Renal Clearance of Endogenous Phosphate in Infants and Children. (18686)

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While studying patients with altered phosphate metabolism, it became necessary to establish values for renal clearance of phosphate in normal pediatric subjects. Although values were available for adults from the studies of Ollayos and Winkler(1) and Blatherwick and collaborators(2), no published data were available for infants and children. Since the initiation of our study one report(3) has presented data which compared clearance of endogenous phosphate in a group of 9 newborn infants and one 5-month-old infant with adult clearances. Since no studies of the glomerular filtration rate were performed simultaneously, the relationship of glomerular filtration to tubular reabsorption was not established. Gardner and coworkers(4), while studying tetany in the newborn, performed renal phosphorus clearances in one full term infant and in one premature infant and found that the newborn infant's kidneys respond to parathyroid hormone injections by increased urinary excretion of phosphorus. McCrory *et al.*(5) indicated that the elevation of endogenous serum phosphorus in newborns could be related to the reduced glomerular filtration rate. The injection of parathyroid preparations caused an increase in renal excretion of phosphorus and an associated decrease in reabsorption.

Methods. Our subjects were patients from the pediatric service of the University of Illinois Research and Educational Hospital. The newborn infants were normal; the older infants and children were hospitalized for the surgical treatment of cleft palate, strabismus, or for tonsillectomy. In all instances other abnormalities were excluded insofar as possible by physical examination, urinalysis, blood chemistry and complete blood counts. The infants were fed evaporated milk formulae and the children received a general ward diet. All subjects were fasted for a period of at least 3 hours prior to the clearances. No feedings were permitted during the period of study. Urine specimens were obtained by catheterization. Air was injected via the catheter into the bladder to facilitate the collection of residual urine. Blood specimens were obtained at the midpoint of the 20-minute urine collection periods, except for the infants under one year, for whom one hour periods were employed. The femoral and jugular veins were the sites chosen for venipuncture in infants; the antecubital vein was utilized in older children. Blood and urine were analyzed for inorganic phosphorus by the method of Fiske and SubbaRow(6), and inulin was determined on both urine and blood by the method of Hubbard and Loomis(7). The doses of inulin employed for children and adolescents were proportionate to those suggested by Goldring and Chasis(8) for adults. These doses were calculated on the basis of body weight with the assumption that 30 ml of a 10% solution of inulin is the priming dose and that 70 ml of a 10% solution is the sustaining dose for a 150-lb. adult. The volume of 0.9% saline in the priming solution employed in the older group was 250 ml flowing

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3. Dean, R. F. A., and McCance, R. A., *J. Physiol.*, 1948, v107, 182.

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6. Fiske, C. H., and SubbaRow, Y., *J. Biol. Chem*, 1925, v66, 375.

7. Hubbard, R. S., and Loomis, T. A., *J. Biol. Chem.*, 1948, v145, 641.

8. Goldring, W., and Chasis, H., *Hypertension and Hypertensive Diseases*, The Commonwealth Fund, New York, 1944.

TABLE I. Inulin and Phosphate Clearances in Infants Up to 5 Days of Age.

Subjects	Age in days	Area, sq.m.	Serum P, mg %	Urine P, mg %	Urine vol., ml/min.	Clear P, ml/min.	Inulin clear, ml/1.73 sq.m./min.	% of P resorbed	% of P excreted
P.	3	.21	11.9	15.8	.14	2.37	—	—	—
B.	3	.19	8.1	11.5	.21	4.50	28.2	90.4	9.06
B.B.	4	.19	7.6	35.0	.13	5.4	—	—	—
			7.6	25.0	.14	4.4			
M.	4	.19	7.8	23.2		8.4	58.5	86.0	14.0
			7.8	24.2	.24	6.7	54.0	87.6	12.4
A.	4	.20	7.8	46.2	.22	11.0	32.5	66.2	33.8
B.L.	4	.21	7.6	30.0	.15	3.2	—	—	—
			7.6	40.0	.27	4.6			
B.A.	5	.24	7.8	28.7	.20	5.4	—	—	—
			8.2	35.0	.10	3.1			

TABLE II. Inulin and Phosphate Clearances in Subjects 21 Days to 20 Months of Age.

Subjects	Age	Area, sq.m.	Serum P, mg %	Urine P, mg %	Urine vol., ml/min.	Clear P, ml/min.	Inulin clear, ml/1.73 sq.m./min.	% of P resorbed	% of P excreted
G.	21 days	.22	7.8	81.0	.17	13.1	—	—	—
G.	24 "	.23	7.6	57.0	.21	11.7	—	—	—
			7.6	80.0	.18	14.2	60.0	76.4	23.6
B.	5 wk	.23	5.5	49.1	.36	24.0	69.0	65.3	34.7
			5.4	35.6	.66	32.2	76.0	57.7	42.3
			5.8	16.9	.16	34.5	82.5	57.0	43.0
D.	3 mo.	.30	4.9	27.8	1.03	31.9	141.0	77.4	22.6
			4.7	32.2	.76	29.6	108.0	72.6	27.4
			4.7	56.3	.43	29.6	127.0	76.7	23.3
C.	6 "	.36	7.9	128	.16	13.6	—	—	—
J.	7 "	.38	8.3	245	.11	14.4	—	—	—
S.	20 "	.39	5.5	140	1.3	15.4	137	88.8	11.2
			5.4	490	.26	10.4	94	89.0	11.0

at a rate of 10 ml per minute. This was followed by a sustaining dose of 500 ml at a rate of 4 ml per minute. For infants we employed doses of inulin varying from 2 to 5 ml of a 10% solution for the priming dose, depending upon body weight. This dose was diluted to 10 ml in 0.9% saline prior to injection. Depending upon body weight of the subject, the sustaining solution contained from 4 to 10 ml of a 10% solution of inulin, which was dissolved in 150 to 200 ml of 0.9% saline and was allowed to run at a rate of 40 to 60 ml per hour. In the experiments in which inulin was not administered, water was given orally to promote a diuresis. No glucose containing solutions were employed for any of the subjects.

Results. Our studies indicate that the renal clearances of inorganic endogenous phosphate in the newborn period are relatively low. The clearances in 7 infants from 3 to 5 days of age averaged 5.37 ml/min. per 1.73 square meters of body surface (Table I). In order to determine the age at which phosphate clearances approximate adult values, a group of older infants ranging in age from 21 days to 20 months was studied. These clearances averaged 21.1 ml/min. per 1.73 sq. m. of body surface, thus being comparable to values observed in older children and adults (Table II). Nineteen children ranging in age from 4 to 13 years of age were studied. Six of these subjects in whom simultaneous inulin clearances were performed had an average phosphate clearance of 14.67 ml/min. per 1.73 sq. m. of body surface (Table III). Thirteen additional subjects in this age group had an average clearance value of 13.0 ml. (Table IV).

The tubular reabsorption of phosphate was

TABLE III. Inulin and Phosphate Clearances in Children.

Subjects	Age, yr	Area, sq.m.	Serum P, mg %	Urine P, mg %	Urine vol., ml/min.	Clear P, ml/1.73 m./min.	Clear inulin, ml/1.73 m./min.	% of P resorbed	% of P excreted
T.	10	1.16	5.8	4.45	17.5	19.9	138.0	86.0	14.0
			5.4	5.83	11.0	17.4	140.6	87.0	13.0
F.	12	1.24	4.9	6.25	4.25	22.7	133.8	83.0	17.0
			5.0	5.25	12.5	20.7	125.8	83.6	16.4
			4.5	11.85	14.0	20.5	107	83.3	16.7
C.	12	1.32	4.6	76.0	.95	20.56	112	81.8	18.2
			4.5	13.0	5.25	17.78	102.3	82.7	17.3
			4.5	8.0	5.23	12.1	94.0	87.2	12.8
C.W.	9	1.15	4.9	9.5	4.6	13.3	135.6	90.3	9.7
			4.8	3.2	13.0	12.9	130.5	90.2	9.8
			4.8	5.9	5.5	10.2	104.5	90.3	9.7
S.	12	1.67	5.1	6.4	6.5	8.6	95	91.0	9.0
			5.2	7.4	6.75	9.9	130	92.4	7.6
			5.1	6.0	6.25	7.6	132	94.2	5.8
			5.2	6.0	6.25	7.6	136	94.4	5.6
I.	9	.98	5.8	41	1.1	13.5	92	85.5	14.5
			5.0	28.7	1.2	12.1	86.8	86.1	13.9
			5.4	11.0	4.7	16.7	86	80.6	19.4

calculated by comparing the inulin clearances with the phosphate clearances. Thus of the six children and adolescents in whom both clearances were simultaneously determined an average of 87.7% was reabsorbed by the renal tubules. In subjects from 21 days to 20 months of age, an average of 74.7% was reabsorbed. In 3 infants under 5 days of age an average of 82.6% of the phosphate was reabsorbed by the tubules.

Discussion. Although Schloss and Crawford(9) demonstrated some years ago that the newborn infant has a relatively low urinary phosphate output, it was not until the recent publication of Dean and McCance(3) that endogenous phosphate clearance data for pediatric patients became available. The values reported by these authors are in agreement with those described in this study. The data presented indicate that renal clearance of phosphate in newborn infants is relatively low and thus is in keeping with renal functional immaturity characteristic for this age period(10). This may account, in part, for the higher serum phosphate levels of young infants. The 4 infants from 3 to 12 weeks of age had clearances comparable to adult values. Since Rubin(11) and West(12) and their respective groups have indicated that renal function, as measured by inulin and diodrast clearances, does not attain maturity until 10 weeks to 2 years of age, it would seem that phosphate excretion tends to attain mature values earlier than most renal functions. The work of Gardner *et al.*(4) showed that a full term infant had varying phosphorus clearances depending on the kind of milk consumed. During the days when human milk was ingested, a recalculation of their data expressed in ml/1.73 sq. m./min. shows that the phosphorus clearances were 0.53 ml and 0.395 ml on the 7th and 8th day of life, respectively. On a commercial cow's milk product, the clearances were 1.3, 1.7, and 8.1 ml before the first 11 days of life. These figures are reasonably within range of the values in this study. Clearances during the third week of life when the infants were on human milk were 1.5, 0.75, and 0.25 ml. Gardner and coworkers explain the differences in phosphorus clearances between breast milk and the cow's milk product because of compensatory hyperplasia of parathyroid tissue associated with cow's milk feedings. McCrory *et al.*(5) found that there is no evidence available to completely

9. Schloss, O. M., Crawford, S. L., *Am. J. Dis. Child.*, 1911, v1, 203.

10. McCance, R. A., *Physiol. Rev.*, 1948, v28, 331.

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TABLE IV. Phosphate Clearances in Children.

Subjects	Age, yr	Area, sq.m	Blood P, mg %	Urine P, mg %	Urine vol., ml/min.	Clear P, ml/1.73 m. per min.
N	4	.65	6.0	40.0	8.0	17.7
			6.0	53.7	2.8	23.8
			6.0	11.0	5.0	23.9
D.	5	.75	5.7	55.0	.72	15.6
			6.0	30.0	1.9	18.1
R.	6	.70	5.8	21.0	3.71	33.0
			6.0	16.0	5.5	36.0
M.	9	1.09	5.2	10.7	2.39	8.7
			5.7	12.7	3.44	12.0
			6.2	22.4	2.05	11.7
B.	9	.90	6.4	33.0	1.86	18.7
			6.3	35.0	1.5	16.1
J.	9	1.13	5.75	80	.52	11.0
			5.75	100	.48	12.7
			5.55	18.5	2.45	12.4
C.	9	1.17	5.1	14.9	4.3	18.6
			5.2	31.8	3.0	26.9
C.S.	10	1.07	3.8	45	4.2	8.3
			3.9	38	.7	11.1
			4.1	17.5	1.6	11.5
C.E.	10	.96	5.8	10.0	3.1	8.6
			6.1	60.0	.47	8.2
			6.3	11.0	3.1	10.1
B.L.	10	1.08	7.8	32.0	2.7	17.6
			7.4	11.0	9.2	21.2
			7.4	7.5	9.7	15.5
			7.2	7.5	10.4	17.2
S.	12	1.67	5.5	13.9	3.4	8.8
			5.4	9.5	5.0	7.0
R.B.	13	1.11	4.1	6.5	3.3	8.2
			4.2	13.0	4.0	19.2
			4.7	19.0	3.3	20.7
O.	13	1.07	5.9	6	2.3	15.36
			5.9	7.0	6.0	11.7
			6.1	18.5	9.0	11.2

substantiate the hypothesis that infants with endogenously elevated serum phosphorus levels or with tetany are different from normal infants in their parathyroid function if variations in tubular reabsorption of phosphorus is an accurate reflection of such function.

The values for phosphate clearance in children and adolescents corresponded closely to clearances determined in adults by other investigators. Ollayos and Winkler(1) found an average clearance of 15 ml/min. per 1.73 sq. m. in adults. Blatherwick, Bell, and Hill(2) observed the renal clearance of endogenous phosphate to range from 5.8 to 13.3 ml/min. in normal adult subjects. Dean and McCance(3) found values from 8 to 38 ml/min. per 1.73 sq. m. in normal adults. Thus from all reported studies, phosphate clearance shows a considerable range of variation in normal individuals. It has been demonstrated that this range of variation in the clearance of phosphate is not related to blood level unless it has been elevated by a phosphate infusion(1).

Gamble(13) has determined that the tubular reabsorption of phosphate averages 83% of the glomerular filtrate in normal adult subjects. In our study the tubular reabsorption was observed to be 87.7% of the glomerular filtrate in children and adolescents. The older infants studied had an average tubular reabsorption of phosphate of 74.7% of the glomerular filtrate. This would seem to reflect some immaturity of renal tubular function. The newborn infants had a higher value of 82.6%

13. Gamble, J. L., *Chemical anatomy, physiology and pathology of extracellular fluid.* Dept of Pediatrics, Harvard Medical School, 1945.

tubular reabsorption. This higher value in newborn infants may be more apparent than real, since the tubules presumably have presented to them a relatively smaller load in the glomerular filtrate. Since clearance periods in this age period are admittedly inadequate, no definite conclusions on this point can be drawn.

Summary. 1. The clearance of endogenous inorganic phosphate is relatively low in the newborn period. 2. The clearances of phosphate in older infants, children and adolescents approximate those of the adult. 3. The tubular reabsorption of phosphate was found to average 87.7% of the glomerular filtrate in children and adolescents. 4. The clearances of phosphate at all ages have a wide variation.

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Fate and Excretion of Adrenocorticotrophic Hormone.*† (18687)

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The fate and excretion of adrenocorticotrophic hormone (ACTH) have assumed practical as well as academic significance with the extensive use of the hormone in the treatment of disease. Porcine ACTH disappears rapidly from the blood of man following its intravenous injection(1). Two hours after its administration, only 2% of the biological activity of the injected hormone remains in the vascular compartment; after 3 hours, ACTH activity is no longer detectable in the blood. The hormone is not excreted in appreciable quantities in the urine. Essentially the same results have been obtained in the rat following the administration of porcine ACTH(2) and sheep ACTH(3).

It is not possible to decide from the results of the above experiments whether the rapid disappearance of ACTH activity from the blood stream is a characteristic of the endogenously secreted hormone or is due to the fact that in each instance a protein, foreign to the recipient species, was injected. In order to exclude the latter possibility the present experiments were designed to determine the fate and excretion of rat ACTH injected intravenously into the rat.

Methods. Rat ACTH was prepared as follows. Adult male rats from the Sprague-Dawley farm, weighing 250 to 400 g, were decapitated and the pituitaries carefully removed from the sella turcica. The anterior lobes were dissected away from the posterior lobes and ground in a 0.9% sodium chloride solution made acid to 0.1 M with hydrochloric acid. The mixture was centrifuged and the supernatant solution of ACTH placed in a boiling water bath for one hour. The final concentration of the solution of rat ACTH was 2 anterior pituitaries per ml. Each 0.5 ml of extract had the biological activity equivalent to approximately 100 μg of the ACTH standard, La-1-A. All potencies and doses are expressed as μg equivalents of La-1-A. The confidence limits of the bioassays to be presented below are based on a p value of 0.67. The male rats employed for the study of the distribution of injected ACTH were obtained from the Sprague-Daw-

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