J. Physiol. (1949) 109, 81–97 612.464.1:612.648

THE RENAL RESPONSES OF INFANTS AND ADULTS TO THE ADMINISTRATION OF HYPERTONIC SOLUTIONS OF SODIUM CHLORIDE AND UREA

By R. F. A. DEAN and R. A. McCANCE

From the Medical Research Council Unit of Experimental Medicine, University of Cambridge, England

(*Received* 29 *August* 1948)

Of all the aspects of renal function which have been investigated in the last 20 years, the excretion of minerals is one of the least understood. This is partly because the kidney is not the only organ concerned, and partly because, even if it were, its treatment of chlorides, bicarbonates, sodium and potassium must inevitably be more complicated than its treatment of a substance such as inulin or even diodone. The response of the adult kidney to dehydration and to the administration of hypertonic solutions of sodium chloride and urea has been studied by various people, but few of the many problems have been solved.

Infants have much lower clearances of sodium and of chloride than adults, although the concentration of these ions in their serum is the same. It is also known that the newborn baby passes a very dilute urine *in utero*, and that even during the physiological hydropenia of the second and third days of life the urine is not nearly so concentrated as it would be under similar circumstances in adult life (McCance, 1948). It seemed desirable therefore to compare the reactions of the newborn and the adult kidney to the administration of hypertonic solutions in order to find out more of the ways in which the kidney of the infant differs from that of the adult, and to explore the mechanism underlying osmotic control at all ages. A summary of some of the findings was given by Dean & McCance (1947*a*).

The work now to be described has been done on babies with inoperable meningomyeloceles with the full consent of those responsible for their care. The practice has been for R. F. A. Dean to explain to each mother that it was hoped with her permission to make a test on her baby similar to ones which had already been made on healthy adults. She was assured that the work would not cause pain or harm, and that the information gained would benefit other children, although it could not cure her own child. Permission was always freely given.

METHODS

All the subjects were deprived of fluids for 15 to 16 hr. before the experiments. From adults, urine was collected for a measured time—usually about 2 hr.—before the saline or urea was administered. During the tests they reclined in comfortable chairs or on couches, standing up to pass urine. They were not catheterized and, except in a few instances when slight irregularities of minute volume were found, seemed able to empty their bladders satisfactorily. In the salt experiments, a 10% solution of NaCl was infused by gravity through a 'drip' connexion into one of the veins in the ante-cubital fossa; a cannula with a sharp trocar, which could be withdrawn later, was used. The blood samples were taken from the veins of the opposite arm, the syringes being well lubricated with liquid paraffin, and the blood was immediately centrifuged under paraffin. Heparin, or a mixture of potassium and ammonium oxalates, was used to prevent coagulation.

The first step in an experiment on an infant was to catheterize it. Then, and whenever a specimen was taken, its bladder was emptied as completely as possible with the aid of pressure on the abdomen. The backward end of the catheter was led into a small graduated measuring cylinder; the forward end remained in the bladder throughout the experiment. The resting urine was collected over a period of about 4 hr. The 10% NaCl solution was given by the 'drip' method through a cannula in an internal saphenous vein at the ankle. Blood was taken by needle and syringe through the anterior fontanelle with the precautions already described against exposure to air.

TABLE 1. Age, sex and factor for conversion of surface area of the subjects to 1·73 sq.m.; amount of sodium chloride administered and its effect on the blood chlorides

Name	Age	Sex	Factor	Dose (g./kg.)	Time taken to give dose (min.)	Plasma Cl (m.equiv./l.) Before giving NaCl	Plasma Cl (m.equiv./l.) Maximum
Ro.	Adult	♂	1·24	1·21	105	101	135
Wo.	Adult	♂	0·82	1·03	187	101	141
Wh.	Adult	♀	1·33	1·02	181	102	132
Pe.	Adult	♂	0·92	0·91	65	106	133
B.P.	4 days	♂	7·9	1·43	99	97	174
B.B.	3 days	♀	6·6	1·39	79	112	157
F.L.	8 days	♂	8·0	2·01	125	94	144
M.P.	3 days	♀	9·7	1·14	73	113	154
A.J.B.	5 days	♂	8·0	0·88	83	87	132

Urea was given by mouth as a 50% solution, to the adults from a glass and to the infants through a stomach tube.

The doses of NaCl and urea were calculated on the basis of body weight for they were intended to produce a comparable increase in the plasma at either age, but the infants received slightly more than the adults. The doses and their effects, with other details, are recorded in Tables 1 and 2.

TABLE 2. Quantities of urea given and the effects on the blood urea

Name	Dose (g./kg.)	Time taken to give dose (min.)	Plasma urea (m.mol./l.) Before giving urea	Plasma urea (m.mol./l.) Maximum	Time taken to reach maximum (min.)
Ro.	1·83	10	5·0	25	150
Wo.	1·43	2	5·7	33	240
Wh.	1·86	30	4·7	29	180
Lo.*	1·60	130	4·5	30	60
M.P.	1·82	5	4·4	36	240
A.J.B.	1·86	5	5·0	35	150

* This subject whose name does not appear in Table 1 was an adult female; the factor for the conversion of her surface area is 1·07. She and Ro. each vomited part of the dose.

One adult and two infants were given inulin in order that their glomerular filtration rates might be measured. The inulin was given to Pe., intravenously in 10% solution through the drip connexion. A priming dose of 25 c.c. was followed by a maintenance flow of 0·5 c.c./min. His glomerular filtration rate was measured before and after the salt had been given. The infants were given 10–20 c.c. of a 10% solution of inulin in 0·9% NaCl subcutaneously, over a period of about 5 min. into the loose tissues of the thigh.

The 'start' of each experiment was reckoned from the mid-point of the period of administration of NaCl or urea. The duration of urine collection tended to be long when the minute volume of urine was small and short when it was large. Blood was taken before, at intervals during, and at the end of the experiments. Curves drawn from the data obtained were used for calculating the concentration in the blood at the times required. The concentrations of the various specimens of urine were also plotted against time, making it possible to calculate the concentrations and clearances at 30 min. intervals throughout the experiments.

The methods used for the chemical analysis were as follows: Chlorides—Whitehorn's (1920) method for the adult urines; the method of van Slyke (1923–4) as modified by McCance & Shipp (1933) for the plasma of the adults; Sendroy's (1937) iodine titration method for the urines and plasma of the infants. Urea—the methods of Lee & Widdowson (1937) and Archibald (1945). Inulin—Roe's (1934) method, as modified by Cole (to be published). In presenting the results all the minute volumes have been calculated to a standard basis of surface area which has been taken to be that of a 70 kg. man (1·73 sq.m.). The 'correction' factors are given in Tables 1 and 2. Further information about methods and chemical technique may be found in the paper by Dean & McCance (1947*b*).

RESULTS

Sodium chloride experiments

The plasma chlorides. The administration of large doses of NaCl naturally raised the Cl concentration in the plasma. In adults the highest value was obtained soon after the salt had been given. Thus Ro.'s plasma Cl rose from 101 to 135 m.equiv./l. within 30 min. of the 'start', and thereafter fell very slowly so that it was still 130 m.equiv./l. 240 min. later. In the infants the initial rise was similar, but a small secondary or further rise sometimes took place long after the administration of NaCl had ceased. Thus A.J.B.'s plasma Cl was 87 m.equiv./l. before the experiment began. After 60 min. from the 'start' it was 126 m.equiv./l., and 180 min. from the start it was 131 m.equiv./l. It was still 127 m.equiv./l. after 390 min. Apart from the small secondary rise in the infant's plasma Cl the changes were comparable and similar at both ages and it is not thought that the differences between adults and infants which have been revealed by a study of the urines can be explained by the differences in the composition of the plasmas.

The greatest urine flow did not necessarily coincide with maximum concentration of Cl in the plasma. Thus the adults Pe. and Wh. had their maximum diuresis between the 60th and 90th min. at a time when their plasma Cl were falling. The infant M.P.'s maximum diuresis occurred between the 180th and 210th min., but the maximum plasma Cl was not reached till the 270th min. In the infants B.B. and A.J.B., and in the adult Ro. the two maxima coincided.

The minute volumes. Fig. 1 shows the effect on the minute volumes of administering 10% NaCl in the way described. The results of all the adults and of the infants were averaged for the construction of this figure. The adults' diuresis was rapid in onset, intense while it lasted but short-lived; the infants' diuresis was slow to commence, slight in intensity, but much more prolonged. The production of a diuresis in this way has frequently been demonstrated before in adults but less attention has been directed to the fall in urine flow which takes place while the plasma is still grossly abnormal. Some failure of NaCl to produce a diuresis in infants might have been anticipated from the work of McCance & Wilkinson (1947) on newborn rats, in which no increased flow of urine followed the administration of hypertonic NaCl. The fact that some increased flow of urine has been observed in human infants suggests that their kidneys are further developed at birth than those of the rat.

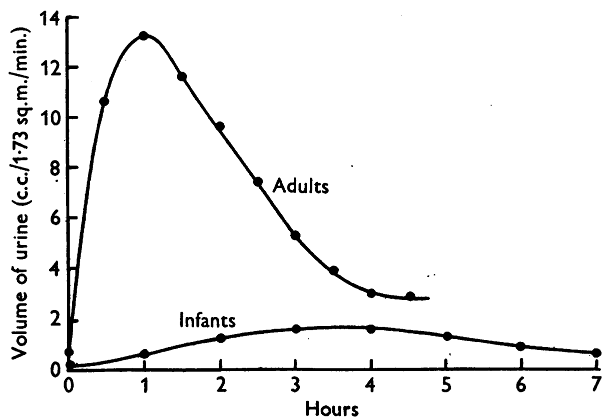

Fig. 1. The effect on the minute volume of the urine of giving hypertonic saline to adults and infants.

TABLE 3. The effect of giving 10% saline intravenously on the volume and composition of the urine of an adult and an infant

Time after saline was given (min.)	Pe. (adult) Min. vol. (c.c./min./1·73 sq.m.)	Urea (m.mol./l.)	Cl (m.equiv./l.)	O.P. (m.mol./l.)*	B.B. (infant) Min. vol. (c.c./min./1·73 sq.m.)	Urea (m.mol./l.)	Cl (m.equiv./l.)	O.P. (m.mol./l.)*
Pre-experiment	0·62	467	185	837	0·23	83	31	145
30	11·00	38	252	542	0·28	78	38	154
60	18·00	30	248	526	0·70	78	106	290
90	19·10	26	239	504	1·12	75	173	421
120	17·00	28	233	494	1·56	71	194	459
150	13·00	35	236	507	1·93	67	205	476
180	8·80	50	253	556	2·14	63	212	487
210	6·08	78	277	632	1·95	64	214	492
240	4·45	99	283	665	1·66	69	216	501

* Reckoned as m.mol. urea + 2 × m.equiv. chloride.

The composition and osmotic pressure of the urine. It was known to Starling (1909), probably from the work of Dreser (1892) and Galeotti (1902), that the administration of hypertonic saline caused a diuresis during which the osmotic pressure of the urine fell. This was shown to apply to man by McCance & Young (1944), McCance (1945) and Hervey, McCance & Tayler (1946*a*, *b*). The figures of Table 3 have been taken from the experiment on Pe. (an adult) and B.B. (an infant) and are characteristic of the present series. The concentrations of urea and of Cl in the initial urine of the adult were high, as was to be expected on a normal diet after 15 hr. without water. The diuresis which took place greatly reduced the level of urea in the urine, and the lowest figure observed was only one-eighteenth of the initial one. The concentration of Cl started at 185 m.equiv./l., varied between 248 and 233 m.equiv./l., while the flow of urine was very fast and then gradually rose to 283 m.equiv./l. (1·72 g. of NaCl/100 c.c.) over the next few hours. The concentration of Cl attained was, at the height of the diuresis, only 1·3 times and at the end 1·5 times the initial one. By contrast the concentration of urea in the infant's pre-experimental urine was only 83 m.mol./l. and the Cl 31 m.equiv./l. The other infants had rather higher concentrations of urea in their 'resting' urines, the highest figure being 148 m.mol./l. The concentration of Cl was, however, a representative one, the figures for the other infants varying from 9 to 34 m.equiv./l. Since the flow of urine increased much less in B.B. than in Pe. the concentration of urea in the urine fell correspondingly less. The concentration of Cl, however, rose slowly to 216 m.equiv./l. Thus, although the concentration was 7 times that at the start, it was never much higher than Pe.'s had been at the beginning. The effect of these changes in concentration were that the osmotic pressure of the adult's urine fell from its high resting value as the diuresis developed, whereas that of the infant rose from a relatively low starting level, but never attained a value appreciably greater than that of the adult during the height of his diuresis.

Osmotic work. In some of these experiments a calculation has been made of the osmotic work involved in altering the concentrations of NaCl and urea in the plasma to those found in the urine. The formula used has been modified from that of von Rhorer (1905). The results obtained probably represent over 80% of the total osmotic work required for the elaboration of the complete urine (Borsook & Winegarden, 1931), and may be taken as a rough measure of it. Fig. 2 shows the data obtained on the adult Pe. and the infant B.B. It can be seen that the osmotic work carried out per min. varied enormously and, roughly speaking, followed the minute volumes, so that before the saline was administered the tubules were capable of carrying out much more osmotic work per min. than they were doing, and there is no evidence that the tubules were ever exerting their full capacity even at the height of the diuresis. This makes the explanation of Hervey *et al.* (1946*a*, *b*) of the fall in the osmotic pressure of the adult urine with the onset of the diuresis rather inadequate for they supposed that the amount of osmotic work carried out by the tubules/min. during such a diuresis was approximately constant and of the same order of magnitude as that being carried out before the diuresis began. Yet some limitation of the capacity of the tubules to do the necessary osmotic work per unit of time seems the most satisfactory way of explaining the fall in the osmotic pressure of the urine.

Fig. 2 also shows that although the osmotic work carried out per min. by adults greatly exceeds that carried out by infants, the amount carried out per c.c. of urine formed is of the same order at both ages.

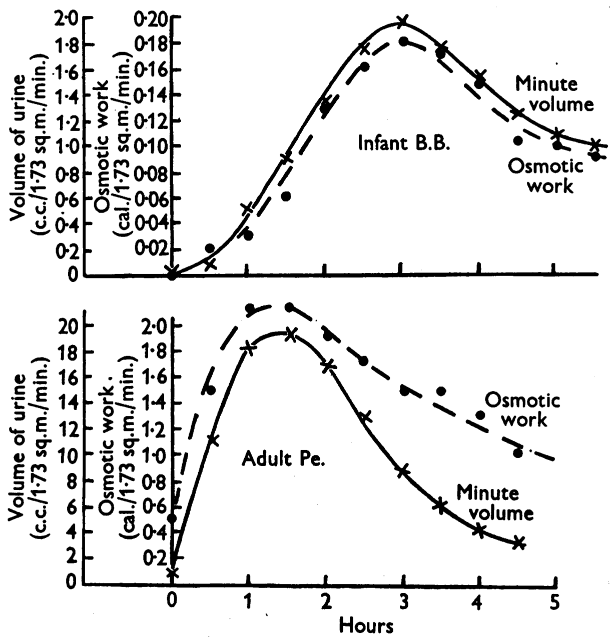

Fig. 2. Changes in the osmotic work of the kidney and in the minute volume of the urine after the administration of hypertonic saline to the infant B.B. and the adult Pe. Note that the scale for the infant's osmotic work and the urine volume is 1/10 that of the scale for the adult's.

Glomerular filtration rate. It has been shown by Dicker (1948) that the administration of hypertonic saline to rats raises their glomerular filtration rates and Mokotoff, Ross & Leiter (1948) used hypertonic saline to raise the glomerular filtration rates in their experiments on men. These papers had not been published when the experiments now being described were made. Table 4 shows our results. No figures were obtained for the glomerular filtration rates of the two infants before any saline had been given, but it will be seen that in the adult Pe. when the diuresis was at its height the rate was more than twice the accepted figure for normal people, to which figure (120–130 c.c./min.) it returned when the urine was still being formed at the rate of nearly 13 c.c./min. It is clear also that the saline greatly raised the glomerular filtration rates of both the infants, but the rise took place more slowly than in Pe. and at no time did the rate approach that of the adult. The comparison brings out once more the apparent inefficiency of the kidney in infancy and its slow response to a change in the internal environment. The alterations in urine flow must have followed to some extent the rise and fall in the glomerular filtration rate, but it appears that the flow of urine was much more subservient to the glomerular filtration rate in infancy than in adult life, for the relationship was much closer in the infants than in Pe. These experiments offer a possible explanation of the fact that some people have found that the glomerular filtration rates in infancy vary with the minute volume (Barnett, Perley & McGinnis, 1942; Young & McCance, 1942) while others have not (Barnett, McNamara, Hare & Hare, 1948). The result may easily depend upon whether the fluid used to induce the diuresis was intravenous saline, water by mouth or intravenous glucose solution.

TABLE 4. The effect of hypertonic saline on the minute volumes and the inulin clearances (glomerular filtration rates) of the adult Pe. and the infants B.P. and B.B.

	Pe. (adult)		B.P. (infant)		B.B. (infant)	
Time after mid-point of giving saline (min.)	Min. vol. (c.c.)	Inulin clearance (c.c./min./ 1·73 sq.m.)	Min. vol. (c.c.)	Inulin clearance (c.c./min./ 1·73 sq.m.)	Min. vol. (c.c.)	Inulin clearance (c.c./min./ 1·73 sq.m.)
	0·63*	127*	—	—	—	—
30	—	—	0·37	6·5	0·28	2·85
60	18·00	293	0·85	14·1	0·70	7·42
90	19·10	286	2·28	19·4	1·12	12·3
120	17·00	208	2·30	20·0	1·56	17·0
150	13·00	131	1·84	19·4	1·93	18·8
180	8·80	131	1·48	16·9	2·14	20·5
210	6·08	120	1·20	14·2	1·95	19·0
240	4·45	132	1·00	11·9	1·66	20·0
270	—	—	—	—	1·42	16·9
300	—	—	—	—	1·28	11·7

* Measured before any saline had been given.

The reabsorbates. Table 5 shows the glomerular filtration rates, the percentages of water and chloride in this filtrate which were reabsorbed in the tubules, and the m.equiv. of Cl reabsorbed/100 c.c. of glomerular filtrate. The inulin plasma clearances were taken as measuring the glomerular filtration rate, although it would probably have been more correct to have taken $I.c. \times \frac{100-x}{100}$, where $I.c.$ = the inulin plasma clearance and x = the percentage of protein in the plasma. The percentage of that filtrate which was reabsorbed was calculated by deducting from it the minute volume of urine. The Cl reabsorbed per min. was calculated as the inulin plasma clearance per min. × concentration of Cl in plasma × 1·05 (a correction introduced because of the impermeability of the glomerular membrane to protein) − Cl excreted per min. It will be seen that the percentage of the filtrate water reabsorbed by Pe. was 99·5 before the experiment began and fell with the onset of the diuresis, so that at first the large increase in the flow of urine was partly due to an increase in the volume of fluid filtered off in the glomeruli per minute, and partly to a decrease in the per-

TABLE 5. The amounts of filtrate water and chlorides reabsorbed by the tubules

	Pe. (adult)				B.P. (infant)				B.B. (infant)			
			Cl reabsorbed				Cl reabsorbed				Cl reabsorbed	
Time from start (min.)	Glomerular filtration rate (c.c./min.)	Percentage of filtrate water reabsorbed	As percentage of filtered Cl	(m.equiv./100 c.c. of glomerular filtrate)	Glomerular filtration rate (c.c./min.)	Percentage of filtrate water reabsorbed	As percentage of filtered Cl	(m.equiv./100 c.c. of glomerular filtrate)	Glomerular filtration rate (c.c./min.)	Percentage of filtrate water reabsorbed	As percentage of filtered Cl	(m.equiv./100 c.c. of glomerular filtrate)
	127*	99·5*	99·0*	10·6*	—	—	—	—	—	—	—	—
30	—	—	—	—	6·5	94·0	96·0	16·6	2·8	89·4	97·5	15·6
60	293	93·8	88·8	12·3	14·1	93·6	93·5	17·0	7·4	89·6	93·5	15·3
90	286	93·2	88·0	12·1	19·4	88·6	87·6	17·1	12·3	91·0	90·0	15·0
120	208	92·0	86·0	12·0	20·0	87·0	86·6	16·4	17·0	90·5	89·5	15·1
150	131	90·1	82·7	11·6	19·4	89·5	88·2	15·8	18·8	90·0	87·5	15·1
180	131	93·2	87·0	11·9	16·9	90·4	88·2	14·8	20·5	88·5	86·5	15·0
210	120	95·0	89·0	11·9	14·2	90·8	88·5	14·1	19·0	88·6	87·0	15·1
240	132	97·0	93·5	12·0	11·9	90·8	87·7	12·8	20·0	91·5	89·0	15·1
270	—	—	—	—	—	—	—	—	16·9	91·7	89·0	14·8

* Measured before any saline had been administered.

centage of that filtrate reabsorbed. As the glomerular filtration rate fell, this percentage continued to decrease and reached 90, which was its lowest point, after the glomerular filtration rate had returned to normal. Thereafter it gradually rose again and thus the urine flow continued to fall. The two infants reabsorbed a somewhat smaller percentage of the water in the glomerular filtrate at most stages of the experiments than did Pe., and in the case of B.P. the percentage reabsorbed was at its lowest about the time of the greatest diuresis. The rise and fall in urine flow were due to the rise and fall in the glomerular filtration rate in both children, but only in B.P. to a fall and rise in the percentage of the filtrate reabsorbed.

The third columns of each section of Table 5 show the percentage of the filtered Cl which was reabsorbed. Owing to the glomerular filtrates having been more than doubled by the hypertonic saline, and the blood Cl considerably raised, much more Cl was passed down the tubules per min. The figure in Pe. rose from about 14 to 40 m.equiv./min., and yet in this subject the percentage of the filtered Cl which was reabsorbed fell but little during the experiment, and the amount of Cl reabsorbed rose from 10·6 to 12·3 m.equiv./100 c.c. of glomerular filtrate at the peak of the filtration rate. It fell to 11·6 as the latter returned to normal and subsequently rose again to 12·0. Had it not risen again the minute volume would no doubt have been larger towards the conclusion of the experiment. The infants reabsorbed 86·5–97·5 % of the filtered Cl after the saline had been given, but the figures over 90 % were confined to the first hour. They would certainly have been absorbing more than 97·5 % before the experiments began. In B.B. the Cl reabsorbed amounted to about 15 m.equiv./100 c.c. of glomerular filtrate throughout the experiment. In B.P. a figure of 17·1 was reached 90 min. after the start, and subsequently the amount reabsorbed gradually fell to 12·8 m.equiv./100 c.c. of glomerular filtrate.

The concentration of chloride in Pe.'s plasma water before the experiment began was 111 m.equiv./l. and almost exactly the same in the reabsorbate. The concentrations in the infants' plasmas were 102 and 117 m.equiv./l., but the concentrations in the reabsorbates before any saline had been given are unknown. They would probably have been slightly more than they were in the plasma. Table 6 shows the concentration of chloride in the serum water and in the fluid reabsorbed by the tubules at various stages throughout the experiments on Pe., B.P. and B.B. The concentration of chloride in the reabsorbate was never very far from that in the serum water and in Pe. it was always lower in the reabsorbate after the saline had been administered. In the infants, even when the concentration of chloride in the serum water had reached highly abnormal figures (Table 6) and had been at those levels for some time, the concentration of Cl in B.P.'s reabsorbate was equal to and in B.B.'s actually greater than that in the plasma. Only after 2 hr. had the relationship to be expected with a hypertonic plasma been established. This is another aspect of the slow renal adaptation of infants to changes in the plasma: even some time after all the hypertonic saline had been administered, the infants were still excreting a urine which contained a smaller concentration of Cl than plasma.

TABLE 6. The concentration of Cl in serum water and in the fluid reabsorbed by the tubules

	At 60 min.		At 120 min.		At 180 min.	
	In serum water	In reabsorbate	In serum water	In reabsorbate	In serum water	In reabsorbate
Pe. (adult)	142	132	137	126	136	128
B.P. (infant)	184	183	179	173	164	158
B.B. (infant)	157	162	164	158	167	159

All the data are given in terms of m.equiv./l.

Urea experiments

Since the urea was given by mouth, the rate and completeness of its absorption from the gastro-intestinal tract were of some importance in interpreting the urinary findings. Table 2 showed that blood values of the same order of magnitude were achieved in both the infants and adults, and that the maxima were attained at about the same time after the urea had been administered. It is justifiable to conclude that urea was absorbed at about the same rate at the two ages and that the urinary differences about to be described originated in the kidney itself.

Fig. 3 compares the results of the experiments on one adult, Wo. and on one infant, A.J.B. In both the urea was given quickly—see Table 2—and the blood concentrations behaved, on the whole, in a similar manner. With regard to the minute volumes of the two subjects it will be seen that, as after giving NaCl, the diuresis fell off while the plasma was still very abnormal. The differences between the two subjects are obvious. As in the salt experiments the failure of the hypertonic solution to produce any noteworthy diuresis in A.J.B. is the most obvious renal peculiarity of infancy. The concentration of urea in Wo.'s urine fell after the urea had been given (Fig. 3). A similar effect was observed by McCance & Young (1944) and is associated with the diuresis. There is, however, no obvious explanation of this at present since there seems to be no rigid limitation to the amount of osmotic work which the kidney can carry out

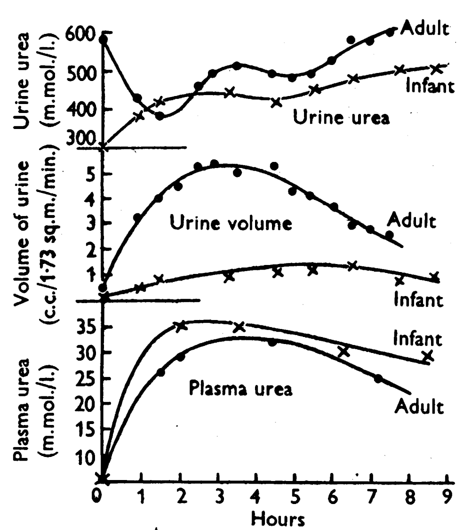

Fig. 3. Urine urea, urine volume, and plasma urea following the administration of hypertonic urea to the adult Wo. and the infant A.J.B.

per minute. The concentration of urea in the infant's urine rose as the blood urea rose, and between the 60th and 120th min. was as great as in the adult's. Thereafter Wo.'s urine became more concentrated as its flow diminished. In Wo. the diuresis and the high concentration of urea in the urine during the latter part of the experiment led to the excretion of a large part of the dose by the 460th min. (The other adults all had concentrations of urea over 670 m.equiv./l.) The comparative failure of the diuresis in A.J.B., coupled with his lower urinary concentrations of urea (in spite of higher serum levels) prevented him getting rid of much of his dose. The other adults responded much as did Wo., and M.P. behaved very like A.J.B., and a figure showing the average urea excretions was given by Dean & McCance (1947*a*). Table 7 shows the urea clearances and the

TABLE 7. The urea clearances after the administration of urea, and the urine osmotic pressures of an adult (Wo.) and an infant (A. J. B.)

	Wo. (adult)		A. J. B. (infant)	
Time (min.) after giving urea	Urea clearance (c.c./1·73 sq.m.)	Urine O.P. (m.mol./l.)*	Urea clearance (c.c./1·73 sq.m.)	Urine O.P. (m.mol./l.)*
Pre-experiment	49	961	11·1	414
45	53	573	7·9	474
90	60	562	8·7	508
150	78	608	10·4	516
240	76	634	13·3	522
330	66	606	15·5	535
450	61	703	16·5	555
600	—	—	14·6	575
660	—	—	13·1	569

* Reckoned as m.mol. urea + 2 × m.equiv. chloride.

urine osmotic pressures (reckoned as m.mol. of urea/l. + 2 × m.equiv. of Cl/l.) of Wo. and A.J.B. The low urea clearances of the infant confirm all previous work. An interesting feature, however, is the fall which took place in them after the urea had been administered. The clearance was not back at its initial level till the 108th min. The fall was due to the rapid rise in the concentration of urea in the plasma failing to increase the rate of excretion fast enough to maintain the clearance. In Wo. the initial clearance was high for a minute volume of 0·55, and it rose slowly in spite of the great increase in the blood urea. The rise of Wo.'s urea clearances was due to the diuresis which increased the output per min. as fast as the blood urea rose, in spite of the fall in the concentration of urea in the urine.

The osmotic pressure of Wo.'s urine was high before the experiment, fell with the diuresis and began to rise again as the flow of urine subsided. This is the characteristic adult response to a sufficiently large dose of hypertonic urea—as it is to a similar dose of hypertonic salt (McCance & Young, 1944). Rabbits (Dreser, 1892), dogs (Galeotti, 1902) and rats (McCance & Wilkinson, 1947) give a similar response. The osmotic pressure of A.J.B.'s urine was low before the experiment began and rose steadily after the urea had been given, because

TABLE 8. Maximum concentrations of chloride and urea observed in the urines, the osmotic pressure of the urines, and the U/P osmotic ratios

	Saline experiments				Urea experiments			
		Urine				Urine		
Subject	Plasma Cl (m.equiv./l.)	Cl (m.equiv./l.)	Osmotic pressure (m.mol./l.)	Osmotic U/P ratio	Plasma urea (m.mol./l.)	Urea (m.mol./l.)	Osmotic pressure (m.mol./l.)	Osmotic U/P ratio
Ro. (adult)	134	285	652	2·4	22	732	834	3·7
Wo. ,,	141	272	618	2·2	24	598	703	3·1
Wh. ,,	125	346	792	3·1	23	683	767	3·2
Pe. ,,	124	286	679	2·7	—	—	—	—
Lo. ,,	—	—	—	—	19	720	884	4·0
B.P. (infant)	155	221	510	1·6	—	—	—	—
B.B. ,,	156	215	496	1·5	—	—	—	—
F.L. ,,	144	243	561	1·9	—	—	—	—
W.P. ,,	151	230	498	1·6	34	513	565	2·0
A.J.B. ,,	131	170	468	1·7	29	500	569	2·5

the concentration of urea was increasing in the urine and the diuresis was so small. This would appear to be the usual response of an infant.

DISCUSSION

A linkage of the chloride reabsorption to the glomerular filtration rate has been demonstrated by Lotspeich, Swan & Pitts (1947), and by Pitts & Lotspeich (1946) in adult dogs, and Mokotoff, Ross & Leiter (1948) found that the m.equiv. of Na reabsorbed by the kidneys of adult men also bore a constant relationship to the glomerular filtration rate. The figure given by them was 13·3 m.mol./100 c.c. of glomerular filtrate. The present experiments make it clear that these statements are approximately true, for in spite of great changes in the glomerular filtration rates in Pe. and in the two infants, the m.equiv. of Cl reabsorbed/100 c.c. of glomerular filtrate did not alter very much (Table 5). There were, however, fluctuations which have already been described. If one can distinguish cause and effect it would appear that the chloride reabsorbed/100 c.c. of glomerular filtrate is relatively constant because: (1) nearly all the water in the glomerular filtrate is always reabsorbed; (2) the concentration of chloride in the plasma water can only vary within relatively small limits; and (3) the concentration of chloride in the fluid reabsorbed cannot differ by very much from the concentration in the fluid filtered off. The variations which may be observed under normal or experimental conditions are due to the facts that: (*a*) the percentage of the filtrate water, which is reabsorbed, can vary from about 87 to 99·5%; and (*b*) the concentration of Cl in the plasma water can be made to vary by experiment from, say, 90 to 180 m.equiv./l. The variations introduced by this, see (2) and (3) above are, however, limited because the concentration of Cl in the reabsorbate tends to be lower than that in the serum when the latter is high, and higher than that in the serum when the latter is low. With some reservations, therefore, the findings of Lotspeich *et al.* (1947) have been shown to hold for an adult man, and evidently apply also to infants. It is interesting that both B.P. and B.B. reabsorbed more Cl/c.c. of glomerular filtrate than Pe., and it is evident that from this point of view the tubules of the infant's kidneys were in no sense inferior to those of adults. These experiments show that if the plasma chlorides are artificially raised the kidney does not, as was at one time supposed, reabsorb a fluid optimal for plasma composition, but only one which is a somewhat better approximation to the optimal than the fluid filtered off.

There has been some debate in the last 4 years as to the ability of an infant to produce a concentrated urine. The evidence was reviewed by McCance (1948), who came to the conclusion that when an infant was first deprived of water its urine was always much less concentrated than that of an adult treated in a similar way. If, however, the infant had been dehydrated for some time and particularly if the serum had become highly abnormal, then comparatively high osmotic pressures might be found in the urine. The present experiments provide some further evidence. Table 8 shows the maximum concentration of Cl and of urea observed in the urine during these experiments, the osmotic pressure of the urines, and the values of Cl or of urea in the plasma at the same time. It will be seen that under these abnormal conditions the infant urines had much higher osmotic pressures than is usual at that age (McCance & Young, 1941), and when the osmotic pressures in the plasma were calculated in the same way as those in the urine, U/P osmotic ratios of 1·5 to 2·0 were regularly found in the Cl experiments and one ratio of 2·5 in a urea experiment. The infant urines, however, never had such high osmotic pressures as those of the adults in whom the U/P osmotic ratios varied from 2·2 to 3·1 in the saline experiments and were all over 3·1 in the urea experiments. It is of some interest that the U/P osmotic ratios were always higher after urea than after saline administration, for Young, Hallum & McCance (1941) considered that a high blood urea was one of the things which might enable newborn infants to produce the high U/P ratios occasionally found by them. It is still a problem to what extent these concentrated urines in infancy are caused by the failure of the kidney to produce a diuresis at that age. If the diuresis produced by hypertonic solutions is due solely to the increase of osmotically active material delivered to the distal tubules (see later) it is difficult to see why these solutions do not cause a better diuresis in infants, and if osmotically active material in the distal tubules does not produce a diuresis in infants, one at once begins to wonder why infants do not always produce concentrated urines 5 or 6 hr. after being deprived of water.

Sodium chloride and urea have very different physiological properties, yet the administration of a strong solution of either of them to an adult produces very similar effects. These are (1) an immediate and often extensive increase in urine flow, which soon subsides, at first rapidly and then gradually, to a more usual rate, and (2) a fall in the osmotic pressure of the urine as the diuresis develops, to be followed by a rise to high levels as the flow of urine falls off. It is usually supposed that these diuretic effects are due to the excess of osmotically active material reaching the distal tubules. In infants, hypertonic solutions of sodium chloride and urea also produce effects which are very similar to each other, but these effects differ from those produced in adults, for (1) the diuresis develops and subsides very slowly and is always trifling in amount, and (2) the osmotic pressure of the urine tends to rise from the time the hypertonic solutions have been administered.

Before offering any explanation of these findings, it may be helpful to summarize some of the other ways in which the renal function of infants differs from or resembles that of adults. Thus: (1) the glomerular filtration rates are much lower as are the urea, phosphate, sodium and chloride clearances; (2) the percentage of the urea in the glomerular filtrate which reaches the urine is perhaps slightly lower in infants than in adults, but is roughly the same at both ages; (3) infants and adults reabsorb about the same percentage of the Cl in their glomerular filtrates; (4) infants reabsorb rather more Cl/100 c.c. of glomerular filtrate than adults; and (5) infants cannot produce urines with such high osmotic pressures as normal adults. The first of these points suggests that infants have very defective glomerular function, but the second, third and fourth that their tubular function is fully developed so far as urea and Cl are concerned, and that it is linked with the glomerular filtration rate as it is in adults. It is suggested, therefore, that it is the difference in glomerular function which must underlie the differences in adult and infant responses to hypertonic urea and NaCl. It is possible that *in utero* and for some time thereafter the glomeruli are outside the main renal blood flow, or it may be that the layer of cubical cells overlying the glomerular tufts prevents effective filtration. It is impossible at present to decide one way or the other.

Since infants cannot produce such concentrated urines as adults, it might be suggested that the distal tubules were unable to prevent the back diffusion of urea and Cl, and that this was the reason for the failure of the diuresis to develop. This, however, is not in keeping with observations 2, 3 and 4 above, and that being so, one would expect a failure of the distal tubules to concentrate the urine to increase rather than diminish the diuresis due to hypertonic solutions.

If the fall in the osmotic pressure of an adult's urine, following the administration of hypertonic solutions is due to the intense diuresis, then its absence in infancy is easily explained by the small, and perhaps also the slow, change in urine flow which takes place at that age:

A rise in glomerular filtration rate follows the administration of hypertonic saline. Like the urine flow the rise in the adult Pe. was short and violent, that in the two infants slow, prolonged and relatively somewhat greater. It would probably be very helpful to know the reason for these time-relationships, but it is not yet known why the hypertonic saline should raise the glomerular filtration rate as it undoubtedly does. The rise may be due, in part at any rate, to an increase in plasma volume, and consequently a decrease in plasma colloidal pressure, caused by the withdrawal of water from the cells (Eggleton, Pappenheimer & Winton, 1940). It seems certain, however, that these changes in glomerular filtration rate must underlie and in part determine the observed changes in urine flow.

SUMMARY

1. When hypertonic saline was administered to normal adults after 15 hr. without water: (*a*) the urine flow increased rapidly and extensively and then fell, at first rapidly but subsequently more slowly; (*b*) the glomerular filtration rate rose at the same time as the urine flow, but it had returned to normal long before the diuresis had subsided.

2. When hypertonic saline was administered to infants after the same length of time without water: (*a*) the urine flow increased slowly and to a very moderate degree, and fell again equally slowly; (*b*) the glomerular filtration rate rose and fell with the same time-relationships as the urine flow.

3. In these infants the reabsorption of Cl/100 c.c. of glomerular filtrate was appreciably greater than it was in adults.

4. When a strong solution of urea was administered to adults and infants the changes produced in the flow of urine were not so great as those produced by hypertonic saline, but resembled them in other respects. The mechanism is likely to be the same, but the glomerular filtration rate may not increase.

5. The diuresis produced in adults by hypertonic saline or urea was accompanied by a fall in the osmotic pressure of the urine with a subsequent rise to high levels as the diuresis subsided.

6. The administration of hypertonic saline or urea to infants was characteristically accompanied by a rise rather than a fall in the osmotic pressure of the urine, and it is suggested that this was due to the fact that the diuresis was so small.

7. Owing to their greater diuresis, and to the higher osmotic pressure of their urines, adults excreted a much larger percentage of the hypertonic saline or urea than infants—at all events within the time limits of the experiments.

The authors wish to thank all those physicians who have allowed their patients to be investigated, the adults who have acted so willingly as subjects, and Dr J. R. Robinson, who has helped very much with the preparation of the section on osmotic work. Miss L. A. Thrussell has been responsible for many of the practical details involved in these investigations. Dr Grace Eggleton kindly read through the manuscript and made some helpful suggestions.

REFERENCES

Archibald, R. M. (1945). *J. biol. Chem.* **157**, 507.
Barnett, H. L., McNamara, H., Hare, R. S. & Hare, K. (1948). *Federation Proc.* **7**, 5.
Barnett, H. L., Perley, A. M. & McGinnis, H. G. (1942). *Proc. Soc. exp. Biol., N.Y.*, **49**, 90.
Borsook, H. & Winegarden, H. M. (1931). *Proc. nat. Acad. Sci., Wash.*, **17**, 3.
Dean, R. F. A. & McCance, R. A. (1947*a*). *Nature, Lond.*, **160**, 904.
Dean, R. F. A. & McCance, R. A. (1947*b*). *J. Physiol.* **106**, 431.
Dicker, S. E. (1948). *J. Physiol.* **107**, 8.
Dreser, H. (1892). *Arch. exp. Path. Pharmak.* **29**, 303.
Eggleton, M. G., Pappenheimer, J. R. & Winton, F. R. (1940). *J. Physiol.* **98**, 336.
Galeotti, G. (1902). *Arch. Anat. Physiol., Lpz.* (Physiol. Abt.), p. 200.
Hervey, G. R., McCance, R. A. & Tayler, R. G. O. (1946*a*). *J. Physiol.* **104**, 43*P*.
Hervey, G. R., McCance, R. A. & Tayler, R. G. O. (1946*b*). *Nature, Lond.*, **157**, 338.
Lee, M. H. & Widdowson, E. M. (1937). *Biochem. J.* **31**, 2035.
Lotspeich, W. D., Swan, R. C. & Pitts, R. F. (1947). *Amer. J. Physiol.* **148**, 445.
McCance, R. A. (1945). *J. Physiol.* **104**, 196.
McCance, R. A. (1948). *Physiol. Rev.* **28**, 331.
McCance, R. A. & Shipp, H. L. (1933). *Spec. Rep. Ser. med. Res. Coun., Lond.*, no. 187.
McCance, R. A. & Wilkinson, E. (1947). *J. Physiol.* **106**, 256.

McCance, R. A. & Young, W. F. (1941). *J. Physiol.* **99**, 265.
McCance, R. A. & Young, W. F. (1944). *J. Physiol.* **102**, 415.
Mokotoff, R., Ross, G. & Leiter, L. (1948). *J. clin. Invest.* **27**, 1.
Pitts, R. F. & Lotspeich, W. D. (1946). *Amer. J. Physiol.* **147**, 138.
von Rhorer, L. (1905). *Pflüg. Arch. ges. Physiol.* **109**, 375.
Roe, J. W. (1934). *J. biol. Chem.* **107**, 15.
Sendroy, J. (1937). *J. biol. Chem.* **120**, 405.
van Slyke, D. D. (1923–4). *J. biol. Chem.* **58**, 523.
Starling, E. H. (1909). *The Fluids of the Body*. London: Constable and Co.
Whitehorn, J. C. (1920). *J. biol. Chem.* **45**, 449.
Young, W. F., Hallum, J. L. & McCance, R. A. (1941). *Arch. Dis. Childh.* **16**, 243.
Young, W. F. & McCance, R. A. (1942). *Arch. Dis. Childh.* **17**, 65.