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THE EXCRETION OF UREA, SALTS AND WATER DURING PERIODS OF HYDROPAENIA IN MAN

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It is now well known that, even during periods of severe dehydration, urine continues to be formed. This is the so-called 'urine obligatoire' of Ambard & Papin (1909). This urine is concentrated and of high specific gravity and, if it is passed by a healthy person, usually freezes at about $-2{\cdot}2$ to $-2{\cdot}6°$ C. There are, however, many unsolved problems about such urine, and statements have been made about it which are very difficult to reconcile with each other. In the first place, it is still not clear what regulates the volume of water passed by a dehydrated person. Ambard & Papin (1909) believed that it was the presence in the urine of one of the constituents at its limiting concentration, and that maximum concentrations of urea and salt could co-exist. 'Il exist une independance absolue des concentrations de l'urée et de NaCl.' Davies, Haldane & Peskett (1922) also considered that 'the simultaneous excretion of urea' by man was 'without effect on the kidneys' capacity for concentrating chlorides', and Gilman & Kidd (1938) that 'the presence of high concentrations of urea in the urine' of the dog 'had absolutely no effect on the osmotic ceiling of NaCl'. These statements imply that the kidney should be able to produce maximum concentrations of urea and salt simultaneously. If this were the case, it ought to be possible to demonstrate it during dehydration. Adolph (1923), however, did not do so consistently to his own satisfaction, and Chaussin (1920) found that the concentrations of urea and NaCl tended to vary inversely in concentrated human urine. McCance & Young (1944) confirmed this, and also showed that the volume passed during dehydration depended upon the intake of NaCl. They therefore suggested that, under the conditions of their experiments, the volume passed depended upon the total osmotic pressure of the urine rather than upon the concentration of any one constituent (Smith, 1937). Reference should perhaps be made here to the oft-quoted work of Gamble, McKhann, Butler & Tuthill (1934). These authors came to the conclusion that animals required less water to excrete urea than they did to excrete NaCl or other substances. This was

held to be an important feature of the water economy of terrestrial animals, and it was explained by 'the physical properties which urea exhibits to degrees which are almost unique'. In these experiments, however—and this has generally been overlooked—the rats were allowed to drink as much as they wished. The findings, therefore, would seem to have more bearing upon the mechanism of thirst production than of water excretion, and they certainly have no place in the present discussion. Secondly, Chesley (1938) found that, when urine volumes were below 0·35–0·5 c.c. per min., the percentage of urea was constantly at its maximum value for that person, and the clearances depended only upon the minute volume. He also found at these low volumes that (*a*) the creatinine, inorganic P and also the total solids were always maximally concentrated, (*b*) the clearances of endogenous creatinine, which some have considered to measure the glomerular filtration rates, varied directly and quantitatively with the urine volumes. McCance & Young (1944) did not find any evidence for a fixed percentage of urea when they manipulated the volumes by varying the intake of NaCl, for they always observed that the percentage of urea rose as the minute volume fell. Black, McCance & Young (1942), moreover, found that the glomerular filtration rates remained very stable even under conditions of considerable dehydration, and this again is difficult to reconcile with Chesley's results. It was accordingly decided to reinvestigate the secretion of urine during periods of water deprivation, and the results appear to be helpful and clear, although naturally all the conflicting statements cannot be reconciled.

SUBJECTS AND METHODS

The work was carried out between October 1943 and July 1944 on two healthy men, N.J., aged 30 and R.H., aged 20, and on one healthy woman, P.C., aged 28. The general plan was to bring the subjects into a state of mild dehydration in which the kidney was likely to be conserving water to its maximum capacity. Considerable variations in urine flow were then produced by a variety of methods and a study made of the changes in the plasma and urine.

After their usual supper the subjects drank nothing for the rest of the evening and, at a fixed time on the following morning, took a standard breakfast without anything to drink and came to the laboratory at 1 p.m. for lunch. This consisted of bread, butter and jam, but no liquids. On the experimental days they took one dose of urea, or of NaCl or of KCl at 10 a.m. and another larger dose at 12 noon. These substances were dissolved in as little water as possible and the solutions were almost saturated. On the control days nothing was taken between breakfast and lunch. On all days the urine formed between about 2.30 and 5 p.m. was collected as one specimen and blood was taken for analysis about 3.45 p.m. The experiments were carried out in this way to avoid the first diuresis and fall in urinary osmotic pressure which seem to be the immediate results of taking urea or salts (McCance & Young, 1944). After the urine had been collected at 5 p.m., the subjects had a meal, and with it as much to drink as they wished. Several days were usually allowed to pass before the next experiment. On two occasions the subjects were given salt-free diets for 3 or 4 days before the desired experiments were carried out. For special tests, water, and creatinine, were given by mouth, and small quantities of sucrose were injected intravenously. On one occasion 330 c.c. of 3% NaCl were administered intravenously in addition to 24 g. of NaCl by mouth.

On the samples of urine the following determinations were carried out. (1) The volume—in a cylinder of appropriate size. (2) The freezing-point—using a Beckmann thermometer. If precipitates formed, these were at first removed and redissolved, and the freezing-point of this solution was then separately determined and added to that of the original urine. This procedure was later discontinued as the correction was found to be a very small one. (3) The specific gravity—by a specific gravity bottle. This estimation was only carried out on about half the specimens. (4) Na, K and Cl by the methods given by McCance (1937) and McCance & Widdowson (1937). (5) Urea by Lee & Widdowson's (1937) method.

The blood was collected under paraffin, with precautions against venous stasis, and the plasma or serum separated without delay. On the serum the following estimations were made. (1) Na, Cl, urea and the freezing-point by the methods given above. The changes in the last were so small that this procedure was dropped after some 6 months. (2) For K about 2·5 c.c. serum were dried, then heated, without any additions, in a small crucible at 400–450° C. till the ash was perfectly white. 2·5 c.c. of N/10 HCl were then added and the ash dissolved at room temperature. Two samples, each of 1 c.c., were then taken and the K determined by Hubbard's (1933) method.

RESULTS

Control data. On the standardized regimen which has just been described, it was impossible to detect any variations in the concentrations of Na, K, and Cl in the serum from one control day to the next, and the variations in urea were trifling. There were, however, quite definite changes in the urine, some of which are given in Table 1. It will be seen that the freezing-point

TABLE 1. Variations in the control urines from day to day

Subject	Freezing-point −°C.	Min. vol. c.c.	F.P. × 1000 / 1·86	Urine urea m.mol./l.	Urine Na m.equiv./l.	Urine Cl m.equiv./l.	Urine K m.equiv./l.	Urea + Na + Cl + 2 × K m.mol./l.
R.H. 1	2·42	0·52	1300	525	265	254	90	1225
2	2·60	0·63	1400	542	270	270	89	1260
3	2·67	0·46	1430	625	156	195	119	1214
P.C. 1	2·12	0·39	1140	433	170	173	82	940
2	2·35	0·32	1260	527	178	165	136	1142
N.J. 1	1·86	0·64	1000	394	200	192	57	900
2	2·14	0·46	1150	492	193	180	69	943
3	2·33	0·36	1260	542	137	171	94	1038
4	1·94	0·49	1040	421	165	195	50	881

of N.J.'s urine varied from −1·86 to −2·33° C., and of R.H.'s from −2·42 to −2·67° C. These variations in the freezing-point showed that the maximum osmotic work of which the kidney was capable was not nearly such a constant quantity as the concentrations of some of the constituents of the internal environment of the body. Adolph (1923) drew attention to the inconstancy of the urinary maxima for Cl and urea, and for the two together, and also pointed out that in spite of it Ambard had had the vision to establish the fact that there were these limiting concentrations.

There were variations of considerable size in the concentrations of some of the principal osmotically active constituents in these control urines. Thus, the urea in R.H.'s urine varied from 525 to 625 m.mol./l., and the K in that of N.J. from 50 to 94 m. equivalents/l. Sometimes the urea and salt varied inversely from day to day, but sometimes the changes were in the same direction and accompanied by a change in the freezing-point, and it was

clear that factors which were not being taken into account were producing these changes in the excretion of electrolytes and urea.

When the freezing-points were multiplied by the conventional 1000/1·86, and the results compared with those obtained by adding the urea, Na, Cl and 2 × K, it was evident that there was a rough relationship between them. The former exceeded the latter by 75–216 m.mol./l. Urea, Na and K salts, therefore, accounted for most of the osmotic activity of these urines, while undetermined substances were responsible for the remaining 10–20%.

Serum urea. McCance & Young (1944) observed a considerable fall in the excretion of Na and of Cl when 35 g. of urea were injected intravenously into a dehydrated woman. No change was detected in the serum Na but there was a large fall in the serum Cl. Adolph (1925) probably had a similar phenomenon under observation. 50 g. of urea by mouth did not produce such an effect in these three subjects, but some evidence of a reciprocal change was noted in the serum chemistry of two of them. It was best shown by R.H., and data from his experiments are given in Table 2. It will be seen that the

TABLE 2. The effect of NaCl and of $NaHCO_3$ on the serum urea of a man (R.H.) who was not fully hydrated

Nature of experiment	Serum urea mg./100 c.c.
Control	42·2
15 g. NaCl by mouth	34·5
Control	42·0
25 g. NaCl by mouth	32·8
21 g. $NaHCO_3$ by mouth	37·3
Control	42·5
21 g. $NaHCO_3$ by mouth	36·0
30 g. NaCl by mouth	32·7

The experiments are given in the order in which they were performed.

serum urea was always lower on the days on which the doses of NaCl had been administered, and that $NaHCO_3$ appeared to have a similar effect. It has been suggested that these salts were so nauseating that they delayed the passage of lunch from the stomach and hence the formation of urea from the protein in that meal. This is not a very satisfactory theory because the small doses of K salts were quite as nauseating but they did not depress the serum urea. If, however, this simple explanation is not accepted it is as difficult to explain these observations in terms of conventional body chemistry and membrane permeability as it is to explain those of McCance & Young (1944) or of Adolph (1923). Nevertheless, it may be helpful to place them on record.

The excretion of urea. The composition of the control urines has been given in Table 1. The effect of a 'salt-free' diet for a few days was to reduce to a very small figure the Na and Cl in the urine. The accompanying changes were a fall in the minute volume of the urine—see Table 3, a rise in the percentage of urea in the urine, and a rise in the urine/plasma urea ratio. There was no

TABLE 3. The relationship between the excretion of urea and that of other osmotically active substances

Subject P.C.

Nature of diet and experiment	Blood urea		Urine					
	mg./100 c.c.	m.mol./l.	Min. vol. c.c.	Urea m.mol./l.	Na×2 m.mol./l.	K×2 m.mol./l.	Sum of urea+2 (Na+K)	F.P.×1000 / 1·8
Controls (average)	25·3	4·22	0·355	480	346	224	1050	1200
„ +25 g. of urea	61·8	10·30	0·830	835	133	91	1059	1200
„ +50 g. of urea	112·0	18·60	1·72	752	150	67	969	1050
Low salt (average)	23·0	3·94	0·24	662	49	212	923	1200
„ +25 g. of urea	66·2	11·00	0·80	860	9	149	1018	1090
Control +25 g. urea and 15 g. NaCl	65·0	10·80	2·20	409	452	95	956	1100

change in the averaged freezing-points. These results, which were anticipated from the findings of McCance & Young (1944), may be explained as follows. The salt-free diet reduced the number of osmotically active substances to be excreted per minute and, since the kidney continued to concentrate the urine to the same extent as before, there was also a fall in the volume of water excreted per minute. The percentage of urea in this water naturally rose.

Urea was taken by mouth both when the subjects were on normal and on salt-free diets, and P.C.'s data are given in Table 3. The findings were (1) a rise in the concentrations of urea both in the blood and urine, (2) a rise in the minute volume of the urine, (3) a fall in the percentage of Na and K salts in the urine, (4) no consistent change in freezing-point over a range of volumes up to 1·72 c.c./min. If the small fall at that volume is significant, it may be attributed to the hurried passage of the urine through the distal tubules (McCance & Young, 1944). It is suggested that these changes were brought about as follows. The rise in the blood urea caused a considerable increase of urea molecules to appear in the distal tubules per minute. The kidney continued to concentrate the urine to the limit of its capacity, but the osmotic activity of the urea forced the kidney to excrete much more water per minute and the concentration of Na and K salts in this water naturally fell.

The evidence then is that, in mild dehydration, the volume of the urine passed per minute depends upon the number of osmotically active substances claiming excretion per minute (*a*) at the lowest minute volumes when the urine is free of salt, (*b*) when the urine contains normal quantities of salt, (*c*) when a diuresis has been provoked by taking urea by mouth. Gamble (1942, 1944) has set out this aspect of volume control and appears to consider it of general application.

662 m.mol. of urea/l. (3·97%) may be taken as the maximum to which P.C. concentrated urea in her urine when her blood urea was normal, and the only other osmotic competitors in the urine were the K salts. After a large dose of urea by mouth she produced a urea concentration of 835 m.mol./l. of urine on a normal diet and 860 m.mol. on a salt-free diet (5 and 5·15% respectively). This was achieved because the diuretic effect of urea reduced

the concentration of Na and K in the urine to a level which permitted the rise in urea to take place without exceeding the osmotic limitations of the kidney. There is nothing in these results to suggest that maximum concentrations of NaCl and urea could be achieved simultaneously (Davies, Haldane & Peskett, 1922; Gilman & Kidd, 1938), but, to see if this could be done, the subjects took both urea and NaCl by mouth on the same day, and P.C.'s results are given in Table 3. There was a large diuresis, and the concentration of Na was well below her maximum for this ion, for the figure of 574 m.mol. was reached in another experiment after taking 15 g. of NaCl (without urea) by mouth. When the salt and urea were taken together the Cl, which is not shown in Table 3, only reached a value of 244 m.equiv./l. against 318 on another occasion, and the concentration of K was low. The urea was well below the level attained on a low salt diet, but the freezing-point of the urine was almost within the range of maximum values, and this is the clue to the whole matter. P.C.'s kidney was incapable of producing simultaneously the concentrations of NaCl and of urea which it could be demonstrated to produce separately. Similar results were obtained on R.H. After 12 g. of NaCl and 20 g. of urea by mouth he passed 1·38 c.c. urine/min. and the concentrations of Cl and of urea in this urine were 1·0% and 2·86% respectively. Cl concentrations exceeding 1·3% were achieved in several of his other experiments; 4% of urea was found in the urine passed when he was on a salt-free diet, and 5·7% after taking 25 g. of urea by mouth. The freezing-points varied from $-2{\cdot}2$ to $-2{\cdot}65°$C.

Fig. 1 shows P.C.'s urine/plasma ratios for urea plotted against her minute volumes. The symbols indicate the nature of the experiments. It will be seen that the U/P ratios fall on or about the smooth curve which has been drawn on the figure, and that this was so whatever the nature of the experiment, and even when urea itself was the agent provoking the diuresis. In other words, whether the minute volume was being fixed by the needs of the body for water, or by the osmotic limitations of the kidney, the U/P ratio taken up was characteristic of that minute volume and largely independent of everything else. This means that, for any given minute volume, the percentage of urea reabsorbed from the glomerular filtrate was unaffected by the amount filtered off, or by the osmotic pressure within the tubules, and this seems to be a matter of considerable theoretical interest. The results certainly support the view that urea is returned to the plasma by diffusion rather than by tubular activity (Dole, 1943).

It will be noted that, in Fig. 1 after a water diuresis on a control diet, two of the U/P ratios were rather far from the curve. In N.J.'s experiment all the U/P ratios were close to the curve, but in R.H.'s experiments the U/P ratios during a water diuresis were more irregular than in P.C.'s, and the ratios were scattered on both sides of the curve. These irregularities were not

due to the phenomena associated with a sudden rise of minute volume after a period of oliguria (Shannon, 1936; Dole, 1943), and it is suggested that they may have been due to spontaneous variations in the glomerular filtration rate. For suppose 'C' to be the number of c.c. filtered off in the glomeruli per minute, and 'V' the minute volume of the urine, then the U/P ratio for a substance such as inulin will be given by C/V. Owing to the fact that some urea is always reabsorbed in the tubules, the U/P ratio for this substance is not

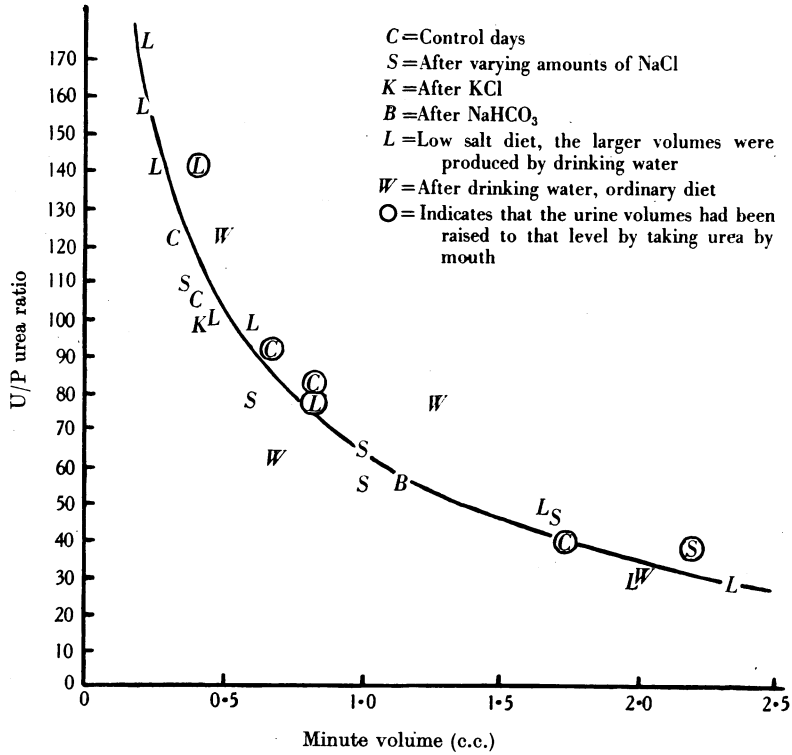

Fig. 1. The effect of various diuretic agents on the U/P urea ratio.

given by C/V, but by C/fV where 'f' is a factor, always greater than 1. In the case of urea, f varies from about 3·6 at low minute volumes to about 1·7 at minute volumes of the order of 2. When the need of the body for water is the sole factor regulating V (as it is in a water diuresis), C, and hence C/fV, can fluctuate without necessarily producing any change in V. If, however, V is being regulated by the osmotic limitations of the kidney, then, since a rise in C must lead to an increase of osmotically active material to be excreted per minute, a rise in C must produce a corresponding rise in V, and this prevents the C/fV ratio going up. Actually, in practice C/fV will fall since the plasma value of the substance under consideration may be

assumed to remain constant. In these experiments the U/P ratios were only far from the curve in a water diuresis produced when the subject was taking an ordinary diet. Similar variations were not found when the subjects were on a low salt diet, and it is suggested that the low salt diet had produced enough shrinkage in the volume of extracellular fluids to curtail for some reason spontaneous variations in the rate of glomerular filtration.

The excretion of NaCl. Table 4 shows data from some of R.H.'s experiments. These illustrate some of the effects of a low-salt diet and of various doses of NaCl by mouth. It will be seen that the serum Na and Cl fell slightly on

TABLE 4. The effect of varying the intake of salt on the serum and urinary concentration

	Serum		Urine				
Experimental procedure	Na mg./ 100 c.c.	Cl mg./ 100 c.c.	Min. vol. c.c.	Na mg./ 100 c.c.	Cl mg./ 100 c.c.	K mg./ 100 c.c.	Freezing-point −°C.
Low salt diet	318	355	0·28	74	61	604	2·2
Control diet 1	330	369	0·46	360	690	466	2·67
2	328	367	0·52	610	899	351	2·42
3	330	366	0·63	620	957	348	2·60
8 g. NaCl	333	380	0·86	527	1190	575	2·28
15 g. NaCl	333	386	1·32	695	1330	423	2·12
25 g. NaCl	343	400	2·04	557	1250	330	1·96
30 g. NaCl	347	403	2·15	590	1160	347	1·85

the low salt diet, and that the serum Na rose only from 330 to 347 mg./100 c.c. even after eating 30 g. of NaCl. The serum Cl rose considerably more—from 367 to 403 mg./100 c.c. after the dose of 30 g.—and this difference in the behaviour of Na and of Cl has been observed in the other two subjects. After being given 35 g. of NaCl, for instance, 11 g. of them intravenously as 3% NaCl, P.C.'s serum Na rose from 335 to 348 mg./100 c.c., the Cl from 379 to 427 mg./100 c.c. Increasing the intake of salt always increased the minute volume of the urine, but an intake of 15 g. of NaCl raised the urinary Cl to a concentration higher than that produced even by the larger doses. This was also noted in other subjects (Fig. 2). It is an old observation (Davies *et al.* 1922) that 1300 mg./100 c.c. is about the maximum concentration of Cl which the kidney can achieve, and these observations fully confirm it. It will next be seen (Table 4) that the concentrations of K were 348–466 mg./100 c.c. urine on the control days, and that the concentration rose on a low salt intake as the minute volume fell. After NaCl, however, the concentrations of K fell off very little, and on some days not at all, in spite of a large increase in the minute volume. It was found in other experiments that, after taking water by mouth, the concentration of K in R.H.'s urine was generally between 80 and 160 mg./100 c.c. when the minute volume was between 0·8 and 2·0 c.c., so that the great increase in K excretion after taking NaCl was no doubt the result of taking NaCl, for others have reported similar findings (McCance & Young, 1944). Finally, it will be noted that the freezing-

point of the urine was appreciably lower on the control diets than it was after taking the large doses of salt. This is better and more convincingly shown by Fig. 2, which gives data from P.C.'s experiments. The concentration of NaCl, and the total osmolar concentrations of the urine, are plotted against the minute volume. It will be seen that, as the intake of salt rose and increased the minute volume of the urine, the concentration of salt remained at or just below the accepted maximum, and the total osmolar concentration of P.C.'s urine fell far below the limits which her kidney achieved on the

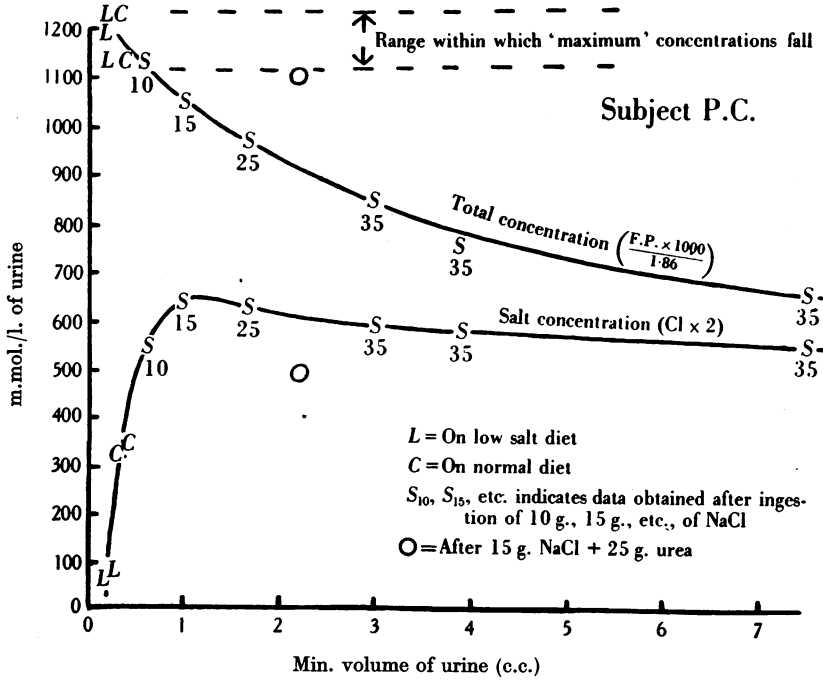

Fig. 2. The effect of a diuresis brought about by salt on the total osmolar concentration of the urine.

control and salt-free diets. In other words, the diuresis after salt was not an osmotic diuresis, and the output of water was being controlled by the forces responsible for the excretion of Na, Cl and possibly K. It is impossible at present to disentangle the separate roles played by the plasma levels, the U/P ratios, the suprarenal cortex and the pituitary gland, and they may all be involved. This fall in the osmolar concentration of the urine is a perfectly logical finding, and was mainly due to the fall in the concentration of urea as the minute volume rose. Further proof that the diuresis after NaCl was in no sense an osmotic diuresis was provided by the experiment in which P.C. took 15 g. of NaCl and 25 g. of urea simultaneously. These results also are given on Fig. 2. At a minute volume of 2·2 c.c. the salt concentration in the

urine was only 490 m.mol./l. so this was not a salt diuresis. The rise in the blood urea, however, to 65 mg./100 c.c. so increased the output of urea that the osmotic concentration of the urine was virtually up to the renal limits, and the diuresis may be regarded as an osmotic one. If a large dose of urea had been taken with the 35 g. of NaCl there is little doubt that the osmolar concentrations of the urines would have been higher than they were. They might even have reached maximum limits at minute volumes of 5 and 6 c.c., but this would have meant that the kidneys' output of osmotic work per minute would have been 14 to 18 times as great as it had been before the doses were taken, and the kidney might not have been able to achieve such a crescendo of power. It may be worth pointing out in this connexion that very little work is involved in maintaining maximum concentrations of Cl in the urine, even when the volumes are high, for the U/P Cl ratio is never above 4. The production of high concentrations of urea, however, at large minute volumes might be difficult to achieve experimentally owing to the large amounts of urea which would have to be introduced into the system, and would involve so much work that the tubules might well be unable to accomplish it in the limited time at their disposal. These matters are being investigated.

The effects of $NaHCO_3$ *and of* K *salts.* All the subjects who took 15 g. NaCl also ingested on another occasion, 21 g. of $NaHCO_3$. These are equimolecular doses. In R.H. and in N.J. the bicarbonate caused a smaller diuresis, 0·7–0·8 c.c./min. as against 1·3 c.c./min. with NaCl, and produced the highest concentration of urinary Na which those persons achieved. It is uncertain

TABLE 5. A comparison of the effects of ingestion of KCl and of NaCl upon the composition of the urine

Subject and dose	Min. vol. c.c.	Freezing-point −°C.	Urea m.mol./l.	Na m.equiv./l.	K m.equiv./l.	Sum Na+K m.equiv./l.	Cl m.equiv./l.
R.H. No dose	0·46	2·67	625	156	119	275	195
5 g. KCl	0·45	2·52	440	137	154	291	296
15 g. NaCl	1·32	2·12	277	302	109	411	375
15 g. KCl	1·27	2·28	288	236	224	460	375
No dose	0·63	2·60	543	270	89	359	270
10 g. KCl	0·62	2·51	417	165	254	419	330
N.J. 5 g. NaCl	0·72	1·97	390	256	54	310	239
5 g. KCl	0·76	1·96	344	210	92	302	260
P.C. Mean of 5 g. and 10 g. NaCl	0·46	2·17	380	212	101	313	222
5 g. KCl	0·46	2·44	382	140	167	307	316

whether this has any general significance for, in P.C., the two salts had almost equal effects. Strong solutions of KCl were found to be very nauseating, even in small doses, but 5–15 g. were taken by each subject to study the reciprocal relationships of Na and K. The results are given in Table 5 where the effects of KCl are compared with those of doses of NaCl which produced similar minute volumes. It will be seen that, in terms of m.equiv./l., (1) the sum of

the Na and K in the urines generally exceeded the Cl, but twice after taking KCl it did not do so, (2) Na and K did replace one another, (3) after taking a K salt the sum of the Na and K equalled or exceeded the sum of the two after taking the Na salt and the concentration of urea was about the same or less. One of the factors limiting the concentration of Na and K is probably the osmotic pressure of the urine, but the present results do not prove this because of the variability of the osmotic maximum.

Discussion

The control of urine volume. The present work makes it clear that in hydropaenia the urine volume may be regulated in at least two ways. The total amount of osmotically active material claiming excretion per minute usually fixes the output of water in mild dehydration, and when the output of NaCl does not exceed 20 mg./min. Chaussin's (1920) results and those of McCance & Young (1944) were obtained under these conditions. The amount of NaCl to be excreted per minute may, however, itself control the output of water, although it is not at present quite clear how. This mechanism becomes effective when the concentration of NaCl in the urine has risen to its maximum, and is most easily demonstrated when the urine volume is over 1 c.c./min. Ambard & Papin (1909) visualized the volumes as being controlled in this way, and Adolph (1923), Baird & Haldane (1922) and Davies *et al.* (1922) were certainly working at times with this mechanism of control. If the output of water is low, it will never be possible to obtain 'maximum' concentrations of NaCl and urea in the same specimen of human urine, because osmotic activity will prevent it. It would probably be easier to obtain really high concentrations of NaCl and urea simultaneously by taking a large quantity of each by mouth. The diuresis which would result would dilute the K salts and other osmotically active constituents of the urine, and allow urea to take their place, and, if the kidney were able to do the necessary amount of osmotic work per minute, the desired result might be obtained. Some of Davies *et al.* (1922) conclusions may be accounted for in this way.

An appreciation of the two ways in which the urine volumes may be regulated in hydropaenia may help to clarify some of the findings in disease. A change over from control by total osmotic activity to control by NaCl concentration probably explains the results reported by Alving & van Slyke (1934) on a patient who was recovering from nephritis.

There are suggestions in the literature (Addis & Shevky, 1922) that healthy persons, deprived of water, produce urines with subnormal specific gravities when their diets contain little salt and protein, but the difference between their averages does not seem to be statistically significant. These results were not in line with those of Addis & Foster (1922), nor did Miller, Price & Longley (1941) confirm them but, in their case, the diets were not low in protein.

The uraemia 'par manque de sel' of the French clinicians (Chabanier & Lobo-Onell, 1934) might be quoted in support, but it is scarcely comparable for all the observations were made on patients, most of them seriously ill and all of them with high blood ureas. The present experiments are of little help in this connexion. P.C. produced urines with freezing-points fully as low as her controls when she was on a diet low in salt (Tables 1 and 6, and Fig. 2) but R.H. and N.J. did not do so quite so convincingly (Table 2). All three might have failed in this if their diets had been low in protein as well as salt, for there may be a maximum U/P urea ratio for each person, and, if there is, some interesting experimental possibilities are opened up. It might, for instance, be possible to demonstrate that this ratio, and not the quantity of osmotically active material, controlled the output of water when the intakes of water, protein and salts were very low. An attempt is being made to do so, and if it succeeds it will be necessary to recognize a third method by which the urine volumes may be controlled in hydropaenia. A consideration of maximum U/P urea ratios leads naturally to the next point.

Chesley's experiments. Chesley's (1938) conclusions have been widely accepted and it should be stated at once that none of the recent experiments directly contradict his results for they have been carried out under somewhat different conditions. They do, however, suggest that Chesley's conclusions require to be carefully rescrutinized, and for the following reasons:

(*a*) Working well within Chesley's range of 'minimal' volumes, it is easy to lower the output of water by reducing the output of NaCl, and this can be counted upon to raise the percentage of urea in the urine. Hence the percentage of urea in urine is not necessarily fixed when the minute volumes are very low.

(*b*) When Black *et al.* (1942) determined the glomerular filtration rates of persons who had lost up to 7·2% of their body weights by dehydration, they found the glomerular filtration rates to be almost or absolutely normal. In a way this is not a direct refutation of Chesley's findings since the subjects studied by Black *et al.* were taking a diet which maintained their urine volumes above Chesley's limiting values. On the other hand, Black's subjects had gone much longer without water than had Chesley's, and one must suppose that glomerular filtration rates vary, if they do vary, with the hydration of the animal rather than with the final volume of the urine.

(*c*) The present results might be taken to support some of Chesley's findings, for, if the volume of the urine is controlled by the output of osmotically active material, a maximum concentration of total solids might be expected at all low minute volumes—and this is what Chesley found.

(*d*) The present results have shown that the osmotic maximum is rather a variable quantity, and it is felt that this should be more carefully watched if Chesley's experiments were being repeated. P.C., for instance, provided

four specimens of urine during her two low salt regimens. The minute volumes, freezing-points, urea concentrations and clearances are given in Table 6. With the freezing-points in the table it is easy to see that variations in the urea

TABLE 6. Variations in the freezing-point and percentage of urea in the urine with no change in the minute volume

Min. vol.	Freezing-point	Urea	Urea clearances (UV/P)
c.c.	−°C.	%	c.c.
0·24	2·10	3·25	34
0·24	2·23	3·90	42
0·22	2·37	3·94	35
0·24	2·00	3·20	31

percentages and clearances were mainly due to changes in the osmotic work of the kidney. Had the freezing-points not been determined, and had the minute volumes varied rather than the percentages of urea, these results would have been a direct confirmation of Chesley's conclusions.

SUMMARY

1. After deprivation of water for from 19 to 21 hr., the levels of urea, Na, K and Cl in the serum were constant from day to day within the limits of experimental error, but the concentrations of these substances in the urine, and the freezing-point of the urine varied appreciably.

2. In one subject, large doses of NaCl depressed the level of urea in the serum.

3. The U/P urea ratio depended primarily upon the minute volume of the urine, even when urea itself was the diuretic. Hence, the percentage of urea reabsorbed from the glomerular filtrates must have been independent of the amount filtered off or of the osmotic pressure of the fluid within the tubules.

4. (*a*) Reducing the intake of NaCl lowered the minute volume of the urine and increased the concentration of urea and K in it. (*b*) Taking urea by mouth raised the minute volume of the urine and the percentage of urea in it. The percentage of Na and K fell. In all these experiments the freezing-point of the urine was depressed to the limits which must be regarded as 'maximal', and the flow of urine is considered to have been regulated by the osmotic limitations of the kidney.

5. Administering 25–35 g. of NaCl raised the percentage of NaCl in the urine to its recognized maximum of about 2%, and the volume of the urine to 2–7 c.c./min. In these experiments the freezing-point of the urine indicated that its osmotic pressure was not high, and it is thought that the output of water was being regulated by the amount of NaCl to be excreted per minute.

6. The present experiments explain some of the contradictory findings and conclusions which have been obtained by other workers but they do not support the view that at very low minute volumes the percentage of urea in

the urine is necessarily fixed, or that dehydration lowers the glomerular filtration rate in man.

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