JCI The Journal of Clinical Investigation

RENAL EXTRACTION OF PARA-AMINOHIPPURATE IN INFANTS AND CHILDREN

Philip L. Calcagno, Mitchell I. Rubin

J Clin Invest. 1963;42(10):1632-1639. https://doi.org/10.1172/JCI104848.

Research Article

Journal of Clinical Investigation
Vol. 42, No. 10, 1963

RENAL EXTRACTION OF PARA-AMINOHIPPURATE IN INFANTS AND CHILDREN *

BY PHILIP L. CALCAGNO † AND MITCHELL I. RUBIN

(From the Statler Research Laboratories, Buffalo Children's Hospital, and the Department of Pediatrics, School of Medicine, State University of New York, Buffalo, N. Y.)

(Submitted for publication April 6, 1961; accepted July 3, 1963)

Earlier publications questioned the reliability of measurements of renal plasma flow in young infants, since the extraction ratios for para-aminohippurate (E_{PAH}) used were those obtained in adults (1–3). It was suggested that the use of these high values for E_{PAH} to determine renal plasma flow and filtration fraction might not be valid and could account for the high filtration fraction reported in infants under a year of age (1–5). This high fraction was interpreted to indicate that the rate of glomerular filtration is greater in comparison to renal plasma flow than that in adults. The present study was designed to measure E_{PAH} in young infants in order to arrive at the true value for renal plasma flow and calculated filtration fraction.

METHODS

Fifteen children between 8 days and 10 years old were studied; eight were under 3 months, and seven between 5 months and 10 years old. Pertinent clinical and laboratory data are listed in Tables I through IV. Forty-five minutes before testing, eight of the fifteen patients were given a sedative; [1] five were infants (no. 1 and 5–8) and three were older children (no. 10, 11, and 15). Inulin [2] and para-aminohippurate (PAH) were administered in normal saline or 5% dextrose in water after base-line control venous blood determinations were made. The diluent and the intervals from the mixing of PAH with the diluent to the end of the test are recorded in Tables II and III. Saline as the diluent for the PAH injection was used in four infants and in two children. Five per cent dextrose in water was the diluent in four infants and in seven children. Two infants and two children were studied with both diluents. All blood samples were collected in heparinized tubes. Inulin and PAH were given to maintain arterial blood concentrations above 25 mg per 100 ml for inulin and below 4 mg per 100 ml for PAH. These values were not always obtained, but in the four infants given PAH in normal saline, the level of renal arterial PAH was over 3.1 mg per 100 ml in only one period of Patient 1.

A no. 10 French catheter was placed in the bladder for urine collections. The femoral artery and vein were catheterized with Birds Eye catheters no. 5, 6, or 7. Under direct fluoroscopic supervision, the right renal vein was entered, and an attempt was made to enter the right renal artery; if it was unsuccessful, arterial blood samples were obtained from the aorta close to the renal artery. Spot films were taken to demonstrate the location of catheters before collections were made. Measurements of glomerular filtration rate and effective renal plasma flow measurements were made in three infants and in one older child. Complete emptying of the bladder was obtained by instilling air, and blood was withdrawn simultaneously from the right renal vein and the right renal artery or aorta at the mid-point during the 20-minute urine collection periods. On several occasions, duplicate blood samplings were obtained during a single urine collection period. At least three clearance periods were obtained during the study from each patient. For comparison in the same patient of E_{PAH} with normal sa-

TABLE I

Pertinent clinical data of patients

Patient no.	Diagnosis	Age	Weight	BSA
			kg	m^2
1	Mongolism	8 days	2.47	0.188
2	Cleft palate	10 days	2.90	0.209
3	Aortic stenosis	14 days	3.95	0.252
4	Mongolism	16 days	3.45	0.230
5	Mongolism	1 mo	2.55	0.190
6	Mongolism	1 mo	2.75	0.186
7	Mental retardation	2 mos	3.04	0.217
8	iv Septal defect	3 mos	4.42	0.256
9	Tetralogy of Fallot	5 mos	6.75	0.369
10	Mental retardation	8 mos	7.55	0.360
11	Pulmonary stenosis	5 yrs	22.3	0.816
12	iv Septal defect	5½ yrs	17.5	0.725
13	iv Septal defect	6 yrs	18.2	0.750
14	Essential hypertension	8 yrs	45.5	1.263
15	Tetralogy of Fallot	10 yrs	27.9	0.948

* Aided by U. S. Public Health Service grants A-3257 and HE-07927.

† Present address: Georgetown University Medical Center, 3800 Reservoir Road, N.W., Washington 7, D.C.

[1] Chlorpromazine, 6.25 mg per ml; promethazine, 6.25 mg per ml; and meperidine hydrochloride, 25.00 mg per ml. The dose was 1 ml per 20 pounds of body weight, up to a maximum of 2 ml.

[2] Kindly supplied by the General Diagnostics Division, Warner-Chilcott Laboratories, Morris Plains, N. J.

TABLE II

Renal vein extraction (E) for inulin and para-aminohippurate (PAH) in infants

Patient no.	Age	Diluent*	Mixing time†	Renal artery or aorta		Rt. renal vein		E_{in}	E_{PAH}
				Inulin	PAH	Inulin	PAH		
			min	*mg/100 ml*				%	%
1	8 days	Saline	480	23.9	1.82	19.5	0.63	22.6	65.4
				34.8	1.40	29.1	0.42	16.5	70.0
			50 ml blood + 200 ml normal saline						
				45.9	4.06	36.3	1.35	20.2	66.7
				49.0	2.95	34.2	1.02	30.2	65.4
				46.8	2.58	32.4	0.83	30.7	67.8
2	10 days	Dextrose	240	157.9	5.70	101.2	1.87	36.0	67.2
				163.9	5.20	108.4	1.94	34.2	62.7
			25 ml blood, iv						
				177.1	5.94	131.5	2.23	25.4	62.5
3	14 days	Dextrose	60		2.49		0.62		75.1
					2.93		0.75		74.6
					3.47		0.85		74.9
4	16 days	Dextrose	210	79.5	6.00	65.5	5.03	17.6	16.2
				77.4	6.15	66.4	4.42	14.2	28.0
				72.0	5.70	59.6	2.40	17.2	58.0
5	1 mo	Saline	340		2.58		0.74		71.3
					2.88		1.05		63.5
					2.92		0.88		69.8
		Dextrose	390		4.63		2.71		41.5
					5.24		2.23		57.4
					5.39		2.85		50.8
6	1 mo	Saline	190		2.59		2.34		9.7
					2.70		2.61		3.3
					3.14		2.86		8.9
		Dextrose	240		4.28		4.53		
					4.59		4.53		1.4
					4.53		4.86		
7	2 mos	Dextrose	165		1.37		0.60		56.0
					1.70		0.89		47.8
					1.20		0.59		51.2
8	3 mos	Saline	60		1.53		0.36		76.7
					1.69		0.26		84.4
					1.69		0.26		84.4

* Saline = normal saline; dextrose = 5% dextrose in water.
† Time of mixing PAH to completion of test.

line and with 5% dextrose in water, 15 minutes was allowed for iv equilibration of the second fluid administration. In each case, the normal saline diluent was administered first. After the tests, the femoral artery was sutured with no. 60 silk, and the patients were given an antibiotic for 48 hours. No serious untoward reactions were noted in any subject.

Inulin was determined by the method of Hubbard and Loomis (6), with the acid mixture for hydrolysis of inulin as modified by Harrison (7). PAH was determined as described by Goldring and Chasis (8). Standard solutions of inulin and PAH were analyzed for construction of a calibration curve for each set of unknown solutions. All determinations were made in duplicate. The a-v differences for inulin in blank determinations on three infants varied from 0.5 to 1.0%. The a-v differences for PAH blank determinations were negligible. No correction was made for the delay in passage of the urine from the renal parenchyma to the catheter. Inulin and PAH plasma E were calculated from the formula $E = (A - V)/A \times 100$, where A is arterial concentration and V is renal venous concentration, both in milligrams per milliliter. Oxygen content was determined by a cuvette oximeter (9).

To ascertain that the renal vein was properly catheterized, three criteria were used: *1*) direct fluoroscopic visualization and spot films of the catheter in position, *2*) the difference in arterial and renal venous oxygen saturation of less than 10%, and *3*) significant differences in inulin concentrations between arterial and venous blood

TABLE III

Renal vein extraction (E) for inulin and para-aminohippurate in children

Patient no.	Age	Diluent*	Mixing time†	Renal artery or aorta		Rt. renal vein		E_{in}	E_{PAH}
				Inulin	PAH	Inulin	PAH		
			min	*mg/100 ml*				%	%
9	5 mos	Dextrose	135		3.52		0.27		92.4
					4.96		0.48		90.4
					4.27		0.50		88.4
10	8 mos	Dextrose	210	44.4	1.73	35.3	0.21	20.6	87.9
				44.7	1.85	36.4	0.26	18.7	86.0
				45.2	1.85	37.5	0.24	17.0	87.0
11	5 yrs	Saline	5		1.06		0.08		92.4
					0.99		0.05		94.9
					0.94		0.01		99.3
		Dextrose	50		1.24		0.05		96.0
					1.30		0.08		93.8
					1.27		0.05		96.1
12	5½ yrs	Dextrose	75		1.61		0.14		91.2
					1.67		0.14		91.6
					2.03		0.15		92.6
13	6 yrs	Dextrose	60		0.46		0.00		100.0
					0.81		0.02		97.6
					0.99		0.02		98.2
14	8 yrs	Dextrose	240	29.2	0.84	20.5	0.20	29.8	76.2
				24.0	0.72	18.0	0.15	25.0	79.2
				24.0	0.71	18.0		25.0	
				22.8	0.63	14.3	0.07	37.3	88.9
15	10 yrs	Saline	5		0.72		0.10		86.1
					0.72		0.11		84.3
					0.72		0.08		89.5
		Dextrose	70		1.44		0.08		94.7
					1.38		0.03		98.6
					1.31		0.08		94.3

* Saline = normal saline; dextrose = 5% dextrose in water.
† Time of mixing PAH to completion of test.

TABLE IV

Renal function in several patients

Patient no.	Age	Glomerular filtration rate*	Renal plasma flow	Filtration fraction	Renal a-v O_2 difference
		ml/min/1.73		%	*ml/100 ml*
1	8 days	26	139	18.7	
		21	129	16.4	
		50 ml blood + 200 ml normal saline			
		18	86	20.4	
		33	108	30.6	
		34	112	30.4	
2	10 days	61	277	22.0	1.4
		25 ml blood			
		56	215	26.0	
4	16 days	39	183	21.3	1.3
		53	232	22.8	
10	8 mos	143	579	25.0	0.8
14	8 yrs				1.1

* Measured by inulin clearance.

(14.2 to 37.3%). These criteria were not met in three children, whose data are not included in this report.

To determine whether or not significant diffusion of PAH occurs from the red blood cells to the plasma after blood samples are obtained from the renal artery and vein, blood was obtained from three patients (no. 3, 9, and 12) and allowed to stand for different periods before separation of red cells from plasma and before determination of PAH concentration.

RESULTS

Table II lists the pertinent data obtained. Inulin extractions (E_{in}) averaged 24.0% for the three young infants so studied (Patients 1, 2, and 4) and were not significantly different for the older children (Patients 10 and 14) (see Tables II and III). The arterial blood concentrations of inulin ranged between 23.9 and 177.1 mg per 100 ml. Renal E_{PAH} with normal saline as the diluent averaged 58.6% for the four young infants (no. 1, 5, 6, and 8) and 91.0% for the two older children. The arterial plasma PAH concentrations ranged between 1.40 and 4.06 mg per 100 ml, while the renal venous plasma PAH ranged between 0.25 and 2.86 mg per 100 ml for the four young infants.

In the four infants (no. 2, 3, 4, and 7) who received PAH in the dextrose and water diluent, the

TABLE V

Diffusion of para-aminohippurate from cells to plasma

Patient no.	Age	Period	Start of PAH infusion to bleeding	Renal PAH concentration		E_{PAH}*	Standing time†
				Artery	Vein		
			min	*mg/100 ml*		%	*min*
3	2 wks	B_0	0	0.11	00.0		
		B_1	15	2.49	0.62	75.1	3
				2.13	0.68	68.0	11
				2.85	0.62	78.3	24
		B_2	20	2.93	0.75	74.4	6
				3.14	0.75	76.1	10
				2.94	0.66	77.6	58
		B_3	25	3.47	0.85	75.5	15
				3.23	0.85	73.7	33
				3.04	0.90	70.4	92
Average						74.3	
9	5 mos	B_0	0	0.03	0.00	00.0	
		B_1	15	3.52	0.27	92.4	4
				3.49	0.34	90.4	16
		B_2	20	4.96	0.48	90.4	11
				4.83	0.48	90.4	27
		B_3	25	4.27	0.50	88.4	6
				4.10	0.49	88.0	22
				4.01	0.49	87.8	37
Average						89.6	
12	5½ yrs	B_0	0	0.06	0.06	00.0	
		B_1	15	1.61	0.14	91.2	3
				1.61	0.13	91.9	22
				1.64	0.18	89.0	34
		B_2	20	1.67	0.14	91.6	7
				1.53	0.14	90.9	31
				1.53	0.14	90.9	47
		B_3	24	2.03	0.15	92.6	17
				2.06	0.18	91.2	36
				1.98	0.18	90.9	84
Average						91.1	

* E_{PAH} = extraction ratio for para-aminohippurate.
† Standing time of whole blood before centrifugation.

individual average E_{PAH} were 64.5, 74.9, 58.0, and 52.0%. The interval from mixing the PAH and dextrose solution until completion of the test in these cases was between 60 and 240 minutes.

In the two infants who received both diluents (Patients 5 and 6), average E_{PAH} with saline diluent were 68.2 and 7.3%, respectively; with 5% dextrose in water the diluent average E_{PAH} were 49.9 and 1.4%. The mixing times for PAH in dextrose in water diluent were 390 and 240 minutes, respectively.

Table III lists data obtained in older infants and children (5 months old and older). Individual average E_{PAH} in the two children in this group (no. 11 and 15) given PAH in normal saline were 86.6 and 95.5%. For the seven children given PAH in 5% dextrose in water (Patients 9–15), individual average E_{PAH} were 90.4, 87.0, 95.3, 91.8, 98.6, 81.4, and 95.9%. The interval between mixing PAH and dextrose solution and completion of the test was between 50 and 240 minutes.

In the two older children who received both diluents, average E_{PAH} with saline diluent were 95.5 and 86.6% in Patients 11 and 15, respectively; with 5% dextrose in water the diluent average E_{PAH} were 95.3 and 95.9%. The mixing times for PAH in dextrose in water diluent were 50 and 70 minutes, respectively.

Table IV lists, for the young infants (no. 2 and 4), glomerular filtration rates that are within 1 SD of the values reported for infants in this age group (2). Patient 1 had a low glomerular filtration rate owing to dehydration from water deprivation (10). Patient 10, who was 8 months old, had a glomerular filtration rate comparable to the average adult value.

Filtration fractions calculated from the ratio of glomerular filtration rate to renal plasma flow (with the determined E_{PAH}) averaged 23.2% for the three young infants studied and compare closely with the average renal E_{in} of 24.0%. Renal a-v oxygen differences ranged between 0.8 and 1.4 ml per 100 ml in the four patients studied.

Table V lists renal vein and renal artery blood concentrations obtained at varying intervals after administration of PAH. A portion of each blood sample was centrifuged immediately in a cold room. The other blood samples were allowed to stand at room temperature for varying intervals before centrifugation in a cold room and determination of PAH. Plasma concentrations of PAH in the renal artery and vein did not vary appreciably with standing for as long as 92 minutes before centrifugation, indicating minimal diffusion from red cells to the plasma. This is also apparent in the relative constancy of E_{PAH}.

DISCUSSION

Baldwin and co-workers (11) showed that infusion of PAH dissolved in 5% glucose solution in man leads to a reduction in E_{PAH}. They point out that with glucose a reaction product develops that apparently has a low clearance, as indicated by the low extraction ratio of PAH-glucose mixtures. Some of our studies were done with glucose as a diluent, and it was important to determine whether or not a PAH-glucose complex would alter E_{PAH} in the infant. In only one of our fifteen patients was the mixing time of the PAH-glucose mixture over 240 minutes, and in this instance, a normal saline control was also obtained. In the subjects studied by Baldwin and co-workers (11), the intervals of PAH-glucose mixing to completion of the tests were 19, 7½, and 22 hours, respectively. In the present study, E_{PAH} are lower in infants than in the older children at all time intervals. When the mixing time is less than 70 minutes and dextrose in water is the diluent, E_{PAH} for the older children are still well within normal adult values; the one 2-week-old infant studied within the same mixing time nevertheless shows a lower E_{PAH}. Individual average E_{PAH} in infants who received the saline diluent also are lower than those in adults (see Table II). Infant no. 6, 1 month old, had an exceptionally low E_{PAH} of 7.3%. The other two 1-month-old infants had E_{PAH} of 67.1 and 68.2%, respectively, and the 3-month-old infant had a value of 81.8%. The 2-week-old infant (no. 3), who received dextrose in water as diluent with a 60-minute interval, had an average E_{PAH} of 74.8%.

In four instances, of two young infants and two older childen, E_{PAH} were compared with the two diluents on the same subject (Tables II and III). In the two older children, with intervals of 50 and 70 minutes, there is no significant difference in E_{PAH} with the two diluents. In the two infants, with intervals of 240 and 390 minutes,

E_{PAH} were significantly reduced from the even lower levels found in infants with saline as diluent, which confirms findings of Baldwin and co-workers (11) in adults when the mixing time was prolonged. The few subjects studied make it difficult to use a fixed average value for young infants. If the one subject with the extremely low value is discounted, however, there appears to be some consistency in the values for young infants. E_{PAH} of those more than 5 months old closely approximate those of adults (12).

When the renal venous blood was obtained from dogs previously primed with an infusion of PAH and allowed to stand, maximal diffusion of PAH from the cells to plasma occurred within 20 minutes (13). This is not true, however, for man (14, 15). If it were true for renal venous blood obtained from infants, the low E_{PAH} could conceivably be explained by this artifact. Table V shows, however, that little change occurs in the concentration of renal venous blood standing as long as 92 minutes before centrifugation, so standing time is not a factor in the low E_{PAH} in these infants. In this study, all analyses were made on blood samples centrifuged within 30 minutes of collection.

With reduction in E_{PAH} in the young infants, previous calculations of effective renal plasma flow must be revised upward, depending on E_{PAH} extraction. Thus, if the adult value for E_{PAH} of 93.5% is used, then the calculated value for effective renal plasma flow of young infants must be increased by about 30%. An average correction is only an approximation, since individual values for E_{PAH} vary.

Reduction in E_{PAH} was not associated with a similar reduction in E_{in} in the young infants. Their average E_{in} was 24.0, which closely compares with the average calculated filtration fraction (ratio of glomerular filtration rate to renal plasma flow) of 23.2 and the average E_{in} for adults of 20.7 [this value was obtained in eighteen normal adults with a range from 11 to 31 (16)]. The slightly higher average value for E_{in} and calculated filtration fraction in our smaller group of infants most probably is a result of the smaller sample. The high calculated filtration fractions reported previously in full-term infants with a range of 16.4 to 47.0 (1–4) and in premature infants with an average of 34 (5) may be explained largely by the falsely low renal plasma flow estimations made from the higher adult values for E_{PAH}.

Three possible mechanisms were considered in explanation of the lowered E_{PAH}. *1*) Arterial blood may escape into the venous circulation without being acted upon by the nephron. Since E_{in} is not similarly depressed in these young infants, there would seem to be no significant preglomerular shunting of blood. *2*) Postglomerular blood may be shunted from the renal tubule. The data in these young infants showing the renal a-v oxygen difference to be 0.8 to 1.4 ml per 100 ml, which agrees well with those values in adults, argue against shunting of postglomerular blood away from tubular tissue in greater proportion than in the adult. The a-v oxygen differences as determined, however, are gross estimations at best and are too few to help to exclude this second possible mechanism. *3*) A decrease in cellular function or tubular mass would also account for a decrease in E_{PAH}. This third possibility is in keeping with the lowered maximal tubular capacity (T_m) to transport PAH (2, 4) and glucose (16–18) found in young infants, and seems to be the most likely explanation for the lowered E_{PAH}.

From the determined values for PAH clearance (C_{PAH}), the ratio of C_{PAH}/T_mPAH for young infants (2) is roughly 30% higher than those reported in the literature when 93.5 is used as the average E_{PAH}, suggesting a high degree of perfusion in proportion to the tubular mass in the younger infant.

In young infants the filtration fraction calculated from the determined E_{PAH} compares with values in older children and adults, indicating that there is not a "supernormal" development of glomerular filtration in the young infant in comparison with the adult, and is in keeping with the following: *1*) low blood pressure, *2*) assumed low intraglomerular arterial pressure, *3*) persistent fetal glomerular membranes, and *4*) glomerular vascular underdevelopment. Recalculation of previously published data of the filtration fraction in infants of comparable age (2), using the rough average value for E_{PAH} determined here, gives values comparable to those obtained in the present study, values identical with the average values for filtration fraction reported in adults (16).

Since sedative drugs were used in many of our

subjects, it is important to determine whether or not E_{PAH} was influenced by them. Procaine hydrochloride, a local anesthetic agent, is said to interfere with PAH determinations (12), but our sedation contained none. In three children, no significant differences were found in PAH and inulin determinations of arterial and venous blood before and after the administration of CM[3],[3] the sedative used in eight of the fifteen patients. Patients 1 and 3 (receiving saline diluent and glucose diluent at 60 minutes) received no sedation before the test, and their E_{PAH} compare with the others. CM[3] therefore appears not to alter either the biochemical determinations of PAH or E_{PAH}.

In this study, five of the eight infants under 2 months old were mentally defective, four with mongolism and one with a congenital cerebral defect. A previous publication discussed the influence of such defects on renal function (10), and in general, the conclusion from data in the literature (19, 20) was that renal functional impairment, when it occurs, would be most conspicuous in children older than the infants in this study. In addition, there is no significant difference in E_{PAH} between the normal infants and the infants with cerebral defects in this study.

SUMMARY

1. Renal vein catheterization was performed in eight infants 8 days to 3 months old and in seven older infants and children between 5 months and 10 years old to determine the renal extraction ratios (E) of para-aminohippurate (PAH) and inulin.

2. In four infants 3 months old or younger, with PAH in normal saline diluent, there was a reduction in E_{PAH} about 30% below the average adult value. The older children have values comparable to the adult average of 93.5. This decreased E_{PAH} in infants under 3 months old is presumably due to a decrease in either total tubular mass or tubular cell function.

3. When PAH is administered in 5% dextrose in water and the mixing time interval is less than 70 minutes, there is no difference between E_{PAH} so obtained and those when normal saline is the diluent. Whenever glucose is a diluent and at various intervals, E_{PAH} are lower for infants under 3 months old than for the older children.

4. Values for effective renal plasma flow reported in the literature for young infants (under 3 months old) must be revised upward, depending on the E_{PAH} used in the original calculations. From the average adult value of 93.5, the average increase would be roughly 30%.

5. The filtration fraction calculated from the corrected values for renal plasma flow (both for the saline and dextrose diluents) in the young infant averaged 23.2. This closely approximates the average E_{in} of 24.1 and is closer to the adult filtration fraction of 20.7 than previously reported. The small sample for determining average values is noted.

6. The ratio of PAH clearance to maximal tubular capacity to transport PAH, from the revised values for renal plasma flow, indicates a high degree of perfusion in proportion to tubular mass in young infants.

[3] CM[3] = chlorpromazine, promethazine, and Merperidine hydrochloride.

ACKNOWLEDGMENTS

We are greatly indebted to Drs. Peter Vlad, Edward C. Lambert, and Arno R. Hohn, of the cardiac catheterization team, Buffalo Children's Hospital, for performing the renal vein catheterizations; to Dr. Erika Bruck for participating in one of these catheterizations; to Drs. Phatick K. Mulherji and Manuel J. Esperanca and Nurse Sara Panzarella for assistance in collecting some of these data; and to Mary K. Wypych and Margaret M. Stubbins for technical assistance.

REFERENCES

1. Dean, R. F. A., and R. A. McCance. Inulin, diadone, creatinine and urea clearances in newborn infants. J. Physiol. 1947, **106**, 431.
2. Rubin, M. I., E. Bruck, and M. Rapoport. Maturation of renal function in childhood: clearance studies. J. clin. Invest. 1949, **28**, 1144.
3. Smith, H. W. The Kidney. Structure and Function in Health and Disease. New York, Oxford University Press, 1951, p. 411.
4. West, J. R., H. W. Smith, and H. Chasis. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J. Pediat. 1948, **32**, 10.
5. Barnett, H. L., W. K. Hare, H. McNamara, and R. S. Hare. Influence of postnatal age on kidney function in premature infants. Proc. Soc. exp. Biol. (N. Y.) 1948, **69**, 55.
6. Hubbard, R. S., and T. A. Loomis. The determination of inulin. J. biol. Chem. 1942, **145**, 641.

7. Harrison, H. E. Modification of the diphenylamine method of determination of inulin. Proc. Soc. exp. Biol. (N. Y.) 1942, **49**, 111.
8. Goldring, W., and H. Chasis. Hypertension and Hypertensive Disease. New York, The Commonwealth Fund, 1944.
9. Wood, E. H., and J. E. Geraci. Photoelectric determination of arterial oxygen saturation in man. J. Lab. clin. Med. 1949, **34**, 387.
10. Calcagno, P. L., and M. I. Rubin. Effect of dehydration produced by water deprivation, diarrhea and vomiting on renal function in infants. Pediatrics 1951, **7**, 328.
11. Baldwin, D. S., G. E. Schreiner, E. S. Breed, L. G. Wesson, Jr., and M. H. Maxwell. Depression of apparent *p*-aminohippurate extraction ratio by glucose. J. clin. Invest. 1950, **29**, 614.
12. Bradley, S. E., G. P. Bradley, C. J. Tyson, J. J. Curry, and W. D. Blake. Renal function in renal disease. Amer. J. Med. 1950, **9**, 766.
13. Phillips, R. A., V. P. Dole, P. B. Hamilton, K. Emerson, Jr., R. M. Archibald, and D. D. Van Slyke. Effects of acute hemorrhagic and traumatic shock on renal function of dogs. Amer. J. Physiol. 1946, **145**, 314.
14. Smith, H. W., N. Finkelstein, L. Aliminosa, B. Crawford, and M. Graber. The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. J. clin. Invest. 1945, **24**, 388.
15. Barker, H. G., J. K. Clark, A. P. Crosley, Jr., and A. J. Cummins. The volume distribution and equilibrium time of para-aminohippurate. Proc. Soc. exp. Biol. (N. Y.) 1949, **72**, 616.
16. Maxwell, M. H., E. S. Breed, and H. W. Smith. Significance of the renal juxtamedullary circulation in man. Amer. J. Med. 1950, **9**, 216.
17. Tudvad, F. Sugar reabsorption in prematures and full term babies. Scand. J. clin. Lab. Invest. 1949, **1**, 281.
18. Calcagno, P. L., and M. I. Rubin. Physiology of prematurity. Transactions of the Fourth Conference, J. T. Lanman, Ed. New York, Josiah Macy, Jr. Foundation, 1959, p. 1970.
19. Benda, C. E. Mongolism and Cretinism. New York, Grune & Stratton, 1946.
20. Roosen-Runge, E. C. Retardation of postnatal development of kidneys in persons with early cerebral lesions. Amer. J. Dis. Child. 1949, **77**, 185.