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A STUDY OF DEHYDRATION BY MEANS OF BALANCE EXPERIMENTS

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A survey of the literature purporting to deal with the effects of water deprivation shows that most of it has really been concerned with the results of a deficiency of salt. In 1935, however, Kerpel-Fronius distinguished between the changes in the body due solely to a deficiency of salt, and those due simply to a shortage of water, but this important distinction has been little appreciated either in this country or in America, although Nadal, Pedersen & Maddock [1941] set out to contrast the features of these two syndromes in man. Unfortunately, in one of Nadal *et al.* two subjects the period of water deprivation followed directly upon one of salt deficiency, while in the other deprivation of water was accompanied by fasting. Hence, although results of great interest were obtained, the effects of water deprivation were complicated in one person by salt deficiency, and in the other by fasting. Admittedly, in clinical medicine, deprivation of water is usually accompanied by one or other of these complications, but warfare by sea or land may subject men with plenty of food to a shortage of water.

The present paper describes the results of metabolism studies on two subjects, who abstained from water for 3 and 4 days respectively, during which they took a 'dry' diet adequate in protein, salt and calories. Although a balance experiment on a human being cannot be carried to the point where the biochemical cause of death becomes clearly stigmatized, it is possible to distinguish physico-chemical happenings in the early days of water deprivation which would, if they went on long enough, provide a reasonable *modus moriendi*. It is this chain of events which it is now proposed to describe.

METHODS

A preliminary experiment was carried out on R. M. with the object of studying the general features and particularly the function of the kidney during dehydration. This made it clear that some people would certainly be able to maintain a normal calorie intake for the first few days of dehydration. D. B. and J. H., two normal men aged 28 and 33, and weighing 63 and 70 kg., were then studied in the following way. Each subject selected his own diet with a view to its palatability without water, and this diet was kept constant in weight and composition from day to day. D. B.'s diet comprised brown bread, butter and marmalade, cheese, dates, meat paste, shortbread, oatcakes and toffee. It contained 2·9 g. of K, 9·1 g. of NaCl, and 13·8 g. of N per day, 470 g. of carbohydrate, 80 g. of protein, 115 g. of fat, and its calorie value was 3164. J. H.'s diet consisted of biscuits of various types, butter and jam, cheese, bacon, potato crisps, chocolate and toffee. It yielded 1·8 g. of K, 9·6 g. of NaCl, and 10·4 g. of N per day, 286 g. of carbohydrate, 64 g. of protein, 161 g. of fat, and its calorie value was 2846. D. B.'s daily food contained 251 c.c. of water, and a further 439 c.c. of water would have been derived from its complete metabolism. For J. H. the corresponding figures were 115 and 359 c.c. For 4 days each person took his diet with as much water, tea or coffee as he felt inclined. All fluids were then withheld for 3 days from D. B., and for 4 days from J. H. A further period of 3 days with fluids concluded each experiment. Both men were weighed every day. Urine and faeces were collected for 2 days before fluids were withdrawn and thereafter to the end of the experiment. Urine was collected under toluol in 24 hr. periods; faeces were collected as described by McCance & Widdowson [1942]. Blood was always withdrawn at the same time of day. Chlorides in the plasma were determined by Sendroy's [1937] method, and, apart from this, urea and the mineral elements by the methods given by McCance [1937] and McCance & Widdowson [1937].

Results

General changes

In addition to the subjects described in this paper there have been opportunities for observing the general effects of experimental dehydration in eight men and two women. The experience of voluntary dehydration is inseparable from some degree of 'self consciousness'. Even allowing for this, the subjects exhibited a change in behaviour which could be interpreted as an exaggeration of their temperamental type. Serious people became positively sombre; while others, normally cheerful, exhibited a somewhat hollow vivacity. The subjects were intellectually capable of performing estimations and calculations, but their concentration was impaired. They found that the days of dehydration were not actually uncomfortable but they seemed very long. The experimenters were never unbearably thirsty, but by the third day their mouths and throats had become dry, their voices husky, and they had begun to find it difficult to swallow. By the third or fourth day their facies had become somewhat pinched and pale and there was a suggestion of cyanosis about their lips which was rather characteristic. This general appearance of ill-being vanished within a few hours of the restoration of fluid, and the symptoms of dehydration passed off long before physiological rehydration was complete. Many of the subjects lost all their desire to drink as soon as the first pint of fluid had been taken. Both D. B. and J. H. were rehydrated slowly [McCance & Young, 1944], and this should be borne in mind when considering the metabolic changes of the first day of rehydration. The subjects lost weight at rather different rates. D. B., for example, lost 3·8 kg. in 3 days, and J. H. 3·8 kg. in 4 days.

Changes in the circulating fluids

The haemoglobin and haematocrit values changed very little, and there was no evidence that either of them rose during the periods of dehydration. D. B.'s plasma proteins increased from 7·2 to 7·4 % and J. H.'s from 7·3 to 7·6 %, and, although they fell again during the after periods, it is doubtful if these changes have much significance. It may be inferred that under the conditions of these experiments there was little if any reduction in the blood volume. These findings are in accordance with those of Nadal *et al.* [1941], and demonstrate that some highly efficient mechanism must have been at work to prevent such a reduction taking place, for, at the same time, the volume of other fluid compartments of the body measurably declined.

TABLE 1. Changes in the serum induced by dehydration

Subject	Last day of	Plasma Na mg. per 100 c.c.	Serum K mg. per 100 c.c.	Plasma Cl mg. per 100 c.c.	Plasma urea mg. per 100 c.c.
D. B.	Fore period	340	19·3	377	38
	Dehydration period	369	15·1	406	57
	Rehydration period	340	16·6	374	29
J. H.	Fore period	327	15·6	364	20
	Dehydration period	356	13·2	384	47
	Rehydration period	334	13·5	361	27

The changes in the serum chemistry are given in Table 1. The blood urea always underwent a moderate increase during the dehydration period. The figures in Table 1 may be regarded as fairly typical, although greater increments have been recorded in other subjects. The plasma Na rose steadily in the dehydration period to a value about 10 % in excess of its initial one, and fell to its original level after rehydration. There were similar changes in the plasma Cl. There was a fall in the serum K of both men during the dehydration period. This is particularly noteworthy when it is recalled that there was an increased excretion of K in the urine at this time [McCance & Young, 1944].

Nitrogen metabolism

The N balances of both men are given in Table 2. Since D. B. was in positive and J. H. in negative balance during the two preliminary days, it is difficult in some ways to compare the two experiments. Both subjects, however,

TABLE 2. Nitrogen balances before, during and after dehydration

	D. B.			J. H.		
Day	Intake g. per day	Total output g. per day	Balance g. per day	Intake g. per day	Total output g. per day	Balance g. per day
Preliminary (average)	13·5	12·3	+1·2	10·4	11·3	−0·9
Dehydration 1	14·0	10·0	+4·0	10·4	10·3	+0·1
2	14·0	12·6	+1·4	10·4	14·3	−3·9
3	14·0	14·4	−0·4	10·4	15·3	−4·9
4	—	—	—	10·4	16·1	−5·7
Rehydration 1	13·9	17·0	−3·1	10·4	15·1	−4·7
2	13·9	17·5	−3·6	10·4	17·6	−7·2
3	13·9	13·4	+0·5	10·4	14·4	−4·0

showed a fall in the excretion of N on the first day of dehydration, during which most of the rise in the blood urea took place, and an increased elimination of N during those parts of the after period when the blood urea was regaining its original level. In order to assess the daily formation of urea, these changes in the levels of urea in the body fluids had to be taken into account, as well as the urinary excretion, and when this was done the figures shown in Table 3 were obtained. It will be seen that the urea production

TABLE 3. The effect of dehydration on the production of urea

	D. B.	J. H.
Average preliminary period g. per day	19·5	14·9
Average dehydration period g. per day	22·8	20·6
Average rehydration period g. per day	21·8	18·0

increased during the dehydration period and remained somewhat high into the after periods. This increase was greater in J. H. than in D. B., but in both it was greater than could be accounted for by dietary variation or experimental inaccuracy. It may be attributed to a breakdown of tissue protein. In one sense the quantities involved were small, for they amounted, even in the case of J. H., to less than 20 g. of body protein per day. Had the dehydration been prolonged, however, and the losses continued, they might later have become a serious matter.

The water balance

When Newburgh & Johnston's [1942] method of calculating changes in the body water was applied, the figures given in Table 4 were obtained. These findings agree quite well with those of Coller & Maddock [1935], whose two subjects, studied under similar conditions, also lost about 3 kg. of water in 3 days. The loss of water by the skin and lungs tended to decrease during the dehydration period. This may have been due to diminishing activity, for Newburgh & Johnston [1942] have shown that when they controlled the activity of a subject his insensible water loss did not diminish during dehydration of a similar degree. Neither subject can have been losing much water or

TABLE 4. The water balances during the periods of dehydration

Subject and duration of dehydration	Intake c.c.			Output c.c.			Balance c.c.
	In food	By metabolism	Total	Urine	Lungs and skin	Total	
D. B. (3 days)	753	1287	2040	1933	3637	5570	-3530
J. H. (4 days)	460	1436	1896	2360	3066	5426	-3530

NaCl by the active production of sweat for it is accepted that the water lost by the insensible perspiration of the skin and by the lungs is usually of the order of 1000 c.c. per day. This conclusion is important in connexion with the mineral balances now to be considered.

Mineral balances

The figures obtained from D. B. were more satisfactory than those from J. H. for D. B. was in mineral balance during the preliminary period, while J. H. was gaining slightly in weight and was in slightly positive Na and Cl and in negative K balance. Nevertheless, the subjects agreed in showing a small retention of Na and Cl during and after dehydration and a negative K balance during dehydration. Similar results were obtained by Wiley & Wiley [1933], who studied the mineral balances of a man whose water intake was restricted to 1185 g. per day for a period of 6 days. The present results are summarized in Table 5. The output by the faeces was measured and taken into account,

TABLE 5. The mineral balances

Average for:	D. B. (3 days dehydration)			J. H. (4 days dehydration)		
	Na g. per day	Cl g. per day	K g. per day	Na g. per day	Cl g. per day	K g. per day
Preliminary period	±0·0	±0·0	±0·0	+0·7	+1·3	-0·7
Dehydration period	+0·5	+0·7	-1·1	+0·6	+2·4	-1·0
Rehydration period	+1·1	+2·0	+0·5	+1·2	+0·7	+0·1

but not the losses on the surface of the body. The figures indicate that these men did not excrete quite all the salt in their diets while they were being dehydrated and none of the salt from their extracellular fluids. Since these fluids underwent a considerable shrinkage in volume before the dehydration was relieved, it is easy to understand why the serum Na was observed to rise (Table 1). In the experiment of Nadal *et al.* [1941] the diet was salt free and the Na and Cl balances were, therefore, negative. In 3 days of dehydration, however, their subject lost less than 1 g. of Na, which would correspond roughly to 300 c.c. of extracellular fluid. He must have lost much more of his extracellular fluids than this—perhaps in all as much as 1000 c.c.—and retained the equivalent amount, about 2 g., of Na. Similar happenings were observed when dogs were deprived of water [Elkington & Taffel, 1942] and are likely to be found in all mammals. The retention of Na and Cl in the after period was part of the reaction of the body to rehydration. During this time drinking water was diluting the body fluids and (for some reason) Na and Cl were retained concurrently.

As already mentioned, both men had a negative K balance while they were being dehydrated. D. B. excreted 3·28 g. of K over and above the amount in his food. This corresponds to about 600 c.c. of cell fluid, and J. H. excreted in the same way K corresponding to about 740 c.c. of cell fluid. It is interesting to compare these volumes with those corresponding to the amounts of tissue being broken down, as estimated from the increased urea production during the dehydration periods. In D. B. 10 g. of 'extra' urea were formed during dehydration (Table 3) and this is equivalent to 30 g. of protein. Protein is associated with three to five times its own weight of water in the tissues [Best & Taylor, 1939] so that only about 125 c.c. of intracellular water were set free by the destruction of protein. Similarly in J. H. the 'extra' urea formed during dehydration had a protein equivalent of 70 g. corresponding to about 300 c.c. of cell water. In passing it is to be noted that Kerpel-Fronius [1935] found that when fasting rabbits were deprived of water they too excreted a higher K/N ratio than is present in cell fluid. D. B. and J. H. both lost over 3000 c.c. of body fluids during dehydration and of these at least 2000 c.c. probably came from the cells. Hence during dehydration the happenings in the cells may be summarized as follows: (*a*) There was a considerable loss of fluid. (*b*) There was a loss—by excretion—of *some* of the K corresponding to this fluid but nevertheless a rise of osmotic pressure within the cells. (*c*) There was a loss—by destruction—of *some* of the cell protein, but not enough to correspond to the loss of K. Hence during dehydration the cells become smaller, more concentrated with respect to K ions and still more concentrated with respect to protein.

The positive Na and negative K balances during the dehydration periods show that K from the cellular fluids had priority in excretion over Na from the extracellular fluids, and this in spite of the fact that the K in the plasma fell during dehydration while the Na in the plasma rose. This preferential excretion of K was noted and discussed by Elkington & Taffel [1942]. These authors pointed out that by this means more water was withdrawn from the intracellular compartments of the body than would otherwise have been the case, and hence that the volume of the extracellular fluids was to the same extent preserved. This may help to explain the maintenance of the blood volume, previously described, and commented upon also by Nadal *et al.* [1941].

It is instructive in summary to contrast the course of events in dehydration and in salt deficiency. In the former the excretion of minerals did not keep pace with that of water, the osmotic pressure of the plasma and of the whole body rose, some K passed out of the cells, and this helped to preserve the volume of the extracellular fluids. The plasma volume did not fall. In salt deficiency [McCance, 1936; McCance & Widdowson, 1938] the excretion of water did not keep up with the loss of salt and consequently the osmotic pressure of the plasma fell. Water passed into the cells and there was a great fall in the volume of the extracellular fluids. The volume of the plasma and of the circulating blood fell also, and this was probably the cause of much of the subjects' embarrassment and discomfort.

The osmotic balances

D. B.'s diet contained 155 m.eq. of Na, 155 m.eq. of Cl, 74 m.eq. of K and enough protein to produce 325 mM. of urea, giving a total of 709 mM. of osmotically active material per day. J. H.'s diet contained 631 mM. of these four substances per day. Table 6 shows the amounts of osmotically active material

TABLE 6. The osmotic balances

	Subject D. B.		Subject J. H.	
Period and day of period	Diet mM. per day	Urine mM. per day	Diet mM. per day	Urine mM. per day
Preliminary (average)	710	702	631	614
Dehydration 1	710	577	631	528
2	710	702	631	666
3	710	754	631	676
4	—	—	631	722
Rehydration 1	710	669	631	528
2	710	628	631	588
3	710	697	631	626

(as represented by the Na, K, Cl and urea) excreted by both men. It will be seen that the osmotic excretion in the urine was low on the first day of dehydration, and later rose, so that by the last day the kidneys were excreting more mM. of the four substances together than the diet provided, in spite of the small volume of water available to them [McCance & Young, 1944]. These daily fluctuations in osmotic output were due to urea (see Table 2) and not to the minerals. Over the whole dehydration periods the kidneys may be said to have excreted the osmotically active material in the diet, and, but for the changes in body water, the men would have been in osmotic equilibrium. In the same period, however, 3·5 l. of body fluids were lost, and each of these would have contained about 320 mM. of osmotically active material, making a total of about 1100 mM., which were either retained or, more probably, partly excreted with the retention of an equivalent amount of osmotically active material from the food. This retention corresponds to an increase of about 28 m.osmol./l. in the 40 l. (approx.) of body fluids. The percentage of Na in the plasma increased by about 30 mg./100 c.c., or about 13 m.eq./l. There must have been an equivalent increase in acid radicles and a small change due to urea—say 30 m.osmol. in all. There is thus good agreement between two very different methods of estimating the increase in the osmotic pressure of the body.

It might quite reasonably be supposed that if the kidneys were able to excrete 600 to 700 mM. of osmotically active material per day on a diet containing just that amount, they might do so on a diet poorer in salt and protein so that on such a diet the loss of body fluid by dehydration might not involve any increase in the osmotic pressure of the body. The results of Nadal *et al.* [1941] show, however, that even with a fasting subject the excretion of minerals derived from the mobilization of body water is not complete. In their experiment IIB, the losses of minerals and urea in the urine during a 3-day period of dehydration were: Na, 41 m.eq., Cl, 59 m.eq., K, 150 m.eq. and urea 93 mM.—a total of 343 m.osmol. Since no food was taken, all this was derived from the body fluids, but in the same period there was a loss of 3264 c.c., which would have contained 1045 m.osmol. Even in complete fasting, therefore, there was a retention of 702 m.osmol. in 3 days. Other aspects of this phenomenon are discussed by McCance & Young [1944].

This osmotic retention, which appears to be somewhat greater on a full diet than in fasting, must be seriously considered as the cause of death in dehydration. Kerpel-Fronius & Leövey [1929] found that after ligating the ureters the osmotic pressure of both the blood and the tissues tended to rise, and that death could be hastened by giving either salt or urea. They concluded that the rise in the total osmotic pressure of the body and not the accumulation of any specific substance was the cause of death. Kerpel-Fronius & Leövey [1931] later found a similar increase in the osmotic pressure of the blood and tissues in experimental dehydration in puppies, and suggested that here too death might be due to the same disturbance in the osmotic pressure of the tissues. Elkington & Taffel's [1942] observations on dehydrated dogs lend some support to this suggestion, for the increase in the total ionic concentration of the body fluids was greatest in the animals which died or became moribund. It would be unreasonable to expect absolutely definite indications of the cause of death in dehydration from experiments such as these lasting but 3 or 4 days, since it is known that men may survive on very small amounts of water for several weeks. Within the limits imposed by human experiments, however, the present findings support the conclusions of Kerpel-Fronius that death from gradual dehydration may be due to the increased osmotic pressure of the body.

Summary

1. Balance experiments have been carried out on two men before, during and after a period of experimental dehydration.

2. During dehydration there was no reduction in the plasma volume. The serum Na rose and the serum K fell.

3. Dehydration increased the amount of urea produced by the body.

4. The men lost over 3500 c.c. of their body water, but none of the Na from

their extracellular fluids and only a little of the K from their cellular fluids.

5. The osmotic pressure of the body rose, and it is considered that this may be the cause of death in dehydration.

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