



## PEAK RATES OF DIURESIS IN HEALTHY HUMANS DURING ORAL FLUID OVERLOAD

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**Objective.** To determine whether rates of intestinal fluid absorption and renal diuresis can match high rates of fluid ingestion in healthy humans exposed to oral fluid overload, thereby preventing the development of hyponatraemia either by reverse sodium movement across the intestine (the Priestley-Haldane effect) or by expansion of the extracellular fluid volume.

**Methods.** Changes in renal function and in plasma chemical measurements in response to an oral fluid overload (0.9 - 1.8 l/h x 3 h) were investigated in 6 healthy control subjects at rest, and in a subject with a history of exercise-induced symptomatic hyponatraemia, during both prolonged (160-minute) exercise and at rest.

**Findings.** All control subjects gained weight ( $2.7 \pm 0.2$  kg, mean  $\pm$  standard error of mean (SEM)) because the rate of oral fluid intake exceeded the peak rate of urine production ( $778 \pm 39$  ml/h). Blood volume rose by 7.1 ( $\pm 0.5$ )% and plasma sodium concentrations fell progressively from 144  $\pm$  2.6 to 136  $\pm$  1.1 mmol/l ( $P < 0.05$ ) in the control subjects. Plasma potassium and angiotensin II concentrations were unchanged and creatinine clearance was normal ( $\sim 125$  ml/min). Free water clearance reached a maximum of 11.2  $\pm$  0.9 ml/min after 2 hours. The increase in body mass could be accounted for by calculated or measured changes in extra- and intracellular fluid volumes. Similar changes were measured in the subject with a previous history of symptomatic hyponatraemia.

**Conclusion.** The rate of intestinal fluid absorption appeared to match the rate of oral fluid ingestion and there was no

evidence of fluid accumulation in the intestine with reverse sodium movement from the extracellular space into intestinal fluid. The results of this study are therefore at variance with the Priestley-Haldane hypothesis and suggest that reverse sodium movement did not contribute to the hyponatraemia induced by oral fluid overload in these subjects. Rather it appears that humans may have a limited capacity to excrete fluid at rates in excess of  $\sim 900$  ml/h in response to higher rates of oral fluid intake. When the rate of intestinal fluid absorption matches the rate of fluid ingestion and exceeds the kidneys' maximum capacity for fluid excretion, the excess fluid accumulates in the extra- and intracellular fluid compartments, inducing the dilutional hyponatraemia of water intoxication. These findings may have relevance to other clinical conditions in which hyponatraemia develops in response to high rates of oral or intravenous fluid provision.

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Since it was first reported in 1981,<sup>1</sup> symptomatic hyponatraemia of exercise induced by oral fluid overload<sup>2,3</sup> has been increasingly recognised in athletes competing in ultra-endurance events including 90 km<sup>24,5</sup> and 160 km/24 footraces,<sup>6,7</sup> and the 226 km Ironman Triathlon.<sup>8</sup> More recently the condition has been described in 42.2 km marathon runners, in military personnel<sup>10</sup> and even in recreational hikers.<sup>11,12</sup>

There are two potential mechanisms by which oral fluid overload can induce hyponatraemia. If the rate of fluid absorption from the intestine exceeds the maximum rate of renal diuresis, then the total body water will increase causing dilution of the serum sodium concentration.

Alternatively, as proposed by Priestley<sup>13</sup> in 1916, 'Pari passu with absorption of water from the intestine, salts at first pass out of the blood into the water in the intestine. As a consequence of this loss of salts the conductivity of the blood plasma is diminished, and its proportion of salts to water is similarly diminished.' If it is of a sufficient magnitude, this reverse sodium movement into the unabsorbed intestinal fluid could induce hyponatraemia by a third space effect. It is now well established that, when hypotonic solutions with low ( $< 50$  mmol/l) sodium content are ingested, sodium is rapidly transferred from the extracellular space into the ingested fluid as it enters the duodenum.<sup>14-16</sup>

Accordingly, the principal aim of this study was to determine whether normal humans have a limited capacity for diuresis when they ingest fluid at high rates and whether this causes hyponatraemia either due to rapid fluid absorption with dilution of the serum sodium concentration, or as the result of a probable third space effect if the rate of intestinal fluid absorption is less than the rate of oral fluid ingestion.

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To evaluate this, we compared the changes in renal function and in plasma chemical measurements in response to oral fluid overload in 6 healthy control subjects under resting conditions and in 1 experimental subject who had developed severe symptomatic hyponatraemia during the 1992 90 km Comrades Marathon, the ultramarathon race where hyponatraemia of exercise was first recognised.<sup>14</sup>

## MATERIAL AND METHODS

The experiments on 6 healthy, athletic male controls with ages ranging from 28 to 44 years ( $34 \pm 2.6$  years, mean  $\pm$  standard error of the mean (SEM) with masses of 64.9 - 90.3 kg ( $78.8 \pm 7.7$  kg) and 1 male ultramarathon runner aged 32 years, with a body mass of 69.5 kg and a history of hyponatraemia during exercise, were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association and approved by the Research and Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. All subjects signed an informed consent before participating in the study and were free to withdraw at any time.

The 6 control subjects were studied while each drank 500 ml of fluid per hour. Fluid was ingested for 3 hours at a rate of 250 ml every 10 minutes in order to maximise the rate of gastric emptying.<sup>17</sup> Subjects then recovered for a further 24 hours. Subjects remained at rest during the study.

Body mass (Seca Balance, Germany) and urine volume were measured at regular 15-minute intervals during the trial. Blood samples were collected for subsequent determination of haemoglobin concentrations. After centrifugation for 10 minutes at 2 500 g the plasma was removed and stored frozen for subsequent analyses. Total plasma protein content was determined using the Biuret method. Plasma creatinine, sodium and potassium, and urinary creatinine, sodium and potassium concentrations were determined on a Beckman Astra Synchron AS8 multichannel analyser (Beckman Instruments, California). Plasma angiotensin II concentrations were determined by radio-immunoassay, as previously described.<sup>18,19</sup> Haemoglobin was determined by the standard spectrophotometric cyanomethaemoglobin technique. Changes in blood volume were calculated from the measured dilution of the haemoglobin concentration.

Plasma and urine osmolalities were measured in an Osmerte A Automatic osmometer (Precision Systems Inc., Newton, Mass., USA).

The experimental subject was studied because he had been admitted to hospital with severe symptomatic hyponatraemia following his participation in the 90 km Comrades Marathon footrace. He estimated that he had ingested approximately 1 500 ml/h during the 10 hours 28 minutes that he ran the race (average speed 8.6 km/h). Following the race, he became confused and was referred to hospital where, on admission, he

was found to be semi-comatose with a serum sodium concentration of 123 mmol/l, a haemoglobin concentration of 14 g/dl and a haematocrit of 42%. Plasma vasopressin concentration was 7.6 pg/ml (normal range 2 - 10 pg/ml), plasma renin activity was 9.8 ng/ml/h (normal range 1.0 - 2.4 ng/ml/h (erect), 0.5 - 2.6 ng/ml/h (supine)) and plasma aldosterone concentration 632 ng/100 ml (normal range 50 - 350 ng/100 ml). Urinary sodium concentration ranged from 10 to 21 mmol/l. He was treated with the diuretic, furosemide, and a slow intravenous infusion of normal saline (1 000 ml/12 h).

During the next 36 hours he passed 6.1 litres of urine, indicating a fluid excess on admission of greater than 3 litres. After 36 hours, serum sodium concentration stabilised at 141 mmol/l, haemoglobin concentration was 12.6 g/dl and haematocrit 37%, plasma vasopressin concentration was 9.4 pg/ml, plasma renin activity was 1.6 ng/ml/h and plasma aldosterone concentration was 169 ng/100 ml. Plasma volume increased 17% during recovery, as estimated from the equations of Dill and Costill.<sup>20</sup> Further recovery was uneventful. The athlete returned to running within a week of hospital discharge.

Five months after this episode of hyponatraemia, the subject consented to being studied in the laboratory in order that his response to high rates of fluid ingestion both at rest and during exercise might be compared with those measured in the control subjects.

In the first study, he ingested 900 ml/h (150 ml every 10 minutes) of tap water for 3 hours while resting in the supine position. This was followed by a 3-hour recovery period during which he did not ingest any additional fluid.

On the following day he ran on a treadmill for 4 hours at the average pace he had sustained during the Comrades Marathon (8.6 km/h). He began by ingesting tap water, as before, at a rate of 900 ml/h for the first 80 minutes of the trial. Thereafter the rate of fluid ingestion was doubled to 1 800 ml/h (300 ml every 10 minutes) while he continued to run for a further 160 minutes. He then recovered for a further 2 hours while lying supine on a bed. He did not drink any additional fluid during recovery.

Attempts to contact and study additional South African subjects who have developed hyponatraemia of exercise, have yet to be successful. However, a collaborative study of subjects who developed hyponatraemia during the Auckland Ironman Triathlon has been initiated (D Speedy *et al.* — completed manuscript in press).

## Calculations and statistical methods

Creatinine and free water clearance were calculated according to conventional equations.<sup>21,22</sup>

Extracellular fluid (ECF) volumes were calculated from





changes in blood volume (dBV) according to the following equation:

$$ECF_2 = ECF_1 + \frac{dBV\%}{100} \times ECF_1$$

Similarly, intracellular fluid (ICF) volumes were calculated from changes in plasma osmolality (dOSM) according to the following equation:

$$ICF = ICF_1 + \frac{dOSM\%}{100} \times ICF_1$$

The initial ECF volume (l) was calculated as  $0.375 (0.57 \times \text{body mass in kg})$  and the ICF volume (l) as  $1.66667 \times \text{ECF volume}$ .<sup>23</sup>

## Statistical methods

Results from the control group are the means ( $\pm$  SEMs) of 6 subjects. The statistical significances of changes over time were assessed with a one-way analysis of variance (ANOVA) for repeated measures and located using a Scheffé *post hoc* test. A value of  $P < 0.05$  was regarded as significant.

## RESULTS

Responses to high rates of fluid intake in the control subjects are shown in Fig. 1. Cumulative urine production was less than the rate of fluid ingestion, hence body mass rose progressively

with fluid ingestion; the peak increase was in excess of 2.5 kg after 3 hours of fluid ingestion. Body mass was still elevated by more than 1 kg at the end of the experiment, 2 hours after the cessation of fluid ingestion.

Plasma sodium concentrations and osmolality fell progressively for the first 2 hours of the experiment and were significantly below the starting value from 100 - 180 minutes. Plasma sodium concentrations then rose during the final 80 minutes of the experiment.

Blood volume rose progressively by up to  $7.1 (\pm 0.5)\%$  for the first 240 minutes of the experiment and was still elevated at 300 minutes. Neither plasma potassium nor angiotensin II concentrations changed during the water ingestion experiment, whereas plasma protein and creatinine concentrations fell, albeit insignificantly.

Measures of renal function in the control subjects are shown in Fig. 2. Urinary sodium, potassium and creatinine concentrations and urine osmolality fell steeply in the first 90 minutes of the experiment and remained low thereafter. Total urinary sodium and potassium losses during the first 3 hours of the study were  $120 \pm 24$  and  $26 \pm 8$  mmol respectively.

Creatinine clearance calculated from successive urine samples was in the normal range and did not change between 60 and 300 minutes. The unphysiologically high initial values

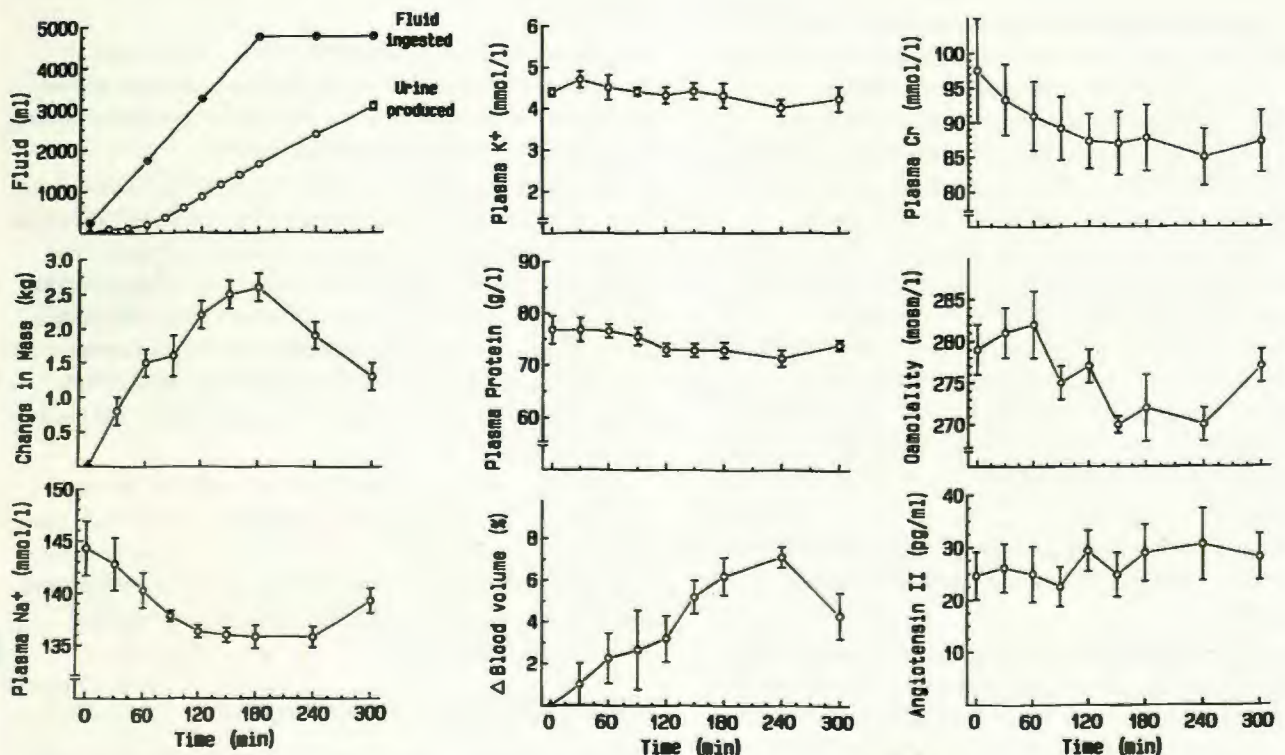


Fig. 1. Serial changes in cumulative fluid ingested and urine produced, mass, plasma sodium ( $\text{Na}^+$ ), potassium ( $\text{K}^+$ ) and protein concentrations, blood volume, plasma creatinine (Cr) concentrations, osmolality and angiotensin II concentrations in 6 control subjects studied at rest for 5 hours.



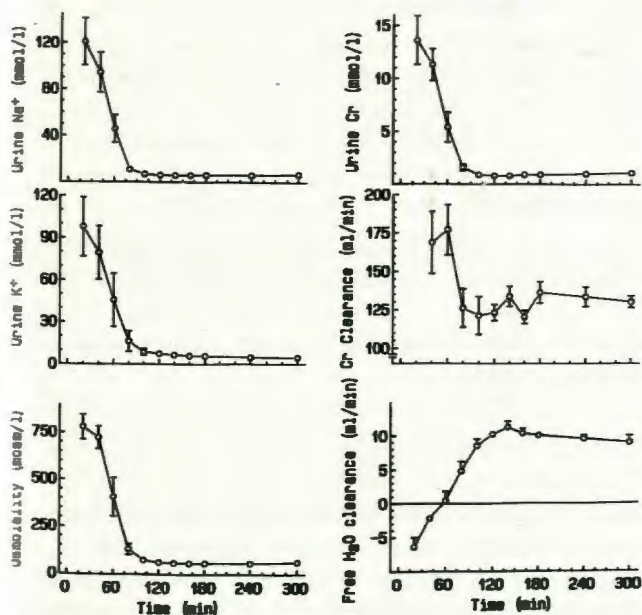


Fig. 2. Serial changes in urine sodium ( $\text{Na}^+$ ) and potassium ( $\text{K}^+$ ) concentrations, osmolality, urine creatinine ( $\text{Cr}$ ) concentrations, and free water ( $\text{H}_2\text{O}$ ) clearance in response to oral fluid overload in 6 control subjects studied at rest for 5 hours.

presumably result from the delay in the initial diuresis (Fig. 1) causing unrepresentative urinary samples.

Free water clearance increased for the first 150 minutes of the study, reaching a plateau thereafter. The peak rate of free water clearance was  $11.2 (\pm 0.9)$  ml/min.

Fig. 3 shows cumulative volumes of fluid ingested and urine produced, and the hourly changes in body mass, plasma sodium, protein and angiotensin II concentrations in the symptomatic subject at rest and during exercise.

Under both experimental conditions, rest and exercise body mass increased steadily while fluid was ingested. In both trials, the change in mass was similar and exceeded 2 kg at the end of

fluid ingestion. Plasma protein concentrations rose during exercise but fell progressively under resting conditions. Plasma sodium concentrations fell while fluid was ingested in both trials but began to rise when fluid ingestion ceased. The extent of the fall was similar in both trials. Plasma angiotensin II concentrations also fell progressively and equally in both trials. The rate of urine production lagged behind the rate of fluid ingestion but was similar in both trials. The greater evaporative sweat losses during exercise probably explains why the change in mass was the same in both trials even though considerably more fluid was ingested during the exercise trial.

During both trials, the symptomatic subject first passed urine at 3 hours by which time there was already a large fluid excess (Fig. 3). Palpation of the bladder confirmed that retention of urine in the bladder did not explain this failure of urine production. Rates of urine production continued to rise and were highest (660 ml/h) during the last hour of the experiment, that is 4 hours after the initiation of drinking and 1-2 hours after the cessation of drinking.

When compared with the control subjects, the extent of the fall in the plasma sodium concentration was similar in the symptomatic subject. Indeed, responses to oral fluid loading in the symptomatic subject and the controls were essentially the same except that the control subjects began to pass urine at higher maximum rates in excess of 799 ml/h within 120 minutes of initiation of fluid ingestion. In contrast the peak rate of urine production tended to be lower (660 ml/h) but not significantly so in the symptomatic subject and was reached only 4 hours after commencement of fluid ingestion.

In addition, the onset of urine production was significantly delayed in the symptomatic subject (180 v. 20 minutes). Plasma angiotensin II concentrations declined over time in the symptomatic subject during both exercise and control experiments but were maintained in the controls (compare Figs 3 and 1).

Fig. 4 shows cumulative changes in calculated intra- and extracellular fluid volumes and measured changes in urine

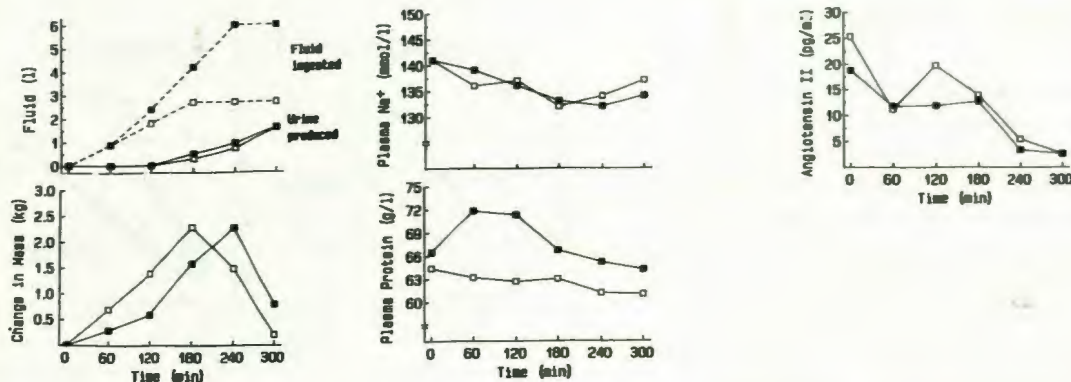


Fig. 3. Serial changes in cumulative fluid ingested and urine produced, mass, plasma sodium ( $\text{Na}^+$ ), protein and angiotensin II concentrations in the symptomatic subject studied at rest for 5 hours ( $\square$ ), and during 4 hours of low-intensity exercise followed by 1 hour of rest ( $\blacksquare$ ).



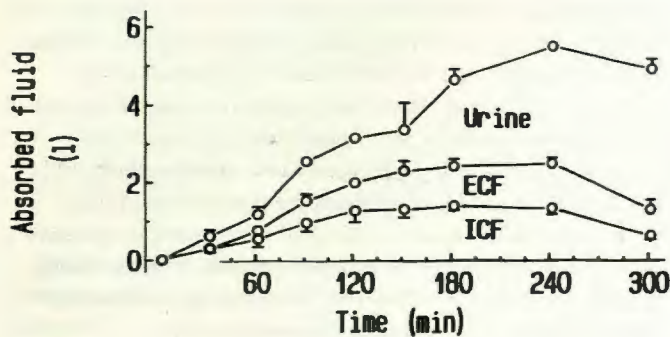


Fig. 4. Serial changes in absorbed fluid in 6 control subjects studied at rest for 5 hours. Cumulative urine production and fluid accumulation in the intracellular (ICF) and extracellular (ECF) spaces matched the rate of oral fluid ingestion suggesting that intestinal fluid absorption matched the rate of oral fluid ingestion.

production. Summing these volumes at each time point indicates that these changes account for the measured changes in body mass. Thus the calculated rate of intestinal fluid absorption matched the rate of fluid ingestion in these subjects.

## DISCUSSION

The most striking finding of this study was that none of the control subjects nor the ultramarathon runner with a history of symptomatic hyponatraemia was able to increase his rate of urine output to equal the high rates of fluid intake. As a result each subject gained weight during the trial. The maximum rates of urine production varied from 735 to 970 ml/h (Fig. 1) in the control subjects. In the symptomatic subject, the rate of urine production was somewhat lower (660 ml/h) and the onset of diuresis was delayed until 3 hours after the start of fluid ingestion (Fig. 3).

Coincident with the increase in body mass, plasma sodium concentrations declined progressively in all subjects, recovering only after fluid ingestion had terminated. The extent of the fall was similar in both the symptomatic subject who drank 900 ml/h at rest and in the control subjects who drank 1 500 ml/h at rest, despite large differences in ingested volumes (Figs 1 and 3).

There are two possible explanations for the lower rates of urine production than of fluid ingestion leading to fluid retention and the development of hyponatraemia in all these subjects. The first possibility is a limiting maximal rate of urine production of about 1 000 ml/h.<sup>24</sup> As a result subjects retained fluid and gained weight when they ingested fluid at faster rates. This hypothesis predicts that the maximum intestinal absorptive capacity exceeds the maximum capacity of the kidneys to excrete a fluid load, leading to fluid retention. This retained fluid would distribute to all body compartments leading to dilutional hyponatraemia. Figs 1 and 4 provide evidence to support this explanation in these subjects under

these experimental conditions.

Fig. 1 shows that the calculated blood volume rose progressively for the first 240 minutes of the experiment as plasma sodium concentrations fell significantly. The peak rise in the blood volume (7%) approximates the magnitude of the peak reduction in plasma sodium, protein and creatinine concentrations (Fig. 1).

Fig. 4 shows the calculated distribution of the ingested fluid at the different time points during the experiment. It shows that, at each time point, all the ingested fluid can be accounted for either as urine produced or as an increase in intra- or extracellular fluid volume.

Fig. 4 also shows that the time course of fluid distribution into the different compartments matched closely the rate at which the fluid was ingested. This suggests that the rate of intestinal fluid absorption closely matched the rate of fluid ingestion of 1.5 l/h. Hence this study suggests that the maximum rate of intestinal water absorption in these subjects exceeded 1.5 l/h, at least at rest. If this is correct, the corollary must be that the maximum rate of renal free water clearance is somewhat less than that value.

Other studies<sup>25,26</sup> have indeed calculated maximum rates of intestinal fluid absorption at rest and found rates of 0.82 and 1.7 l/h respectively. Intestinal function may indeed be designed to provide 'enough but not too much',<sup>27</sup> but the results of this study suggest that sufficient capacity for intestinal fluid absorption exists to exceed the maximum capacity of the kidneys to excrete the ingested fluid load.

Hence this study would seem to confirm the belief that the maximum rate of urine production is less than 1 000 ml/h.<sup>24</sup> Indeed, in keeping with the findings of Haldane and Priestley,<sup>28</sup> we found that the maximum rate of diuresis in the control subjects was around 900 ml/h (Fig. 1). Fig. 5, redrawn from the data of Haldane and Priestley,<sup>28</sup> shows the response of Priestley to high rates of fluid intake. The maximum rate of urine production was similar in both experiments despite different rates of fluid ingestion.

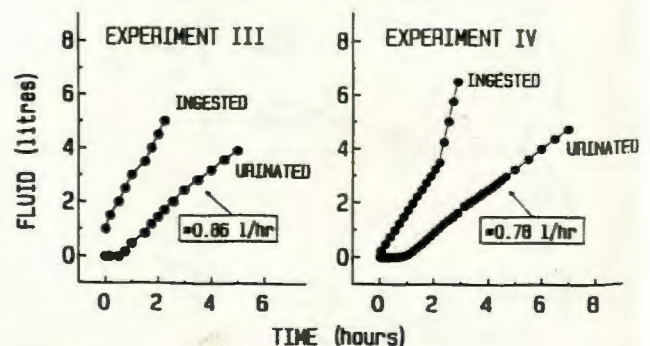


Fig. 5. Priestley's cumulative fluid intake and urine output during two separate experiments in which he ingested fluid orally at high rates. Redrawn from Haldane and Priestley.<sup>28</sup>





The contrasting explanation for the development of hyponatraemia in response to high rates of fluid ingestion, first suggested by Priestley<sup>13</sup> and Haldane and Priestley,<sup>20</sup> is that the low rates of urine production result from rates of intestinal water absorption that are lower than the rates of fluid ingestion, leading to fluid accumulation in the small bowel. Movement of sodium from the extracellular fluid space into the unabsorbed fluid, which has been demonstrated experimentally,<sup>14-16</sup> therefore provides a possible mechanism for hyponatraemia according to the original postulate of Priestley.<sup>13</sup>

For the reasons already described, this study finds no evidence in support of this theory. All the fluid ingested can be accounted for (Fig. 4), without postulation of delayed intestinal fluid absorption with reverse sodium movement from the extracellular fluid into the unabsorbed fluid in the small bowel.

In summary, this study shows that hyponatraemia can be induced in normal subjects at rest, simply by increasing the rates of fluid intake to greater than the maximum rates of urine production of about 900 ml/h in normal humans,<sup>24</sup> and sustaining these rates for some hours. At such high rates, the rate of intestinal water absorption matched the rate of fluid ingestion with distribution of the retained water into the extracellular and intracellular fluid volumes. Movements of fluid into the intracellular compartment occurred in proportion to changes in osmolality and acted to buffer larger changes in ECF osmolality. Hence the conclusion is that the human has a limited capacity to maintain fluid and electrolyte homeostasis when challenged by a sustained high rate of fluid intake in excess of 1 l/h.<sup>29-32</sup>

The practical significance of this study is to show that hyponatraemia can occur in healthy subjects with normal renal function when the rates of hypotonic fluid ingestion exceed their maximum rates of urine production of about 1 000 ml/h either at rest (this study) or during exercise.<sup>2,31</sup> Hence, at least at rest, persons should not ingest fluid at rates > 1 000 ml/h. During exercise, it would be possible to ingest fluid at higher rates as another source of fluid loss, sweating induced by exercise, would assist in preventing an abnormal expansion of the ECF volume, leading to hyponatraemia. However, if exercise reduces the rate of urine production, then hyponatraemia might still occur at these rates of oral fluid ingestion if sweat rates are relatively low, as seems likely in the typical athlete who develops hyponatraemia of exercise.<sup>3</sup>

Persons with a reduced capacity for diuresis, for whatever reason, would be at greatest risk for the development of hyponatraemia; hence rates of water ingestion should probably be less in those subjects. Both the symptomatic subject reported in this study and that of Armstrong *et al.*<sup>32</sup> had maximal rates of urine production somewhat lower than the maximal values measured in the healthy control subjects in this study (Fig. 1) or in Priestley (Fig. 5).

Finally, these findings may be relevant to other clinical conditions in which hyponatraemia develops in response to high rates of fluid provision either orally<sup>29-32</sup> or intravenously.<sup>33,34</sup>

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