Exercise associated hyponatraemia

Case proven: exercise associated hyponatraemia is due to overdrinking. So why did it take 20 years before the original evidence was accepted?

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The reluctance to accept the evidence may be because it conflicted with the prevalent message of the sports drink industry

Late on the afternoon of 1 June 1981, a 46 year old lady of 49 kg was admitted in a coma to a hospital in Durban, South Africa. Before dawn that day, she had begun the 90 km Comrades marathon foot race in the same city. But 20 km from the finish in Pietermaritzburg, she failed to recognise her husband who had come to assist her. He convinced her to stop running and drove her to the medical facility at the race finish. There she received 2 litres of fluid administered intravenously. This is the logical treatment for the ''dehydration'' that was then, and continues to be, the expected cause of all complications that occur during prolonged exercise.[1] But the treatment did not help.[2]

Instead, in the car travelling back to Durban, she suffered a grand mal epileptic seizure and lapsed into coma. She was admitted to hospital where blood testing found her serum sodium concentration to be reduced to 115 mmol/l; a chest radiograph indicated the presence of pulmonary oedema, but there was no evidence of cardiac failure. Thus the diagnosis was exercise associated hyponatraemic encephalopathy (EAHE) with neurogenic (non-cardiac) pulmonary oedema, the first such known case. Treated intravenously with 0.9% (normal) saline, her condition improved only very gradually. Her serum sodium returned to the normal range on the fourth day in hospital, and she was discharged from hospital, fully recovered, two days later.

In 1985 her story and another three similar cases were reported in a paper entitled ''Water intoxication: a possible complication of endurance exercise''.[3] On the basis of the history, the clinical findings, and the estimated sodium and water balance during exercise in these athletes, it was proposed that ''…the etiology of the hyponatremia in these runners was due to overhydration…''. The article concluded with the admonition that ''…the intake of hypotonic fluids in excess of that required to balance sweat and urine losses may be hazardous in some individuals''[3] (p 374).

The following year the *Journal of the American Medical Association* carried personal reports written by two doctors who had developed EAHE during an 80/100 km ultramarathon foot race in Chicago, USA.[4] Notably, these doctors had been advised to drink 300–360 ml at each aid station placed 1.6 km apart on the 10 km lap course on which that race was held. The authors also noted ''In addition, athletes are instructed to drink more than their thirst dictates, since thirst may be an unreliable index of fluid needs during exercise. Runners, as a group, are taught to 'push fluids''' (p 774). As a result, each drank in excess of 20 litres of fluid during the 8–10 hours that each required to finish the race. The authors became aware of our earlier study only after their original manuscript had been accepted for publication. Thus their identical conclusions were derived independently of our own: ''The two runners consumed such large quantities of free water during the race that apparent water intoxication developed'' (p 772) so that ''It seems likely that the hyponatremia was caused primarily by increased intake and retention of water and contributed to the sodium loss'' (p 773). They also noted that ''While this practice (of drinking in excess of thirst) may deter the occurrence of dehydration, large intakes of hypotonic fluids, associated with substantial sodium losses, can lead to hyponatremia as it did in the case of (these) runners …'' (p 774).

In an historic coincidence, the senior doctor in that report received intravenous hypertonic (3%) saline intravenously for the treatment of his EAHE. His serum sodium concentration increased from 118 mmol/l to the normal range (>135 mmol/l) within eight hours of hospital admission. With that treatment, he was able to return to his home in Atlanta the following morning, resuming his medical practice that same afternoon. But his junior colleague was less fortunate. Treated with normal (0.9%) saline intravenously, he remained semi-comatose for 36 hours while his serum sodium concentration remained low. He was discharged from hospital only on the 5th hospital day, four days later than his senior colleague.

Hence the first ''controlled'' clinical trial comparing the effects of isotonic and hypertonic saline in the management of EAHE was completed, by chance, already in 1983 and reported in 1986, antedating by 22 years the conclusion that hypertonic saline is the appropriate therapy for this condition[5] and that the use of isotonic or hypotonic solutions is absolutely contraindicated.[6]

> ''It would take almost another 20 years before this wisdom would be universally applied''

Thus by 1986 a body of evidence showed that: (*a*) EAHE is caused by excessive fluid consumption during exercise; (*b*) athletes who drink to excess during exercise usually do so on the well meaning advice of others, including race organisers; (*c*) the condition responds hardly at all to treatment with 0.9% normal saline,[3 4] whereas recovery is rapid[4] when hypertonic (3–5%) saline solutions are used. It would take almost another 20 years before this wisdom would be universally applied.[6]

After 1985, it became apparent that EAHE was becoming increasingly common in the 90 km Comrades marathon. Indeed 16 athletes were admitted to hospital for the treatment of this condition after the 1987 race. Accordingly it was decided to follow the fluid and sodium balance during recovery of all runners admitted to hospital for the treatment of this condition after the 1988 Comrades marathon.[7] Specifically we wished to determine whether the initial conclusions from the first case reports were correct.

The report of that study, published in 1991, came to the following unambiguous conclusion: ''This study conclusively resolves this issue (of what causes EAHE). It shows that each of eight athletes who collapsed with hyponatremia of exercise (mean plasma sodium concentration of 122.4 ± 2.2 mM) was fluid overloaded by an amount ranging from 1.22 to 5.92 liters. These fluid volumes are conservative because no allowance was made for insensible water losses during recovery. The subjects conservatively estimated that their fluid intakes during exercise ranged

from 0.8 to 1.3 L/h, compared with maximum values of 0.6 L/h in normonatremic runners. We also found that the subjects' sodium losses (153±35 mmol) were not larger than those of runners who maintained normonatremia during exercise'' (pp 344–345). Thus it was concluded that ''…the hyponatremia of exercise results from fluid retention in subjects who ingest abnormally large fluid volumes during prolonged exercise'' (p 342). It was also noted, as had Frizzell *et al*,[4] that ''the potential dangers of severe dehydration and the need to drink adequately during prolonged exercise have been so well publicized[8] that, as a result, some individuals may choose to ingest dangerously large volumes during prolonged exercise'' (p 347).

In our youthful naivety, the Cape Town group assumed that this would be the end of the matter, that these definitive findings would be universally embraced, and that preventive actions based on our conclusions would be enacted immediately around the world with the result that EAHE would disappear as quickly as it had emerged. An initial study to evaluate the potential effects of dehydration on the body temperature during exercise was completed,[8] and a final review article[9] and commentary[10] were written before the Cape Town group turned its focus elsewhere. The research baton would be grasped by a research team in Auckland, New Zealand led by DS.

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With a minimum of resources and little direct funding, including none from the sports drink industry, the New Zealand team harnessed the two ingredients beyond price—enthusiasm and hard labour—to their scientific quest. Whereas others had been prepared to study tens of athletes in competition, this team chose to study many hundreds. By applying simple but relevant measurements to large numbers of subjects, they showed that the post-race serum sodium concentrations of athletes completing the New Zealand 224 km Ironman triathlon were an inverse function with a negative slope of their weight changes during exercise.[11] The authors concluded that ''Hyponatremia is a common (18% of race finishers) and potentially serious medical complication of an ultradistance triathlon … Females are at significantly increased risk … Fluid overload is the likely etiology of severe hyponatremia and the hyponatremia appears to be dilutional'' (p 814).

Thus, as predicted from the two original studies,[3 4] those athletes who gained the most weight during exercise were likely to have the lowest post-race serum sodium concentrations. They also confirmed the finding of Irving *et al*[7] that a large external sodium loss caused by sweating is not a major contributor to EAHE.[12 13]

Sufficiently convinced by then that overdrinking alone causes EAHE, the New Zealand team performed the first controlled clinical trial to determine the effects of fluid restriction on the incidence of this condition.[14] They were able to show that simply by (*a*) advising the athletes not to overdrink during competition and (*b*) restricting fluid availability during the cycling and running legs of the race, the number of cases of EAHE requiring hospital admission was reduced from 14 in the 1997 New Zealand Ironman to three the following year. There was also no evidence that this advice increased the number of athletes requiring medical care because they drank too little during exercise.

The team next showed that acute oral fluid overload caused hyponatraemia to develop to the same extent in separate groups of athletes selected for a laboratory study because they either had, or had not, developed exercise associated hyponatraemia (EAH) in a previous New Zealand Ironman triathlon.[15] Thus, at least when studied at rest, there did not appear to be any specific biological defect that would predispose only some to the development of EAH or EAHE in response to overdrinking. This did not exclude the possibility that the physiological changes induced by exercise would expose a biological difference, not apparent at rest, that made only some susceptible to EAH when they overdrank during exercise.

Two crucial events occurred around the time that the 1988 Comrades marathon study, published in 1991, had unequivocally proven the dangers of overdrinking during exercise. Firstly, sometime around 1990, the US military adopted new drinking guidelines, aimed at reducing the risk of ''heat illness'' in military personnel.[16] These new guidelines required that US army personnel were henceforth mandated to ingest 1.8 litres of fluid every hour that they were exposed to temperatures in excess of 30℃.[17] Such high rates were required even though conscripts were allowed to exercise for only 20 minutes in every hour that they were exposed to these high temperatures.

The immediate result of these new guidelines was that the incidence of EAH increased dramatically in the US military with 125 cases of EAHE requiring hospital admission between 1989 and 1996.[18] In addition, there were at least six recorded deaths.[18–20]

Of these 125 cases, 40 occurred at a single training facility, Fort Benning in Georgia. Evaluation of these 40 cases showed that ''(1) all were associated with excessive water intake; (2) the training cadre often mistook hyponatremia for dehydration, and; (3) afflicted trainees were not given (appropriate) medical care in a timely manner''[18] (p 432).

Suitably alarmed, the US military correctly concluded that their novel guidelines were at fault. As a result, revised guidelines were introduced in April 1998. These new guidelines set upper limits of fluid consumption at 1–1.5 quarts per hour (909–1364 ml/h) and 12 quarts (10.9 litres) per day. As a result, the incidence of hyponatraemia in the US Army fell in 1998 and 1999, with most of the fall occurring as a result of the immediate adoption of these new guidelines at Fort Benning.

> ''the American College of Sports Medicine …produced its modified guidelines, which promoted the concept that subjects should drink 'as much as tolerable' during exercise

In contrast, in 1996 the American College of Sports Medicine (ACSM), an organisation whose only two ''platinum'' sponsors are Gatorade and the Gatorade Sports Science Institute (GSSI), produced its modified guidelines, which promoted the concept that subjects should drink ''as much as tolerable'' during exercise.[21 22] This was linked to an extensive marketing campaign, directed by the sports drink industry through the GSSI,[23] to promote this novel dogma.

Perhaps the most insidious effect of this commercial influence on sports research over the past decade has been the promotion of a novel model of how body temperature is regulated during exercise, as well as a new paradigm of the variables that are homoeostatically regulated during exercise.[24–29]

Thus the original concept developed by Nielsen[30] in 1938 was that the temperature during exercise is homoeostatically regulated in proportion to the metabolic rate. Subsequently it was found that fluid ingestion lowers the rectal temperature during exercise. However, even in those who did not drink during exercise, the rectal temperature remained well below values measured in patients with heatstroke.[31–34]

The concept that fluid ingestion during exercise is essential, specifically to prevent heatstroke, begins to appear in

the writings, first of Wyndham and Strydom[34] in 1969 and later in those of Dr Robert Cade, the inventor of Gatorade. The reasons why the conclusions of Wyndham and Strydom were not evidence based have been described previously[1 8 24]; here it is necessary to review Cade's influence.

Thus in a study of athletes completing a 7 mile (11 km) run, Cade *et al*[35] found that fluid ingestion reduced the ~2℃ rise in rectal temperature by 0.2–0.5℃. Thus the authors concluded that ''The amelioration of temperature rise by ingestion of a hypotonic saline solution or even more strikingly by the saline-glucose solution surely recommends the use of such solutions to decrease the likelihood (sic) of heatstroke when exercise must be performed in a hot clime'' (p 155). In an earlier study, Cade *et al*[36] proposed that the fluid loss from sweating during exercise causes a loss of circulating blood volume which ''adversely affects the ability of the body to dissipate heat … and may, indeed, be of major importance in the genesis of heatstroke'' (p 176). This then led to his ''hyperthermia/volume-reduction hypothesis'' for the development of heatstroke[36 37] which has since be renamed the cardiovascular model of thermoregulation during exercise and which is a predictable extension of the cardiovascular/anaerobic/catastrophic model of exercise physiology[38] that currently dominates teaching in our discipline.

Other support for this paradigm shift came from the proposal of Buskirk *et al*[39] that ''Acute dehydration apparently limits man's ability to work, largely through impaired cardiovascular function[40]'' (p 189) and that ''the excessive hyperthermia that occurs in hypohydrated individuals during exercise in the heat is due to modifications in the control of skin blood flow … A reduction in maximal attainable skin blood flow limits heat transfer during prolonged exercise''[41] (p 720).

More recently Cheuvront *et al*[42] have refined this model: ''Body water deficits will increase cardiovascular strain as indicated by increased heart rate and decreased stroke volume during exercise in temperate or hot environments. If heat strain is present during exercise, the athlete may be unable to sustain cardiac output.[43] Body water deficits reduce cardiac filling because of the reduced blood volume often accompanied by increased skin blood flow and compliance (from increased heat strain) … Dehydration mediated core temperature elevations reduce exercise performance by augmenting cardiovascular strain …'' (p 203). Yet the authors conclude that: ''The exact mechanisms by which the cardiovascular strain translates into reduced performance are unclear'' (pp 202–203).

Thus this novel cardiovascular model of temperature regulation during exercise which became increasingly entrenched after 1969, predicts that cardiovascular function, in particular the cardiac output, is the principal determinant of the body's ability to thermoregulate during exercise as it determines the adequacy of the skin blood flow. Any factor that impairs cardiovascular function must therefore reduce the skin blood flow and the sweat rate, leading to heat retention and ultimately heat stroke. As, according to this model, sweating reduces the total body water and the circulating blood volume, sweating, rather than preventing heatstroke, must ultimately cause it by reducing the filling pressure of the heart, and hence the stroke volume and cardiac output. According to this model, any sweating that is uncorrected by fluid ingestion must inevitably induce a vicious cycle of increasing heat gain terminating ultimately in heatstroke. Therefore the central prediction of this novel cardiovascular model of thermoregulation is that, by impairing cardiovascular function, dehydration becomes the most important determinant of the body temperature during exercise. Indeed this is the interpretation that has been applied universally[1] to the findings of Wyndham and Strydom.[34]

Of course an alternative explanation is that humans developed the capacity to sweat specifically to protect themselves from developing heatstroke during exercise in the heat. In the words of Heinrich[44] ''The fact that we, as savanna-adapted, animals have such hypertrophied sweating responses implies that, if we are naturally so profligate with water, it can only be because of some very big advantage. The most likely advantage was that it permitted us to perform prolonged exercise in the heat. We do not need a sweating response to outrun predators, because that requires relatively short, fast sprinting, where accumulating a heat load is, like a lactic acid load, acceptable. What we do need sweating for is to sustain running in the heat of the day – the time when most predators retire into the shade'' (p 174). Heinrich also notes that modern hunter-gatherers, like the !Kung Bushmen of Southern Africa ''carry no food or water with them (on 30 km hunts in the heat) because that hinders their ability to travel'' (p 180). Indeed it is their inability to sweat that places those with the congenital absence of sweat glands at increased risk of developing heatstroke.[45]

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The outstanding problems of this cardiovascular model of thermoregulation are that it has no logical physiological basis and that it fails to explain what actually happens. In the first place, sweating is regulated independently of skin blood flow[46] so that the capacity to lose heat by sweating is independent of the cardiovascular response to exercise, but requires an intact neural supply to the sweat glands.[45] Secondly, although fluid loss during exercise does cause the body temperature to be regulated at a slightly higher body temperature—about 0.2℃ for each 1% body weight loss—there is no evidence that this is caused by a reduced sweat rate. Thus all the classic studies show that sweat rates are maintained in dehydration.[32 46–49] Indeed Ladell[33] wrote as early as 1955 that ''Abstention from water had no effect on the sweat rate, until water deficits of more than 2.5 L had been incurred'' (p 43). In the original classic industry funded study, Costill *et al*[47] also wrote that, even when they did not drink during two hours of exercise in the heat, ''the runners' skin was sufficiently wetted by sweat to permit maximal evaporation''.

The conclusion must be that the elevated temperature in those who do not drink during exercise is not caused by a dehydration induced failure of sweating as predicted by the cardiovascular model, but must be due to some other effect.

Thirdly, there is no evidence for loss of thermal homoeostasis in those who do not drink during exercise; thermal homoeostasis simply occurs at a higher absolute temperature. This is most clearly shown in the industry funded study of Montain and Coyle,[50] the very study on which the ACSM guidelines to drink either 1.2 litres/h or ''as much as tolerable'' are based. For despite an absence of adequate convective cooling[29] and even though they did not drink, subjects were able to exercise in hot conditions (32℃; relative humidity 50%) for two hours at 62% of their maximum oxygen consumption without developing any evidence of heat illness or achieving rectal temperatures that were elevated anywhere near the heatstroke range. Thus the final (two hour) rectal temperatures of subjects who did not drink at all was 39.2 (0.2)℃ compared with 38.3 (0.1)℃ when they drank ''to replace all their sweat losses during exercise''.

Paradoxically the absence of serious consequences in athletes who did not drink at all during two hours of vigorous exercise in moderately severe heat was used by the ACSM as evidence for the need to drink ''as much as tolerable'' during exercise. This logic appears perverse.

Thus, as a consequence of the adoption of the novel cardiovascular model of thermoregulation, the historic teaching that the body temperature (and the serum osmolality) are homoeostatically regulated[30] and that weight loss as a result of sweating is an essential component of that regulation has been replaced. Now, as a consequence of this industry driven paradigm shift, it is assumed that body weight is the critical variable that must be defended at all costs during exercise.[51 52]

Unfortunately, the new paradigm shift occasioned by the ACSM guidelines and as championed by the GSSI happened at the very time that marathon running, particularly in the United States, underwent its most fundamental change since 1976. Before 1976, there were few runners in marathon races, and most were usually well trained and able to finish the 42 km in less than 3.5 hours. But since 1996 this has changed so that most current marathon runners in the US require four or five or more hours to complete these distances.[53] In publishing its guidelines, the ACSM promoted the concept that it was a good idea for less well conditioned athletes travelling at slow speeds (8–9 km/h) for prolonged periods (>4.5 hours) to drink ''as much as tolerable'' to prevent a condition, heatstroke, that occurs rarely in such slow runners, despite published findings that called into question the validity of that idea.[3 4]

The first reported death from EAHE occurred in the Valley of the Giants marathon in California in 1993.[54] Besides the deaths in the US military, there have been three additional deaths reported in female runners in US marathons: Dr Kelly Barrett in the 1998 Chicago marathon,[55] Dr Cynthia Lucero in the 2002 Boston marathon,[56] and, six months later, Hilary Bellamy in the 2002 Marine Corps marathon.[57] All of these women, it was reported,[54 57] received intravenous isotonic saline solutions for treatment of their EAHE, a treatment established to be ineffective in 1985.[3 4] As subjects with EAH also have the syndrome of inappropriate ADH secretion, such management is contraindicated because it produces water retention and sodium loss as a result of the actions of ADH and a third factor.[6] The correct treatment of EAH is either to do nothing if the condition is mild and the patient does not have EAHE, or to infuse hypertonic saline solutions (3–5%) in modest amounts,[5 6] with or without the use of diuretics.

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For how long these preventable catastrophes might have continued to occur is anyone's guess. But fortunately, at the same race in which Cynthia Lucero participated, a group of enthusiastic hospital residents from the Harvard Medical School decided to perform what would become the definitive study.[58] They chose a large sample size of runners as had Speedy *et al*,[11] but included questions that could be analysed retrospectively to determine predictors of post-race serum sodium concentrations. But the crucial difference between this and all previous studies of EAH was that the Harvard Medical School study leapt across the gargantuan divide between sports science and clinical medicine and was published in arguably the most influential medical journal in the world, the *New England Journal of Medicine*. The authors' conclusions were the following.

(1) EAH occurred in a substantial fraction of the diverse athletic population that they studied. They calculated that, if their sample was representative of all 15 000 finishers in the 2002 Boston marathon, then approximately 1900 of those runners would have developed EAH and about 90 ''critical'' EAHE (serum sodium concentration of 120 mmol/l or less). This contrasts with the commercially driven conclusion that EAH is uncommon and much less prevalent than conditions caused by ''dehydration''.[59] For example, in a press release published on the website of the GSSI on the day that the peer reviewed editorial was published in the *British Medical Journal*,[60] the GSSI, among other claims, proposed that ''Dr Noake's (sic) editorial is not representative of the comprehensive research that is available on the topic of hydration during exercise. Nor does it factor in the very real dangers associated with the more common condition of dehydration''.[59] Which is perhaps understandable as the editorial dealt with the proven dangers of overhydration and not the commercially driven and scientifically unsound claims for the dangers of dehydration.[1 8 24–28 61 62] Thus the GSSI press release concluded with the statement that ''In summary, there is no doubt that hyponatremia is a rare but dangerous condition that affects a very, very small subset of the population. However, dehydration and heat illness occur more frequently and represent the greater threat to anyone who is physically active in a warm environment''. It is perhaps stretching the truth to suggest that a preventable condition that affects 13% of runners and which might possibly have involved 1900 runners, 90 seriously,[58] in a single race, is ''rare''. Whereas it might appear ''rare'' to a sports drink company, whose product was the official race drink for that particular event, the doctors treating such an unnecessary case load might indeed be of a different opinion.

(2) ''Substantial weight gain appeared to be the most important predictor of hyponatremia and correlated with increased fluid intake'' (p 1554).

(3) The nature of the fluid ingested did not influence the risk of EAH.

(4) Race time in excess of four hours increased the risk of EAH. As a result they concluded that EAH may be a preventable condition through ''efforts to monitor and regulate fluid intake''.

These conclusions mirrored those of our original studies and the content of an editorial in the *British Medical Journal*[60] published 21 months earlier, which stated that ''… the athlete most likely to develop hyponatremic encephalopathy is a female marathon runner who runs these 42 km races at speeds slower than 8–9 km/h (about 5 mph). She gains weight during exercise because she drinks excessively both before and during exercise, sometimes in excess of 100 cups of fluid during the race (about 15 litres of fluid during 5–6 hours of exercise) … since the cause of the condition is now known, prevention is possible'' (p 113).

CONCLUSIONS

History is replete with examples of correct ideas that were not accepted until subsequent generations confirmed their validity. Usually there is a logical reason for this delayed acceptance; often the fault lies with the researchers themselves. Historical examples include James Lind's proof that scurvy can be prevented by the ingestion of fresh

fruits, particularly limes,[63] and Semmelweis's conclusion that the agent causing childbed fever (puerperal sepsis) must be carried on the hands of the obstetrician.[64] In both cases, the scientists were at fault. Lind failed to believe his own data,[65 66] and, despite his irrefutable findings, continued to teach that scurvy was caused by multiple factors, whereas Semmelweiss failed to describe his findings timeously.[66] Only 10 years later, when disturbed by mental illness,[67] did Semmelweiss complete his thesis, by which time his writing was unbalanced, causing offence even to those colleagues who had always supported him. He also failed to undertake animal studies to confirm his theory; nor did he subject any infected materials to microscopic study.[67] Had he done so, he would have antedated, by a decade, Pasteur's identification of bacteria as the causative agent of infectious illnesses.

So, are we who first concluded that EAH and EAHE are caused by overdrinking during exercise equally at fault? Here the evidence appears to be the following.

The original papers of Noakes *et al*[3] and Frizzell *et al*[4] were merely case reports and hence little more than anecdotes. That they both independently drew the same conclusions should, however, have been given more credence. In the pre-scientific era of medical research they would certainly have achieved a greater impact.

But the paper of Irving *et al*[7] unequivocally proved that fluid overload was present in all eight cases of EAHE in ultramarathon runners. Had these studies been completed in the 1950s and published in the *Journal of Clinical Investigation*, it is likely that they would have been accepted as ''classical'' and sufficient proof. But they were not, so the question remains: could we have done more?

The clear criticism is that we did not complete a study of the magnitude and impact of that of Almond *et al*[58] published in the *New England Journal of Medicine* with an accompanying editorial. This made all the difference, even though the study did not come to any materially different conclusions from those that we had reached from our studies of runners in Durban, South Africa, and Ironman triathletes in Auckland, New Zealand. But Auckland is not Boston, and the Comrades marathon is not the Boston marathon. For the reality is that the influence of science is not independent of where that science is practised.

But in reality it would have been impossible to undertake a similar study in either New Zealand or South Africa as our preventive actions had ensured that the condition had essentially disappeared from our ultradistance events in New Zealand[14] and South Africa[25–27] and has yet to be reported in a 42 km marathon runner in either South Africa or New Zealand.[68]

And finally there is the issue of timing. An editorial similar to that ultimately published in the *British Medical Journal*[60] was submitted to the *New England Journal of Medicine* about two years earlier, after the death of Dr Kelly Barrett in the 1998 Chicago marathon. But it antedated the death of Dr Cynthia Lucero at the 2002 Boston marathon and hence was too early, too improbable, and advanced by scientists who were geographically too distant from the perceived centre of global medical science.

Perhaps one defence open to us is that we failed to secure our argument because it conflicted with the prevalent message that was being driven by the sports drink industry. Their unsubtle message has become what Dr Cade, the inventor of the industry,[35–37] preached in 1972: that sports drinks are a medicine that must be ingested during exercise in order to prevent heat illness and optimise performance (by preventing or alleviating fatigue) and that the more that is ingested the better. What we have learned is that, in the face of such a message and pitted against the power of modern marketing,[69 70] an opposite scientific message may not be heard. In this case, only the death of Dr Cynthia Lucero in very public circumstances produced the tipping point that allowed the concealed truth to be exposed.

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