES) AND WITHOUT (BLACK SQUARES) KIDNEY DISEASE PLOTTED AGAINST THE INULIN CLEARANCE (C_{IN})

Each symbol represents the integrated mean value for three consecutive clearance periods.

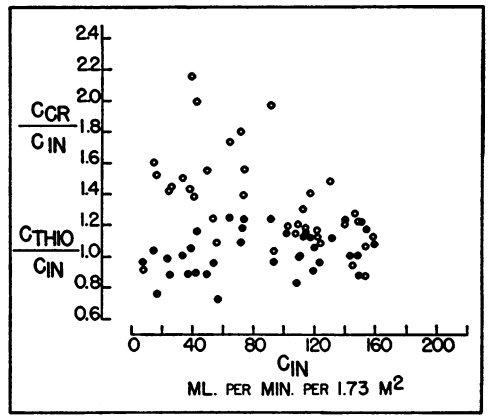

FIG. 2. SIMULTANEOUSLY DETERMINED CLEARANCE RATIOS OF CREATININE: INULIN (C_{CR}/C_{IN}, OPEN CIRCLES), AND THIOSULFATE:INULIN (C_{THIO}/C_{IN}, BLACK DOTS), IN CHILDREN WITH KIDNEY DISEASE PLOTTED AGAINST THE INULIN CLEARANCE, C_{IN}

Inulin clearances at various serum inulin concentrations in children with kidney disease

C_{IN} was measured at three widely separated ranges of serum inulin concentrations in each of two children (LA, SV) with and in one (OR) without kidney disease. Simultaneous measurements of C_{CR}, C_U, and C_{PAH} were made. The results are given in Table I. It can be seen that changes in serum inulin concentrations, varying from 16 to 207, from 12 to 61, and from 24 to 112 mgm. per 100 ml., had no consistent effect on C_{IN}, or on the ratios of C_{CR} : C_{IN}, C_U : C_{IN}, and C_{PAH} : C_{IN}.

Equations for the best fit lines relating serum inulin concentration, S_{IN}, to rate of inulin excretion, $U_{IN}V$, were calculated by the method of least squares from the data on LA, SV, and OR. These equations are given in Table IA and the lines for LA and SV are shown graphically in Figure 3 together with the observed values. The intercept of the curve on the $U_{IN}V$ axis (inulin excretion) does not differ statistically (Table IA) from the origin in either of the children with or in the child without kidney disease. Hence the data support the conclusion that the excretion of inu-

TABLE I

Effect of varying concentrations of inulin in serum on clearances of inulin (C_{IN}) *and on ratios of clearances of creatinine* (C_{CR}), *urea* (C_U) *and para-aminohippurate* (C_{PAH}) *to* C_{IN} *in two children with and one without kidney disease*

Subject	Elapsed time	Urine flow	Inulin			$\frac{C_{CR}}{C_{IN}}$	$\frac{C_U}{C_{IN}}$	$\frac{C_{PAH}}{C_{IN}}$‡
			Serum†	Excreted	Clearance			
	min.	*ml./min.*	*mgm./100 ml.*	*mgm./min.*	*ml./min.*			
LA	0–16	0.21						
Age: 3 yrs. Height: 95 cms. Weight: 19.9 kgm. S. A.: 0.60 M²*	28–32	Priming infusion: 7 ml. of 10 per cent inulin and 1.2 ml. of 20 per cent PAH. Sustaining infusion: 0.53 gm. inulin, 0.27 gm. PAH and 0.90 gm. NaCl per 100 ml., given at 0.5 ml./min.						
Mean C_{IN} = 7.8 ml./min. = 18 per cent normal	75–88	0.21	17.0	1.31	7.7	1.65	0.70	3.81
	89–102	0.24	16.3	1.28	7.9	1.75	0.72	4.01
	103–115	0.25	15.7	1.29	8.2	1.68	0.79	4.16
	117–121	Priming infusion: 20 ml. of 10 per cent inulin. Sustaining infusion: 1.66 gm. inulin, 0.27 gm. PAH and 0.90 gm. NaCl per 100 ml., given at 0.5 ml./min.						
	155–168	0.21	63.0	4.88	7.8	1.72	0.68	4.15
	169–182	0.26	59.1	4.95	8.4	1.65	0.77	4.30
	183–196	0.28	55.5	4.52	8.1	1.79	0.84	4.60
	198–202	Priming infusion: 55 ml. of 10 per cent inulin. Sustaining infusion: 4.0 gm. inulin, 0.27 gm. PAH and 0.90 gm. NaCl per 100 ml., given at 0.5 ml./min.						
	241–254	0.43	206.5	15.81	7.7	1.79	0.84	4.61
	255–268	0.38	193.7	14.09	7.3	1.86	0.88	5.05
	269–282	0.34	183.2	13.02	7.1	2.01	1.00	5.10
SV	0–14	0.52						
Age: 3 yrs. Height: 98 cms. Weight: 19.9 kgm. S. A.: 0.64 M²*	17–20	Priming infusion: 7 ml. of 10 per cent inulin and 1.5 ml. of 20 per cent PAH. Sustaining infusion: 0.40 gm. inulin, 0.20 gm. PAH and 0.90 gm. NaCl in 100 ml., given at 0.5 ml./min.						
Mean C_{IN} = 27 ml./min. = 59 per cent normal	50–67	0.46	16.6	4.34	26.1	1.39	0.58	7.49
	68–80	0.45	14.1	3.48	24.7	1.58	0.64	7.36
	81–93	0.48	12.1	3.01	24.9	1.53	0.64	7.46
	98–102	Priming infusion: 16 ml. of 10 per cent inulin. Sustaining infusion: 1.17 gm. inulin, 0.20 gm. PAH and 0.90 gm. NaCl in 100 ml., given at 0.5 ml./min.						
	132–143	0.46	35.8	9.65	27.0	1.35	0.48	6.06
	144–156	0.41	32.4	8.26	25.5	1.63	0.60	7.05
	157–168	0.42	29.5	8.89	30.1	1.30	0.44	5.50
	171–175	Priming infusion: 25 ml. of 10 per cent inulin. Sustaining infusion: 3.0 gm. inulin, 0.20 gm. PAH and 0.90 gm. NaCl in 100 ml., given at 0.5 ml./min.						
	216–227	0.45	61.1	18.85	30.9	1.49	0.44	6.47
	228–239	0.43	57.6	16.18	28.1	1.53	0.51	7.36
	240–251	0.42	54.3	13.43	24.7	1.60	0.58	7.62

TABLE I—*Continued*

Subject	Elapsed time	Urine flow	Inulin			$\frac{C_{CR}}{C_{IN}}$	$\frac{C_U}{C_{IN}}$	$\frac{C_{PAH}‡}{C_{IN}}$
			Serum†	Excreted	Clearance			
	min.	*ml./min.*	*mgm./100 ml.*	*mgm./min.*	*ml./min.*			
OR	0–10	6.15						
Age: 8 yrs. Height: 136.5 cms. Weight: 43 kgm. S. A.: 1.22 M^2*	14–18	Priming infusion: 14 ml. of 10 per cent inulin and 2.1 ml. of 20 per cent PAH. Sustaining infusion: 1.28 gm. inulin, 0.50 gm. PAH and 0.60 gm. NaCl per 100 ml., given at 1.5 ml./min.						
Mean C_{IN} = 76.2 ml./min. = 76 per cent normal	52–61	1.54	26.1	19.35	74.1	1.23	0.47	5.61
	62–71	1.69	25.2	18.98	75.3	1.26	0.53	5.65
	72–81	2.58	24.2	18.53	76.6	1.28	0.57	5.81
	83–87	Priming infusion: 30 ml. of 10 per cent of inulin. Sustaining infusion: 4.25 gm. inulin, 0.50 gm. PAH and 0.60 gm. NaCl per 100 ml., given at 1.5 ml./min.						
	124–133	1.41	64.0	46.60	72.8	1.28	0.47	5.46
	134–143	1.35	62.1	44.60	71.8	1.25	0.52	5.50
	144–153	1.71	60.3	47.00	77.9	1.16	0.49	5.44
	155–159	Priming infusion: 43 ml. of 10 per cent inulin. Sustaining infusion: 8.50 gm. inulin, 0.50 gm. PAH and 0.60 gm. NaCl per 100 ml., given at 1.5 ml./min.						
	194–203	1.40	112.0	83.50	74.8	1.16	0.49	4.79
	204–213	1.70	106.4	87.50	82.7	1.18	0.55	5.09
	214–223	1.62	101.3	80.00	79.2	1.18	0.51	4.75

* Ideal weight for height and age (21) was used for the estimation of surface area (22) from which expected normal values for renal clearances were calculated.
† Values interpolated to mid-point of period.
‡ Serum PAH concentrations in mgm. per 100 ml. ranged from 2.92 to 1.85 in LA, from 1.34 to 0.42 in SV and from 1.05 to 1.78 in OR.

lin is linearly proportional to the concentration of inulin in serum.

These results, which confirm earlier observations of Miller and Winkler (8), further suggest that C_{IN} measures GFR in these children. If there were tubular reabsorption of inulin, and if there were a limiting rate of reabsorption within the range of serum inulin concentrations obtained, one

TABLE IA

Statistical summary

Subject	Equation of best fit line*	Standard deviation of intercept†	t‡	P§
LA	$U_{IN}V = 0.251 + 0.073\ S_{IN}$	±0.189	1.325	0.22
SV	$U_{IN}V = -0.606 + 0.292\ S_{IN}$	±0.702	0.863	0.41
OR	$U_{IN}V = -1.68 + 0.793\ S_{IN}$	±2.35	0.716	0.50

* Calculated by method of least squares. $U_{IN}V$ is given in mgm. per minute and S_{IN} in mgm. per 100 ml.
† Calculated as described by Youden (20).
‡ t = Intercept ÷ standard deviation of intercept.
§ P is the probability that the observed intercept deviates from the origin by chance alone.

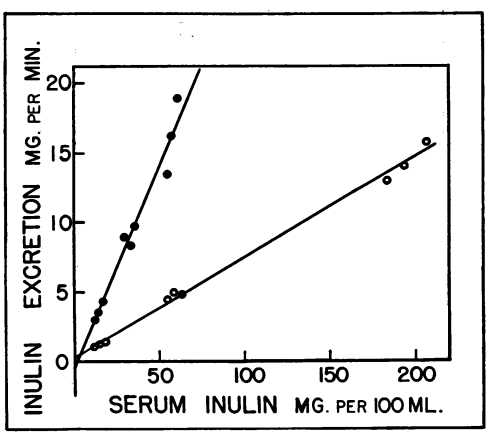

FIG. 3. RELATIONSHIP BETWEEN CONCENTRATION OF INULIN IN SERUM AND RATE OF INULIN EXCRETION IN TWO CHILDREN WITH KIDNEY DISEASE

See text for explanation of fitted lines.

TABLE II

Clearances of inulin (C_{IN}), para-aminohippurate (C_{PAH}), creatinine (C_{CR}) and urea (C_U) and ratios of $C_{PAH}:C_{IN}$ and $C_{CR}:C_{IN}$ before and after single and repeated doses of Carinamide in four children with the nephrotic syndrome

Subject	Age	Surface area	Date	C_{IN}	C_{PAH}	C_{CR}	C_U	$\frac{C_{PAH}}{C_{IN}}$	$\frac{C_{CR}}{C_{IN}}$	Serum Carinamide*
	yrs.	*M^2*		*ml./min./1.73 M^2*						*mgm./100 ml.*
BE	5	0.75	Nov. 27, 1951	55.0	269	79.8	30.4	4.90	1.45	0
				Carinamide: 0.13 gm./Kgm. 1 dose						
				47.4†	117	66.7	28.7	2.47	1.41	5.6–7.7
LO	4	0.66	Nov. 7, 1951	28.6	97	40.1	20.1	3.39	1.40	0
			Nov. 8 to 9, 1951	Carinamide: 0.04 gm./Kgm. q 4h 7 doses						
			Nov. 9. 1951	24.0†	28	34.3	17.0	1.17	1.43	3.6–6.4
			Jan. 21, 1952	26.5	80	36.7	18.6	3.02	1.38	0
				Carinamide: 0.36 gm./Kgm. 1 dose						
				23.8†	28	32.0	16.0	1.18	1.34	4.7–13.3
			Feb. 11 to 13, 1952	Carinamide: 0.06 gm./Kgm. q 6h 9 doses						
			Feb. 13, 1952	22.8†	23	25.9	15.9	1.01	1.14	5.7–6.9
KR	8	0.95	Dec. 28, 1951	25.8	84	37.3	22.7	3.26	1.45	0
			Dec. 31, 1951 to Jan. 2, 1952	Carinamide: 0.04 gm./Kgm. q 4h 13 doses						
			Jan. 2, 1952	22.0†	25	26.0	19.7	1.14	1.18	21.4–25.1
RI	2½	0.54	June 8, 1951	49.3	398	79.0	—	8.07	1.60	0
			June 12 to 15, 1951	Carinamide: 0.03 gm./Kgm. q 3h 24 doses						
			June 15, 1951	41.3†	53	47.4	—	1.28	1.15	?

* Concentrations at beginning and end of clearance periods.

† Post-Carinamide clearances were started between 1.5 and 2 hours after either a single dose or after the last of the repeated doses.

would expect, as pointed out by Shannon and Smith (23), that the amount excreted per unit time would not have been related to serum inulin concentrations in the manner shown in Figure 3. Rather, the curve would, when extrapolated, intersect the ordinate at a negative value.

Contrary to these and the earlier results mentioned (8, 23), Ferguson and his associates (24) have recently reported observations in which lines similarly plotted did intersect the ordinate at a negative value, from which they conclude that tubular reabsorption of inulin occurs. However, in their four observations in three subjects to whom continuous intravenous infusions of inulin were given, the inulin was dissolved in physiologic saline and different serum inulin concentrations

were achieved by changing the rate of infusion rather than by changing the concentration of inulin in the infusion fluid as done here. In the interpretation of all these observations, it is assumed that GFR remains constant throughout. Since each of the 3 subjects studied by Ferguson and his co-workers (24) had hypertension and one was 70 years old, it is possible that changes in the rate of infusion of saline induced changes in GFR. Such induced changes in GFR, if they occurred, could explain the contradictory results.

Effect of Carinamide on the creatinine: inulin clearance ratio in children with kidney disease

If, as suggested by the observations above, C_{IN} measures GFR in children with kidney disease, it follows that creatinine is secreted by the tubules and that it may be possible to suppress this function.[6] Carinamide is known to suppress the tubular secretion of a number of substances (26–28). The effect of varying amounts of Carinamide given by mouth to four children with kidney disease (BE, LO, KR, RI) and with high ratios of C_{CR}: C_{IN} is shown in Table II. It can be seen that a single dose of 0.13 gm. per kgm. given to LO on January 21, 1952 failed to suppress the ratio of C_{CR}: C_{IN}. Similarly, a dosage of 0.04 gm. per kgm. given to LO at four-hour intervals for seven doses had no effect on the ratio measured one hour after the last previous dose on November 9, 1951. However, doses of 0.03 to 0.06 gm. per kgm. given at three- to six-hour intervals for nine to 24 doses decreased the ratio toward one in LO, KR, and RI. The constancy of the ratio, as well as of C_{IN}, in the four observations on LO over a period of three months strongly suggests that the decrease after nine doses of Carinamide was, in fact, due to the drug.

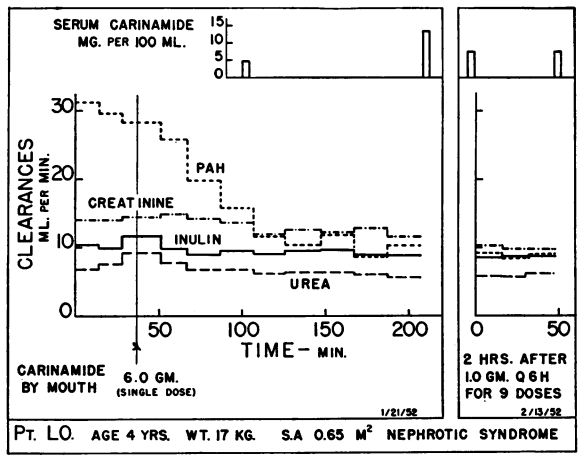

FIG. 4. CLEARANCES OF PARA-AMINOHIPPURATE (PAH), CREATININE, INULIN, AND UREA IN A CHILD WITH KIDNEY DISEASE BEFORE AND AFTER A SINGLE DOSE AND AFTER REPEATED DOSES OF CARINAMIDE BY MOUTH

From these observations, which confirm the earlier reports of Brod and Sirota (29) and Brod and Kotatko (25), it would appear that the high ratio of C_{CR}: C_{IN} occurring in children with kidney disease and reduced C_{IN} can be brought toward one by a decrease in C_{CR} with no marked change in C_{IN}. It is of interest as shown in Figure 4 that when Carinamide had been given to LO every six hours for nine doses and when creatinine secretion was suppressed the concentration of Carinamide in serum was actually lower than that observed after a single large dose which failed to suppress secretion of creatinine. It can also be seen in Figure 4 that C_{PAH} was reduced to the level of C_{IN} and below the simultaneously measured C_{CR}. This observation strongly supports the conclusion that C_{IN} rather than C_{CR} measures GFR. If C_{CR} were at the level of GFR, one would have to conclude that Carinamide not only suppresses tubular secretion but causes tubular reabsorption of PAH which is unlikely.[7]

[6] Brod and Kotatko (25) have reported that in patients with kidney disease who had high ratios of C_{CR}: C_{IN}, high concentrations of PAH in serum depressed the ratio toward one. However, in 5 observations on children with kidney disease who had high ratios of C_{CR}: C_{IN} (1.6 to 2.3) and in whom the ratio was measured at low (0.65 to 1.52 mgm. per 100 ml.) and high (56 to 88 mgm. per 100 ml.) serum PAH concentrations, we observed an *apparent increase* (4 to 32%) in the ratio in four and no apparent change in the fifth. We have found that high concentrations of PAH (25 mgm. per 100 ml.) in a creatinine solution adsorbed onto Lloyd's reagent cause an increase in the color obtained in the Jaffe reaction done on the eluate. Although the magnitude of this effect could account for the apparent *increases* in the ratio of C_{CR}: C_{IN}, we do not believe it is great enough to conceal significant *decreases* in the ratio. We cannot explain the discrepancy between these results and those reported by Brod and Kotatko (25).

[7] Further support would be given to this conclusion if complete suppression of glucose reabsorption raised the clearance of glucose (C_G) to the level of C_{IN} rather than to C_{CR}. Suppression of glucose reabsorption was at-

COMMENT

The data presented, if extended and confirmed, would appear to validate C_{IN} as a measure of GFR in children with kidney disease. However, as is true in normal subjects, the evidence for this concept is indirect. The evidence rests in part on the demonstration that C_{IN} is independent of changes in serum inulin concentration within wide limits, which appears to be true in the present data on children with kidney disease. However, in both the normal and diseased kidney, it is possible, though unlikely, that a very small but constant percentage of filtered inulin is reabsorbed. This type of tubular reabsorption with no definite upper limiting rate is generally believed to occur with urea.

In addition, there is a greater possibility in patients with kidney disease than in the normal subject that there could be more or less complete reabsorption of glomerular filtrate in some nephrons. If so, as stated by Smith (1), it remains beyond the possibility of examination as long as only the total urine is available for analysis. However, even if complete local reabsorption occurs, C_{IN} would still measure the rate of filtration of that part of the glomerular fluid which is elaborated into urine.

These criticisms of part of the evidence supporting the validity of C_{IN} as a measure of GFR do not alter the inferences drawn from the observations with Carinamide concerning tubular secretion of creatinine in children with kidney disease.

The data presented have certain clinical as well as physiologic significance. It has been suggested by Brod and Sirota (27) that "creatinine" chromogen (total creatinine chromogen) clearances may provide a useful clinical approximation of GFR in subjects with kidney disease. On the other hand, Miller and his associates (7) conclude that neither total chromogen nor specific endogenous creatinine clearances should be employed as a precise measure of GFR in patients with kidney disease. Our data strongly suggest that C_{CR} provides neither a precise nor an approximate measure of GFR in children with kidney disease.

If one or two large doses of Carinamide had consistently depressed the ratio of C_{CR}: C_{IN} to unity in children with kidney disease, it might have been possible to utilize this effect in devising a relatively simple means of measuring GFR in these children. However, since Carinamide had to be given over a period of at least 2 days to depress the ratio, it does not appear clinically feasible to use this drug for this purpose.

SUMMARY AND CONCLUSIONS

The data presented indicate that, using a specific method for measuring endogenous creatinine in serum and urine, the creatinine: inulin clearance ratio is close to unity in normal children, but tends to be markedly elevated in children with kidney disease and reduced kidney function.

In observations designed to investigate whether the clearance of inulin or of creatinine provides a valid measure of glomerular filtration rate in children with kidney disease and with high creatinine: inulin clearance ratios, it has been found that in these children:

(a) thiosulfate: inulin clearance ratios are close to unity;

(b) the inulin clearance is constant over a wide range of concentrations of inulin in serum;

(c) Carinamide in dosages that fail to lower the creatinine: inulin clearance ratio depresses the clearance of *p*-aminohippurate to the level of the inulin clearance and below the simultaneously measured creatinine clearances; and

(d) prolonged oral administration of Carinamide may decrease the creatinine: inulin ratio toward one by decreasing the creatinine clearance without increasing the inulin clearance.

The data suggest that:

(a) the clearance of inulin does provide a valid measure of glomerular filtration rate in children with kidney disease;

(b) in children with high creatinine: inulin clearance ratios, creatinine is secreted by the tubules; and

tempted with desoxycorticosterone glucoside (30, 31). However, 100 mgm. given in a single injection intravenously raised C_G only to 60 per cent of C_{IN} in an 8-year-old child without kidney disease. The same dose in two children, 2 and 3 years old, with kidney disease and reduced C_{IN} increased C_G only to 18 and 40 per cent of C_{IN}. The smaller effect in children with reduced function dissuaded us from using larger doses to try to get complete inhibition of glucose reabsorption.

(c) using specific creatinine methods, the endogenous creatinine clearance may measure glomerular filtration rate in normal children, but that creatinine clearances *cannot* be used to measure glomerular filtration rate in children with kidney disease.

ACKNOWLEDGMENTS

We are indebted to Flora Hurwitz, R.N. for nursing and technical assistance and to Emily Matejka and Gladys Folkart for technical assistance.

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