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Sir David Cuthbertson Medal Lecture

Fluid, electrolytes and nutrition: physiological and clinical aspects

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Fluid and electrolyte balance is often poorly understood and inappropriate prescribing can cause increased post-operative morbidity and mortality. The efficiency of the physiological response to a salt or water deficit, developed through evolution, contrasts with the relatively inefficient mechanism for dealing with salt excess. Saline has a $\text{Na}^+:\text{Cl}^-$ of 1:1 and can produce hyperchloraemic acidosis, renal vasoconstriction and reduced glomerular filtration rate. In contrast, the more physiological Hartmann's solution with a $\text{Na}^+:\text{Cl}^-$ of 1.18:1 does not cause hyperchloraemia and Na excretion following infusion is more rapid. Salt and water overload causes not only peripheral and pulmonary oedema, but may also produce splanchnic oedema, resulting in ileus or acute intestinal failure. This overload may sometimes be an inevitable consequence of resuscitation, yet it may take 3 weeks to excrete this excess. It is important to avoid unnecessary additional overload by not prescribing excessive maintenance fluids after the need for resuscitation has passed. Most patients require 2–2.5 litres water and 60–100 mmol Na/d for maintenance in order to prevent a positive fluid balance. This requirement must not be confused with those for resuscitation of the hypovolaemic patient in whom the main aim of fluid therapy is repletion of the intravascular volume. Fluid and electrolyte balance is a vital component of the metabolic care of surgical and critically-ill patients, with important consequences for gastrointestinal function and hence nutrition. It is also of importance when prescribing artificial nutrition and should be given the same careful consideration as other nutritional and pharmacological needs.

Sodium: Water: Electrolytes: Gastrointestinal function: Albumin

There is a close relationship between nutrition and fluid and electrolyte balance, with the intake of food by natural or artificial means being inseparable from that of fluid and electrolytes. The physiological processes of digestion and absorption of nutrients in the small and large intestines are intimately linked to the secretion and absorption of water and electrolytes. Fluid and electrolytes also play an important role in intermediary metabolism and cellular function. In clinical practice nutrient, water, mineral and electrolyte balances are all closely related in the treatment of disease. The changes in fluid and electrolyte physiology linked to the responses to starvation and injury, and the effects of salt and water excess in healthy subjects and on outcome in patients will be discussed in the present Sir David Cuthbertson Lecture.

Body water compartments and internal fluid balance

A detailed description of the anatomy and physiology of the body fluids may be found in appropriate works (Edelman & Leibman, 1959; Moore, 1959; Rose & Post, 2001) and only a brief outline will be attempted. In clinical practice it is not only important to consider the external balance of fluid and electrolytes between the body and its environment, but also the changes that take place as a result of starvation and disease in the balance between the internal compartments of the body. In the average healthy subject body water comprises 60% of the body weight and is functionally divided into the extracellular fluid (ECF) and the intracellular fluid (Fig. 1), separated by the cell membrane, which through its Na, K ATPase pump maintains

Abbreviations: ECF, extracellular fluid; RAAS, renin-angiotensin-aldosterone system.

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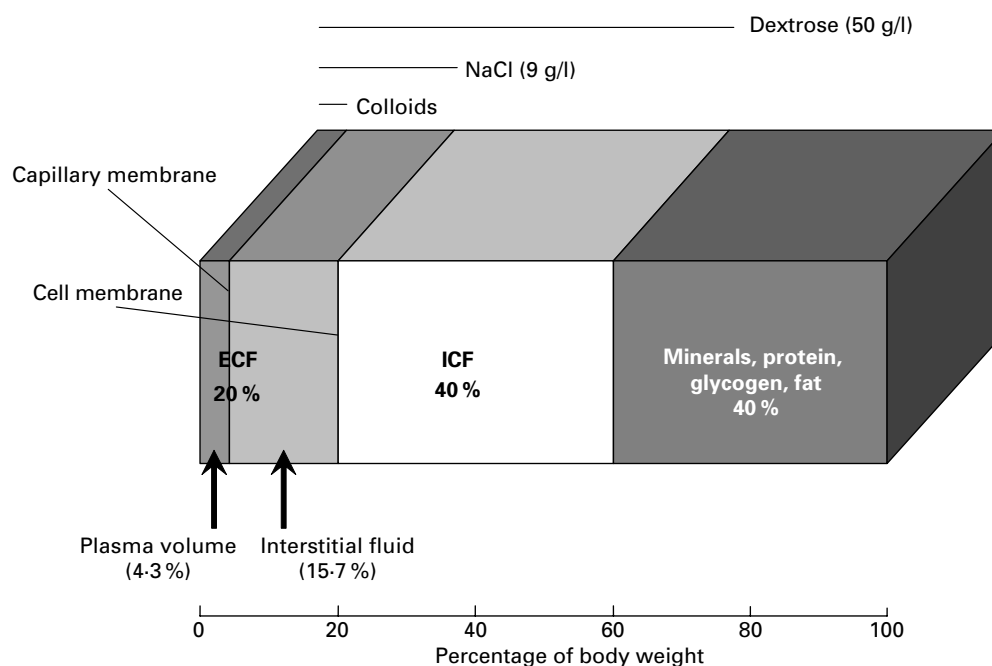


Fig. 1. Distribution of infused fluids (dextrose (50 g/l), saline (9 g NaCl/l) and colloids) in the body water compartments. ECF, extracellular fluid; ICF, intracellular fluid.

equilibrium between the two compartments, so that Na is the main extracellular cation and K is the main intracellular cation. The ECF volume is preserved by the factors controlling body Na content. The kidney can conserve Na very efficiently but, as the present review will show, the capacity to excrete excess Na may be limited, because during mammalian evolution there has been little or no exposure to this circumstance until recent times.

The ECF is further divided by the capillary membrane into its intravascular and interstitial compartments (Fig. 1), the equilibrium between the two compartments being determined by the membrane pore size (increased with inflammation), the relative concentration and hence oncotic pressure of proteins on the two sides of the membrane, and the capillary hydrostatic pressure (Starling, 1896).

External balance and the kidney

The ability to excrete urine with an osmolality different from plasma plays a central role in the regulation of water balance and the maintenance of plasma osmolality and Na concentration (Table 1). The obligatory renal water loss is directly related to the solute excretion, and if 800 mOsm solute/d have to be excreted to maintain the steady-state, and the maximum urinary osmolality is 1200 mOsm/kg, a minimum of 670 ml urine/d will be required to excrete the solute load (Rose & Post, 2001). The kidney responds to water or Na excess or deficit via osmo- and volume receptors, acting through antidiuretic hormone and the renin-angiotensin-aldosterone system (RAAS) to restore normal volume and osmolality of the ECF. Maintenance of volume always overrides maintenance of osmolality if hypovolaemia and hypo-osmolality coincide.

The kidney filters about 22 400 mmol Na/d, with 22 300 mmol being reabsorbed, and the daily Na requirement is

between 1 and 1.2 mmol/kg, which is very similar to that of K. The water requirement varies from 25 to 35 ml/kg. The renal countercurrent mechanism, along with the hypothalamic osmoreceptors that control the secretion of antidiuretic hormone, maintains a finely-tuned balance of water to keep the serum Na concentration between 135 and 145 mmol/l, despite the wide variation in water intake.

Internal balance and fluxes

Across the cell membrane. Regulation of the internal distribution of K must be extremely efficient, as the movement of as little as 2% of the intracellular fluid K to the ECF can result in a potentially fatal increase in the serum K concentration. The Na, K ATPase pump is the most important determinant of K distribution, and the activity of the pump itself is increased by catecholamines and insulin. Critical illness may disturb the balance across the cell membrane (Flear & Singh, 1973, 1982; Allison, 1996; Campbell *et al.* 1998), resulting in a rise in intracellular Na and reduced intracellular K and electrical potential across the cell membrane. These changes lead to the 'sick cell syndrome' and ultimately to cell death.

Across the capillary membrane. This aspect is discussed under the effects of starvation and injury.

Through the gastrointestinal tract. Although 8–9 litres fluid cross the intestine, only about 150 ml are excreted in the faeces. The reabsorptive capacity of the gut may fail in diarrhoeal diseases and in patients with intestinal fistulas or the short bowel syndrome. In patients with ileus or intestinal obstruction as much as 6 litres water may be pooled in the gut and therefore lost from the ECF. It is important to be aware of the content of the various gastrointestinal fluids when replacing fluid and electrolytes in patients with gastrointestinal losses.

Table 1. Response to changes in extracellular water and sodium

Stimulus	Pathway	Outcome
Na deficiency	↓ Baroreceptor activity ↑ Renin–angiotensin–aldosterone-system activity	↓ Urinary Na excretion
Na excess*	↓ Natriuretic peptides ↑ Baroreceptor activity ↓ Renin–angiotensin–aldosterone-system activity ↑ Natriuretic peptides (theoretical, not in practice; in the acute situation the natriuretic peptide response is more to volume increase, atrial stretch, rather than Na excess)	↑ Urinary Na excretion
Water deficiency	Stimulation of osmoreceptors ↑ Antidiuretic hormone secretion	↓ Urinary volume and ↑ urinary osmolality
Water excess	↓ Osmoreceptor activity ↓ Antidiuretic hormone secretion	↑ Urinary volume and ↓ urinary osmolality
Na and water deficiency	↑ Sympathetic nervous system activity (via renal blood flow redistribution)	↑ Urinary Na reabsorption

* The response to Na excess is sluggish, bearing in mind that teleologically man has been exposed to Na excess only in recent times.

Fluid and electrolyte balance: effects of starvation and injury

The effects of starvation and injury on fluid and electrolyte balance have been dealt with extensively (see Wilkinson *et al.* 1949, 1950; Keys *et al.* 1950; Moore, 1959; Winick, 1979; Shizgal, 1981).

Effects on external balance

The response of the human body to starvation, stress and trauma is teleologically designed to preserve vital functions. Sir David Cuthbertson (1930, 1932), in his studies on tibial fractures, recognised two phases in the response to injury: the ebb phase; the flow phase. The ebb phase, usually associated with prolonged and untreated shock, is characterised by a reduction in metabolic rate, hyperglycaemia, hypotension and a retardation of all metabolic processes. These changes subsequently lead either to death or to the flow phase, when metabolism is increased, protein catabolism is maximal and salt and water are retained. Moore (1959) added a third phase, the anabolic or convalescent phase, during which healing is accelerated, appetite returns to normal, net anabolism is restored and the capacity to excrete a salt and water load returns to normal.

Famine and refeeding oedema have been described by several authors (Keys *et al.* 1950; Winick, 1979; Shizgal, 1981). In a detailed study of the effects of semistarvation and refeeding in normal volunteers Keys *et al.* (1950) have shown that although the fat and lean compartments of the body shrink, the ECF volume remains either at its prestarvation level or decreases very slightly. In relative terms, therefore, the ECF volume occupies an increasing proportion of the body mass as starvation progresses. The extent of oedema may be related to access to Na and water and may be exacerbated by refeeding. Na and water balance may also be affected by the diarrhoea that afflicts famine victims, as well as cardiovascular decompensation associated with the effects of starvation on the myocardium. Both starvation and injury, therefore, lead to a state of Na and water retention mediated by complex neuroendocrine mechanisms in response to a perceived diminution in intravascular volume.

Effects on internal balance

In the acutely-ill patient there is frequently a dissociation between compartmental changes and, although the interstitial fluid volume may have even doubled, the plasma volume may be diminished as a result of a gradual loss of plasma into inflamed tissue or from the bowel, or as a result of a generalised increase in capillary permeability. In a healthy subject albumin escapes across the capillary membrane at the rate of 5–7%/h, which is ten times the rate of albumin synthesis. The escaped albumin is then returned into the intravascular compartment via lymphatic channels into the thoracic duct and a steady-state is thereby maintained.

In the early post-operative phase and in patients with sepsis the transcapillary escape of albumin may increase by threefold (Fleck *et al.* 1985) and the rate of flux of albumin into the interstitium becomes greater than the rate of its return into the circulation by the lymphatics. Albumin accumulates in the interstitium resulting in increased interstitial oncotic pressure, causing salt and water to accumulate in the interstitium at the expense of the intravascular volume. Studies (Anderson *et al.* 2002) have shown that after uncomplicated major abdominal surgery transcapillary escape of albumin rises to about three times normal on the first post-operative day, is still more than twice normal on day 5, but returns to approximately normal by day 10, corresponding directly to changes in C-reactive protein and inversely to changes in serum albumin concentration.

Knowledge of the electrolyte content of various gastrointestinal fluids at different levels of the gastrointestinal tract is also essential so that fluid prescriptions in patients with losses from fistulas and stomas may be adjusted accordingly.

Effects of resuscitation

Salt-containing crystalloid and colloidal solutions are used during resuscitation to expand the intravascular volume. The properties of some commonly-used crystalloids are summarised in Table 2. The ability of a solution to expand the plasma volume is dependent on the volume of

Table 2. Properties of commonly-prescribed crystalloids

	Plasma*	NaCl (9 g/l)	Hartmann's	NaCl (1.8 g/l)-dextrose (40 g/l)	Dextrose (50 g/l)
Na ⁺ (mmol/l)	135–145	154	131	31	0
Cl ⁻ (mmol/l)	95–105	154	111	31	0
Na ⁺ :Cl ⁻	1.28–1.45:1	1:1	1.18:1	1:1	–
K ⁺ (mmol/l)	3.5–5.3	0	5	0	0
HCO ₃ ⁻ (mmol/l)	24–32	0	29	0	0
Ca ²⁺ (mmol/l)	2.2–2.6	0	4	0	0
Glucose (mmol/l)	3.5–5.5	0	0	222.2 (40 g)	277.8 (50 g)
pH	7.35–7.45	5.0–5.5	6.5	4.5	4.0
Osmolality (mOsm/l)	275–295	308	274	286	280

* Normal laboratory ranges from Queen's Medical Centre, Nottingham.

distribution of the solute, so that while colloids are mainly distributed in the intravascular compartment, dextrose-containing solutions are distributed through the total body water, and hence have a limited and transient volume-expanding capacity (Fig. 1). Isotonic Na-containing crystalloids are distributed throughout the extracellular space, and textbook teaching classically suggests that such infusions expand the blood volume by one-third the volume of crystalloid infused (Kaye & Grogono, 2000). In practice, however, the efficiency of these solutions to expand the plasma volume is only 20–25%, the remainder being sequestered in the interstitial space (Lamke & Liljedahl, 1976; Svensen & Hahn, 1997; Kramer *et al.* 2001; Lobo *et al.* 2001b; Reid *et al.* 2003).

In severely-injured and critically-ill patients with a major inflammatory response there is leucocyte activation and increased microvascular permeability (Fleck *et al.* 1985; Ballmer-Weber *et al.* 1995; Plante *et al.* 1995). Increased capillary permeability leads to a leak of plasma proteins, electrolytes and water from the intravascular compartment to the interstitial space. This leakage may be protective as it allows immune mediators to cross the capillary barrier and reach the site of injury or infection. However, increased capillary permeability may also lead to intravascular hypovolaemia and an expansion of the interstitial space. Such patients may require large amounts of Na-containing crystalloids to maintain intravascular volume and O₂ delivery to the cells, although artificial colloids allow the use of lower volumes. Overloading with salt and water during resuscitation may be inevitable, but continuing to give large volumes of salt-containing fluids for 'maintenance' may cause unnecessary and increasing cumulative positive balance. Moore & Shires (1967) have rightly criticised the physiological basis of this approach and have recommended that 'the objective of care is restoration to normal physiology and normal function of organs, with a normal blood volume, functional body water and electrolytes'. This outcome, according to them, can never be achieved by inundation.

The average ECF overload after the first 2 d of resuscitation of patients with sepsis has been shown to be in excess of 12 litres and it takes about 3 weeks to mobilise this excess (Plank *et al.* 1998; Plank & Hill, 2000). The association between increased capillary permeability and profound positive fluid balance and multi-organ failure is being recognised (Plante *et al.* 1995; Arief, 1999;

Gosling, 1999; Alsous *et al.* 2000) and attempts to limit interstitial oedema have been beneficial (Mitchell *et al.* 1992; Alsous *et al.* 2000).

In an audit of patients referred for parenteral nutrition after intensive care or surgery (Lobo *et al.* 1999), the extent of fluid overload has been assessed by daily weighing from the time of referral and by subtracting the nadir weight after 7–14 d from the initial weight. The mean fluid overload of the oedematous patients was found to be 10 kg. Using low volume and zero-Na feeds, diuretics and, in a few cases salt-poor albumin (200 g/l), the oedema is resolved over 7–14 d and the serum albumin concentration rises by 1 g/l for every 1 kg loss of excess fluid. This change in serum albumin occurs whether or not albumin is administered. Presuming that by this post-acute stage the albumin escape rate has returned to normal, it may be concluded that the rise in serum albumin concentration results from a reversal of previous dilution.

Clinical relevance

Pringle *et al.* (1905) have demonstrated that both anaesthesia and surgery produce a reduction in urine volume. The use of intravenous hydration gained acceptance in surgical practice (Coller *et al.* 1936) when it was recognised that the intravenous infusion of saline to patients recovering from major surgery decreased both morbidity and mortality, mainly from renal failure. The same authors (Coller *et al.* 1938) recommended that patients should receive 1 litre isotonic saline on the day of the operation, in addition to the replacement of abnormal losses with equivalent volumes of isotonic saline. However, these guidelines were subsequently withdrawn (Coller *et al.* 1944) because of the high incidence of post-operative oedema and electrolyte imbalance. This outcome was described as post-operative 'salt intolerance' and the authors suggested that isotonic Na-containing solutions should be avoided on the day of the operation and during the subsequent 2 d and recommended replacement of water losses with dextrose solutions over this period.

It was then suggested that the administration of saline is satisfactory therapy for patients in good or fair condition who have suffered acute gastrointestinal fluid losses (Power *et al.* 1942). However, these authors also found that patients with chronic illness and those in a poor general condition

commonly accumulate salt and water in the extravascular compartment and develop oedema.

Wilkinson *et al.* (1949) found that the excretion of both Na and chloride is reduced for the first 6 d after surgery. Initially they thought that the reduced excretion may have been a result of lack of salt intake during the usual period of post-operative starvation. However, the condition was found to persist even when the salt intake was maintained intravenously or orally, leading to the conclusion that the decrease in Na and chloride excretion is 'an expression not merely of a failure of intake but also of some active process leading to a retention of Na and chloride'. The authors have also documented an increase in urinary K excretion in the early post-operative period despite a reduction in K intake (Wilkinson *et al.* 1950). This increased excretion results from the fact that K and protein exist in muscle in a ratio of 3:1, so that when protein is catabolised K passes from the intracellular fluid to the ECF and is excreted by the kidneys (Allison, 1996). K is similarly linked to glycogen, being released during glycogenolysis and taken up during glycogen synthesis. These effects, and the action of mineralo-corticoids, account for the increase in K excretion. There is often no fall in serum K concentration despite a reduction in total body K, since K is only lost in proportion to protein and passes continuously into the ECF (Allison, 1996). Once refeeding commences, the cells begin to take up K as glycogen and protein are resynthesised, resulting in a sudden fall in the serum K concentration, revealing the underlying K deficit.

Le Quesne & Lewis (1953) have attributed the post-operative response to the fusion of three separate events: primary water retention; early Na retention; late Na retention. They found that primary water retention is independent of Na retention and is rarely maintained after the first 24 h. The result of primary water retention is oliguria with high specific gravity and is mediated by the release of antidiuretic hormone. Early Na retention also occurs in the first 24 h and is largely adrenocortical in origin. Late Na retention starts 24–48 h after surgery and lasts several d. The authors have suggested that K deficiency may augment late Na retention, concluding that all three phases combine to produce continuous post-operative Na and water retention.

Post-operative patients may excrete only 100 mmol Na during the first 4 or 5 d after surgery without post-operative fluids (Clark, 1977). In patients given intravenous saline the amount of Na retained is proportional to the quantity infused. Intakes of 300 and 1000 mmol Na during the first 4 d after surgery are associated with retention of 200 and 600 mmol respectively (Clark, 1977). In further studies Tindall & Clark (1981) observed the effects of two different post-operative fluid regimens on antidiuresis. With high Na intakes (450 mmol Na in 3000 ml water/d) patients do not develop hyponatraemia, but have marked Na (+1023 mmol) and water retention (+3509 ml) by day 4. Patients given 31 dextrose/d become hyponatraemic on day 1, but subsequently excrete the excess water with normalisation of the plasma Na concentration.

Shires *et al.* (1960, 1961) have suggested that these changes are a response to a deficit in functional ECF post-operatively; however, it has since been shown that

their data were based on a methodological error and that, in fact, most patients have an expanded ECF during the post-operative period (Roth *et al.* 1969). In contrast, Moore (1959) has suggested that Na and water retention may be part of the obligatory reaction mediated directly by the hormonal response to injury itself. Increased secretion of antidiuretic hormone, mineralo-corticoids and catecholamines are described even in the presence of positive fluid balance. The RAAS is also stimulated by injury. Angiotensin is a powerful vasoconstrictor and promotes adrenal production of aldosterone, which in turn enhances Na conservation by the kidneys and the gastrointestinal tract (Dick *et al.* 1994). The catecholamines, adrenaline and noradrenaline released by the adrenal medulla produce vasoconstriction of selected vascular beds such as the skin and splanchnic circulation, resulting in redistribution of blood from non-essential to essential routes such as the coronary and cerebrovascular circulation.

The capacity to excrete an excess salt and water load returns as the flow phase of injury gives way to the recovery or anabolic phase.

The effect of crystalloid infusions in normal subjects

There have been few studies of the effects of intravenous crystalloids on the serum and urinary biochemistry of healthy euvoalaemic human subjects. An infusion of 2 litres saline (9 g/l) over 2 h in high-risk preoperative patients produces a fall in serum albumin concentration from 34 g/l to 30 g/l (Mullins & Garrison, 1989) and a bolus infusion of 30 ml saline (9 g/l)/kg in normal volunteers over 30 min has been shown to produce a maximum drop in haemoglobin and packed cell volume at 1 h followed by a gradual return to baseline over 8 h (Grathwohl *et al.* 1996). This finding is consistent with earlier work in which saline (9 g/l) boluses of 10, 20 and 30 ml/kg were delivered at a mean rate of 115 ml/min, followed by a continuous infusion of either 1 or 5 ml/kg per h (Greenfield *et al.* 1989). It was found that packed cell volumes determined immediately after the bolus infusion are 4.5, 6.1 and 6.3 points below baseline for the 10, 20 and 30 ml/kg groups respectively. At 20 min into the maintenance infusion the packed cell volumes are 1.5, 2.4 and 2.3 points above the post-bolus values respectively. The authors also calculated that approximately 60% of the infused saline, when delivered as a bolus, diffuses from the intravascular space within 20 min of administration.

Studies using mathematical models to analyse volume kinetics of Ringer acetate solution in healthy volunteers have demonstrated a more pronounced dilution of serum albumin when compared with that of haemoglobin and blood water, suggesting a larger expandable volume for albumin (Hahn & Svensen, 1997; Svensen & Hahn, 1997; Hahn & Drobin, 1998) and raising the possibility that rapid crystalloid infusion may increase the albumin escape rate from the intravascular space.

Large volumes (50 ml/kg over 1 h) of saline (9 g/l) infusion in healthy volunteers have been shown to produce abdominal discomfort and pain, nausea, drowsiness and decreased mental capacity to perform complex tasks, changes not noted after infusion of identical volumes of

Hartmann's solution (Ringer's lactate; Williams *et al.* 1999). The authors also noted that Hartmann's solution produces small transient decreases in serum osmolality that are not seen after saline. Saline infusions are also associated with a persistent acidosis and delayed micturition. Singer *et al.* (1987) have also reported a slow excretion of saline after a 2 litre intravenous load, of which only 29% is excreted after 195 min.

Heller *et al.* (1996) have attempted to determine which of three commonly-used intravenous solutions is most effective in establishing urine flow in healthy volunteers. They rapidly infused 20 ml dextrose (50 g/l), dextrose (50 g/l)-saline (4.5 g/l) or saline (4.5 g/l)/kg immediately after voiding. They found that the total mean urine volume after dextrose (50 g/l) is 1181 ml, markedly greater than after the other two solutions (825 ml and 630 ml respectively), which do not differ between each other, suggesting, as might be expected, that 5% dextrose is more effective than Na-containing solutions in promoting rapid diuresis.

A comparison of changes in serum electrolyte concentrations and acid-base and haemodynamic status after rapid infusion of 2 litres saline (9 g/l) or Hartmann's solution in healthy volunteers has revealed that changes within the groups are small and not significant (Kamp-Jensen *et al.* 1990).

Drummer *et al.* (1992) have studied the urinary excretion of water and electrolytes, and simultaneously the alterations in hormones controlling body fluid homeostasis during the 48 h after an infusion of 2 litres saline (9 g/l) over 25 min and after a 48 h control experiment. It was found that urine flow and urinary electrolyte excretion rates are markedly increased during 2 d after the saline infusion. The largest increase in urinary fluid and electrolyte excretion is between 3 and 22 h post infusion. These long-term changes are paralleled by altered water and Na balances and also by elevated body weights that return to baseline values with an approximate half-life of 7 h. The authors have suggested that vasopressin, atrial natriuretic peptide and catecholamines are unlikely to be of major importance for the renal response to this hypervolaemic stimulus. The RAAS is suppressed during 2 d post infusion, which is correlated with the effects of saline load on Na excretion. However, the closest relationship with Na excretion is observed for the kidney-derived member of the atrial natriuretic peptide family, urodilatin, which is considerably increased during the long-term period up to 22 h post infusion. Thus, these data show that the human body in supine position requires approximately 2 d to restore normal Na and water balance after an acute saline infusion and that urodilatin and the RAAS might participate in the long-term renal response to such an infusion and in the mediation of circadian urinary excretion rhythms.

To investigate further the dilutional effects of crystalloids, in the absence of inflammation, a study has been undertaken of normal subjects infused with either 2 litres saline (9 g/l) or dextrose (50 g/l) over 1 h (Lobo *et al.* 2001b). The infusions were compared by giving them to the same subjects at weekly intervals in random order. Following saline the serum albumin concentration was found to drop within 1 h by 20% from baseline. This

dilution is sustained beyond 6 h since only one-third of the administered Na and water has been excreted by this time. In contrast, although dextrose (50 g/l) results in an immediate fall in serum albumin concentration by 16%, this returns to normal 1 h after infusion as the water load is rapidly excreted. The effect of saline infusion on serum albumin concentration may not have been a result of dilution alone, as the serum albumin falls by a greater percentage than the packed cell volume (20 v. 7.5). Other researchers have also suggested that crystalloid infusions may have a convection effect, dragging albumin out of the circulation, causing redistribution as well as dilution (Perl, 1975; Aukland & Nicolaysen, 1981; Mullins & Bell, 1982; Mullins & Garrison, 1989). Dextrose produces an abrupt diuresis with restoration to normal water balance within 1–2 h of stopping the infusion. On the other hand, 60% of the saline is still retained 6 h later (Lobo *et al.* 2001b). Antidiuretic hormone levels fall after infusion of both solutions, reflecting not only the influence of the osmoreceptors but also of the volume receptors on its secretion. Atrial natriuretic peptide rises abruptly during the infusion of both solutions as a result of the activation of the stretch receptors, but falls to baseline when the infusion is discontinued, despite a residual ECF overload. Atrial natriuretic peptide seems therefore not to be involved in the continuing excretion of an excess Na load. The RAAS, however, is switched off and aldosterone levels remain low after saline, suggesting that normal excretion of a salt load may largely be dependent on the slow permissive effects of reduced RAAS activity (Lobo *et al.* 2002d). The problem may be exacerbated in situations when salt and water overload is combined with low effective blood volume or cardiac output, since the volume receptors of the cardiovascular system signal activation of the RAAS to cause further salt retention, despite interstitial overload and oedema.

A further detailed comparison of the effects of 2 litre infusions of saline (9 g/l) and Hartmann's solution over 1 h in healthy volunteers has shown that while saline (9 g/l) has greater and more prolonged blood and plasma volume expanding effects than Hartmann's solution, as reflected by the greater dilution of the packed cell volume and serum albumin, and the sluggish urinary response, these effects are at the expense of the production of a marked and sustained hyperchloraemia (Reid *et al.* 2003). At 6 h body-weight measurements suggest that 56% of the infused saline is retained, in contrast to only 30% of the Hartmann's solution. The greater diuresis of water after Hartmann's solution compared with saline (9 g/l) may be partly explained by its lower osmolality and the reduced antidiuretic hormone secretion that this osmolality may have engendered. Although the difference between the serum osmolality and Na concentration between the two infusions is not significant, there appears to be a slightly greater fall in both variables after Hartmann's solution. Even a small change in osmolality, within the error of the methods of measurement might be sufficient to cause a large change in antidiuretic hormone secretion. The greater excretion of Na after Hartmann's solution despite the fact that it contains less Na than saline (9 g NaCl/l) is more difficult to understand unless an effect of the Cl⁻ concentration and

the $\text{Na}^+:\text{Cl}^-$ of the two solutions is considered (Table 2). Veech (1986) has emphasised that when large amounts of saline are infused the kidney is slow to excrete the excess chloride load. Hyperchloraemia also causes renal vasoconstriction and reduced glomerular filtration rate.

The mechanisms in response to salt and water deficit are extremely efficient, presumably because during evolution animals have been repeatedly exposed to these circumstances. On the other hand, man has not been exposed to salt excess until modern times and it is not surprising that the mechanisms for excreting an excess saline load, even in health, are relatively inefficient.

Consequences of salt and water imbalance

Saline is constituted by dissolving 9 g NaCl in 1 litre water and is often referred to as 'normal' or 'physiological' saline. However, evidence suggests that both these sobriquets are incorrect (Wakim, 1970). Chemically-normal (molar) saline should contain 1 mol (i.e. 58.5 g NaCl)/l water. So, 'normal' saline is, in fact, 1/6.5 of the concentration of 1 M-saline. Although the solution is described as isotonic, its osmolality (308 mOsm/kg) is slightly higher than that of plasma. Moreover, each 1 litre of the solution contains 154 mmol Na and chloride, which exceeds both the Na (135–145 mmol/l) and chloride (94–105 mmol/l) concentration in plasma. Besides, it does not contain the other mineral and organic constituents of plasma, and cannot, therefore, be considered a physiological solution. The low $\text{Na}^+:\text{Cl}^-$ may be a problem, causing hyperchloraemic acidosis. Large amounts of infused saline produce an accumulation of chloride, which the kidney is unable to excrete rapidly (Veech, 1986). This inability may be because the permeation of Cl^- across cell membranes is voltage dependent and the amount of chloride in the intracellular fluid is a direct function of the membrane potential. The cellular content of all other anions, especially phosphate, must accommodate to changes in chloride caused by administration of parenteral fluids (Veech, 1986). This adjustment may account for the decrease in morbidity in infants treated for diarrhoea when Hartmann (1934) replaced some of the chloride in saline (9 g/l) with lactate.

The toxicity of large amounts of saline was recognised when proctoclysis was used for fluid replacement, and Trout (1913) wrote, '... sodium chloride ... is a poison to all people when given in large doses, and occasionally very toxic in small doses to a certain class of cases'. Despite this opinion, it has long been believed that retention of as much as 600 mmol Na in the post-operative period does not have any deleterious effect in the majority of patients who do not have cardiorespiratory or renal disease (Clark, 1977).

It is well known that salt and water excess can precipitate congestive cardiac failure and pre-renal failure in susceptible patients. Even if cardiac and renal failure are not precipitated, salt and water excess can cause tissue oedema irrespective of the transcapillary escape rate of albumin. Oedema compromises both pulmonary gas exchange and tissue oxygenation, and produces an increase in tissue pressure in organs surrounded by a

non-expandable capsule, thereby slowing microvascular perfusion, increasing arterio-venous shunting and reducing lymphatic drainage, all of which facilitate further oedema formation (Stone & Fulenwider, 1977).

Critically-ill patients are frequently acidotic. These patients may also receive large amounts of NaCl-containing crystalloids and colloids that may compound the acidosis (Veech, 1986; Williams *et al.* 1999; Ho *et al.* 2001; Wilkes *et al.* 2001). Acidosis impairs cardiac contractility, reduces responsiveness to inotropes, decreases renal perfusion and can be lethal in combination with hypothermia and coagulopathy (Ho *et al.* 2001).

Starker *et al.* (1983) have retrospectively demonstrated that half their patients receiving preoperative parenteral nutrition had an increase in body weight and a decrease in serum albumin concentration resulting from salt and water retention. These patients had a 50% post-operative complication rate compared with a 4% rate in the remaining patients who were able to excrete a salt and water load with resulting weight loss and increase in serum albumin concentration. Again, in a randomised study in severely-malnourished patients receiving preoperative parenteral nutrition, Gil *et al.* (1997) have compared a group of patients receiving a standard feed containing 70% of the non-protein energy as glucose, 140 mmol Na/d and 45 ml water/kg per d with a group receiving a modified feed containing 70% non-protein energy as fat, no Na and 30 ml water/kg per d. Weight gain with positive Na and water balance and lowering of serum albumin concentration were noted in the standard group while a negative Na and water balance, reduction in overall complications and decreased post-operative stay were noted in the modified group.

Mitchell *et al.* (1992) randomised 101 patients with pulmonary oedema to management based on pulmonary artery wedge pressure (n 49) or extravascular lung water (n 52). They found that the latter group show less than half the cumulative fluid balance, have reduced interstitial oedema and spend markedly fewer days on the ventilator and in the intensive care unit.

The records of thirty-six patients admitted to the intensive care unit with septic shock, excluding those who needed dialysis, have been reviewed (Alsous *et al.* 2000). It was found that while all eleven patients who had achieved a negative fluid balance of >500 ml on one or more of the first 3 d of admission survived, only five of twenty-five patients who had failed to achieve this state of negative fluid balance by the third day of treatment survived. The authors concluded that at least 1 d of net negative fluid balance on the first 3 d of treatment strongly predicts survival.

Post-operative mobility may also be impaired by oedema of the limbs, along with susceptibility to pulmonary oedema, as shown by Guyton (1959) who has demonstrated that pulmonary oedema develops at a lower pulmonary venous pressure in the presence of a lowered serum albumin. Another retrospective study has suggested that post-operative pulmonary oedema is more likely within the initial 36 h when net fluid retention exceeds 67 ml/kg per d (Arieff, 1999). Increased post-operative morbidity and prolonged hospital stay in patients receiving

peri-operative salt and water excess have also been reported in a recent audit of a homogeneous group of patients undergoing colo-rectal resections (Frost *et al.* 2001).

Brandstrup *et al.* (2003) have demonstrated, in a randomised multicentre study, that patients undergoing colo-rectal resections fare better if post-operative fluids are restricted to maintain constant body weight throughout the patients' stay in hospital than if patients are given standard post-operative fluids which may cause a 3–7 kg increase in body weight. This response is especially apparent when cardiopulmonary complications are looked at (24% in standard group and 7% in restricted group, $P=0.0007$). There were no adverse effects in the restricted group and patients in the standard group tended to have decreased O_2 tension and saturation, negative base excess and lower arterial pH in the immediate post-operative period than those in the restricted group.

This goal for fluid replacement is helped by frequent weighing (the most accurate measure of fluid balance) as well as the critical use of fluid balance charts, while remembering the inherent inaccuracies and the problem of estimating insensible loss. Serum biochemical measurements need also to be interpreted in the light of other data, since changes in serum Na and K concentration are influenced by water as well as electrolyte balance and also by changes in metabolism, e.g. refeeding syndrome. Careful and accurate distinction should also be made between requirements for fluid replacement and for maintenance.

Preoperative optimisation of fluid and electrolyte balance is important in the elderly if post-operative outcome is to be improved. Patients receiving preoperative bowel preparation for colo-rectal procedures can be moderately dehydrated (1–2 litres) or have major electrolyte imbalance (Beloosesky *et al.* 2003; Seinela *et al.* 2003). Careful concurrent administration of either intravenous (Sanders *et al.* 2001) or oral rehydration solutions (Barclay *et al.* 2002) may help to restore balance.

A meta-analysis of two studies, randomising a total of 130 patients, to determine the optimal method of fluid volume optimisation for adult patients undergoing surgical repair of hip fracture has been undertaken by the Cochrane group of reviewers (Price *et al.* 2002). Both studies involved invasive advanced haemodynamic monitoring during the intra-operative period only. One study randomised patients to 'normal care' or optimisation using oesophageal Doppler (Sinclair *et al.* 1997). The other randomised patients to 'normal care', oesophageal Doppler or central venous pressure monitoring (Venn *et al.* 2002). In each study invasive monitoring led to a marked increase in the volume of fluid infused and a reduction in length of hospital stay. The odds ratio for in-hospital fatality was 1.44 (95% CI 0.45, 4.62).

The tonicity of the infused fluid must also be taken into account, as it is particularly dangerous to administer large volumes of hypotonic fluids to the elderly as this practice may result in fatal hyponatraemia (Lane & Allen, 1999). Changes in plasma Na are almost always a reflection of changes in water not Na balance. A change of 1 mmol/l in plasma Na concentration is associated

with a gain or loss of 280 ml water in a 70 kg young man, but with half that amount in a 45 kg elderly woman, who is therefore more easily overloaded by ill-informed therapy. Hyponatraemia (<120 mmol/l) can cause cerebral oedema, particularly in the elderly, and the importance of slow correction at a rate <8 mmol/l per d to avoid osmotic demyelination cannot be overstressed (Shafiee *et al.* 2003; Sterns & Silver, 2003). At the other end of the scale, in the very young and the very old there is a risk of cerebral oedema if hypernatraemia and hyperosmolar states are corrected too quickly, e.g. in non-ketotic hyperglycaemia. A volume deficit should be corrected but the osmolar concentration should be reduced slowly to allow equilibration between ECF and brain.

These studies again emphasise the use of fluid therapy to optimise physiological function by achieving not only external balance, but also internal balance between the body fluid compartments. Although some of these studies are retrospective and some have small numbers of subjects, they show that salt and water excess is not without consequence and they suggest that more attention should be paid to Na and water replacement in post-operative and critically-ill patients if clinical outcomes are to be improved.

Fluid balance and gastrointestinal function

There have been few studies on the effects of peri-operative salt and water balance on gastrointestinal function, but the published evidence tends to suggest that salt and water excess can delay both gastric emptying and small intestinal transit.

Subsequent to their observations of cessation of vomiting after salt and water restriction in hypoproteinaemic patients with gastrointestinal anastomoses, Mecray *et al.* (1937) have published a series of experiments on dogs relating serum albumin concentration and salt and water balance status with gastric emptying time. In the first set of experiments the authors rendered a group of ten dogs hypoproteinaemic by a combination of a low-protein diet and repeated plasmapheresis. They infused a volume of NaCl (9 g/l) equal to the amount of blood withdrawn on each occasion. None of these animals underwent surgery and eight survived >1 month. Mean gastric emptying time in the survivors, as measured by fluoroscopic observation of the transit of a Ba meal, was shown to be inversely proportional to the serum protein concentration (Fig. 2).

The authors then studied three dogs that were subjected to a pylorotomy after they had been rendered hypoproteinaemic. They found that gastric emptying time is prolonged soon after the operation when the serum protein concentration is low, and is progressively shortened as the serum protein concentration is restored to normal by a combination of a high-protein diet and fluid restriction. In one of the dogs they were able to demonstrate an acceleration in gastric emptying time as a result of withholding all fluids for several d, subsequent to which an infusion of 800 ml NaCl (9 g/l) resulted in a fall in serum protein concentration and retardation of gastric emptying.

Finally, the authors were able to confirm the inverse relationship between serum protein concentration and

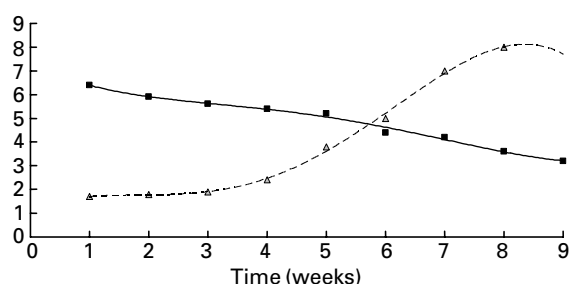


Fig. 2. Inverse relationship between serum protein concentration (g/dl; ■) and gastric emptying time (h; △) in a group of eight dogs that did not undergo surgery but were rendered hypoproteinaemic by a combination of a low-protein diet, repeated plasmapheresis and infusions of sodium chloride (9 g/l). (Redrawn from Mecray *et al.* 1937 with permission from *Surgery*.)

gastric emptying time over several weeks in two dogs subjected to a polya gastrectomy 1 year previously. Serum protein concentrations were manipulated by feeding the animals a high-protein diet or a combination of a low-protein diet and repeated plasmapheresis with infusions of NaCl (9 g/l).

Mecray *et al.* (1937) were able to demonstrate gross oedema of the stomach at operation in the hypoproteinaemic dogs and also histologically at autopsy. They concluded that this oedema resulting from hypoproteinaemia is responsible for the prolongation in gastric emptying time, either by interfering with muscular contraction or by reducing the stoma size. However, the dogs also received substantial quantities of NaCl (9 g/l) infusions at varying stages of the studies and it is impossible to determine whether these effects are a result of fluid gain, hypoalbuminaemia or both, since the two are inseparable.

The same group of workers used a similar model to study the effects of serum protein concentration on small intestinal motility (Barden *et al.* 1938). They were able to demonstrate an inverse relationship between both gastric emptying time and small bowel transit, further strengthening their hypothesis. These findings have subsequently been reviewed by Ravdin (1938), who opined that during the period of impaired gastric emptying, 'it is better to maintain the patient in a state of mild dehydration and hypochloraemia than to push water and salt to the point where tissue oedema is accentuated and prolonged.'

The belief that prolongation of gastric emptying time and persistent ileus post-operatively are related to hypoalbuminaemia led Woods & Kelly (1993) to test the hypothesis that raising the serum albumin concentration to >35 g/l with albumin infusions would result in a shortening of the duration of post-operative ileus. They selected eighty-three patients undergoing elective major vascular surgery and randomised them either to receive (*n* 37) or not to receive (*n* 32) post-operative albumin infusions. Albumin was infused until the serum albumin concentration exceeded 35 g/l. Further infusions were given if the serum albumin concentration fell below that level. Although serial serum albumin concentrations were found to be markedly higher in the albumin-replacement group, the authors were not able to demonstrate a marked

difference in either the duration of ileus (albumin 4.06 d *v.* no albumin 4.16 d) or the time to resume an oral intake (4.0 d *v.* 3.75 d). Post-operative hospital stay and complication rates were also found to be similar in the two groups. These authors (Woods & Kelley, 1993) did not, however, record the fluid balance status of these patients and a similar extent of hydration (or overhydration) in the two groups could explain the almost identical results when the end points were compared. If patients in both groups had been infused with similar volumes of crystalloids, the albumin group would have run the risk of a greater expansion of intravascular volume (Lucas *et al.* 1978), a factor that could explain the lack of difference. This finding lends credence to the theory that salt and water balance and not the serum albumin concentration *per se* is a determinant of recovery from post-operative ileus.

Critically-ill patients are another group in whom fluid overload is commonly seen, especially because of the necessity of large volumes of infusions to meet goal-directed therapy. Heyland *et al.* (1996) have demonstrated, using the paracetamol absorption test, that gastric emptying time is significantly prolonged in a group of seventy-two mechanically-ventilated patients when compared with normal controls. No record of fluid balance was made in this study and the authors attributed the prolongation in gastric emptying to narcotic use.

Hyperchloraemic acidosis, as a result of saline infusions, has been shown to reduce gastric blood flow and decrease gastric intramucosal pH in elderly surgical patients (Wilkes *et al.* 2001), and both respiratory and metabolic acidosis have been associated with impaired gastric motility in pigs (Tournadre *et al.* 2000).

A physiological experiment has been conducted to study the clinical consequences of modest fluid gains by randomising patients undergoing uncomplicated colonic surgery to receive post-operative intravenous fluids according to hospital practice at the time, *i.e.* ≥ 3 litres water and 154 mmol Na/d (standard group) or ≤ 2 litres water and 77 mmol Na/d (restricted group; Lobo *et al.* 2002*b*). The primary end point was solid- and liquid-phase gastric emptying time, measured by dual-isotope radionuclide scintigraphy (Lobo *et al.* 2002*a*) on the 4th post-operative day. The standard group was found to have 3 kg greater weight gain, reflecting positive salt and water balance, compared with zero balance in the restricted group (Fig. 3). No significant difference was found between the groups when urine output, urinary Na excretion and blood urea concentration were compared. In the standard group solid- and liquid-phase gastric emptying times were shown to be significantly longer (medians; 175 min *v.* 72.5 min, $P=0.028$ and 110 min *v.* 73.5 min, $P=0.017$ respectively), passage of flatus 1 d later (medians; 4 d *v.* 3 d, $P=0.001$) and passage of stool 2.5 d later (medians; 6.5 d *v.* 4 d, $P=0.001$). Although the study was not designed to look for a difference in complication rate, patients in the restricted group were found to have fewer side effects and complications and were able to be discharged 3 d earlier. These results show that salt and water retention is not a harmless and inevitable epiphenomenon, and should be avoided, where possible, by restricting maintenance fluids

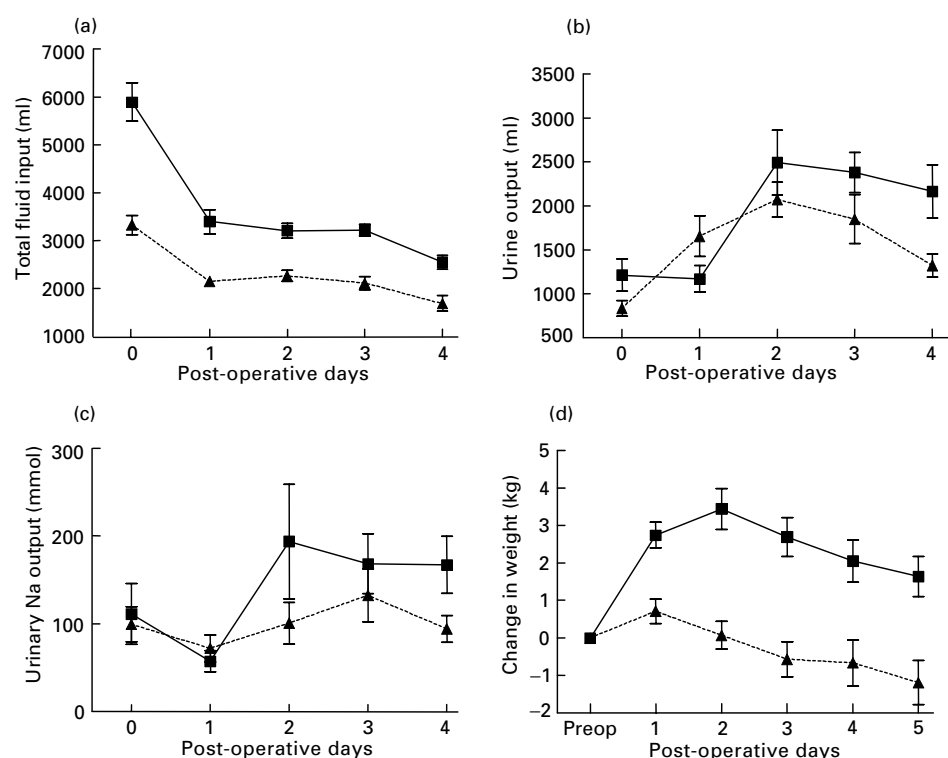


Fig. 3. Total fluid input (a), urinary output (b), urinary Na excretion (c) and change in body weight (d) in patients receiving ≥ 3 litres water and 154 mmol Na/d (standard group; ■) or ≤ 2 litres water and 75 mmol Na/d (restricted group; ▲) after uncomplicated colonic surgery. Values are means with their standard errors represented by vertical bars. Significance values for differences between groups were: (a) $P < 0.0001$, (b) $P = 0.06$ (NS), (c) $P = 0.15$ (NS), (d) $P < 0.0001$. (Modified from Lobo *et al.* 2002b, with permission from *Lancet*.)

to the amount necessary to achieve zero balance. This practice does not deny the need for adequate replacement of additional losses of intravascular or extracellular fluid.

Just as fluid overload causes peripheral oedema, it may also cause splanchnic oedema resulting in increased abdominal pressure, ascites (Mayberry *et al.* 2003) and even the abdominal compartment syndrome (Balogh *et al.* 2003). This outcome, in turn, may lead to a decrease in mesenteric blood flow and a further exacerbation of the process, leading to ileus or functional obstruction of anastomoses, increased gut permeability, intestinal failure and even anastomotic dehiscence (Holte *et al.* 2002). A hypothesis for an impairment of gastrointestinal function in patients with salt and water excess is shown in Fig. 4.

Fluid and electrolyte prescriptions: training and practice

Fluid and electrolytes are the most often prescribed substances in hospital practice and NaCl (9 g/l) solution has been the mainstay of intravenous fluid therapy (Stoneham & Hill, 1997) ever since Thomas Latta (1832) reported that intravenous saline infusions saved cholera victims from almost certain death.

A survey of post-operative fluid therapy over a 4-week period has found that there is a wide variability in the

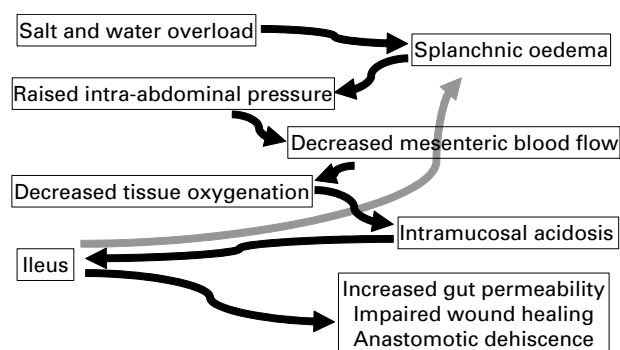


Fig. 4. Hypothesis proposed for the effects of salt and water overload on gastrointestinal function.

prescriptions, with patients receiving a median of 3000 ml water and 242 mmol Na/d (Stoneham & Hill, 1997). The survey also found that fluid balance charts were incomplete in 42% of patients and only 37% of patients received K supplements. The tendency to over-prescribe saline is not a new phenomenon, and dates back to the days when fluid replacement was via rectal infusions, when Evans (1911) noted, 'One cannot fail to be impressed with the danger ... (of) the utter recklessness with which salt solution is frequently prescribed, particularly in the

post-operative period . . .'. Very little has changed over the years. Rhoads (1957) has made the following comment 'the subject of water and electrolyte balance has been obscured by a long series of efforts to establish short cuts. It is not a simple subject but rather one that requires careful study and thought'. Three decades later, these sentiments have been echoed by Veech (1986), 'the use of fluid and electrolyte therapy has become such a familiar part of medicine that it is rarely scrutinised.' The 1999 report of the UK National Confidential Enquiry into Perioperative Deaths (Callum *et al.* 1999) has emphasised that fluid imbalance leads to serious post-operative morbidity and mortality, and has estimated that 20% of the patients studied had either poor documentation of fluid balance or unrecognised or untreated fluid imbalance. The report has suggested that some doctors and nurses lack awareness of the central role of good fluid management. Recommendations include training in fluid management, for medical and nursing staff, to increase awareness and spread good practice and that fluid management should be accorded the same status as drug prescription.

A telephone survey has been used to assess the state of knowledge and fluid prescribing patterns among 200 junior doctors working in surgical wards in the UK (Lobo *et al.* 2001a). It was found that in 89% of instances fluid prescribing is the responsibility of the most junior member of the team (the pre-registration house officer). The perception of quality of teaching on fluid and electrolyte balance in medical schools is very variable, with 33% of respondents rating it as either unsatisfactory or poor. The majority of respondents had not been given any formal or informal guidelines on fluid and electrolyte prescribing. Most respondents did not know the Na and K content of commonly-used intravenous crystalloids and colloids and only 39% of the pre-registration house officers were aware of the inability of the body to excrete an excess salt and water load in the early post-operative period. Although most respondents were aware of the daily requirement of K, <20% knew that Na requirements are similar to those of K. Post-operative weighing is not practised on surgical wards in any of the hospitals surveyed and <10% of the respondents knew that regular weighing is the best serial measure of fluid balance. While 89% of those surveyed thought that 3 litres/d is an ideal post-operative fluid prescription for maintenance requirements, over one-quarter were prescribing >300 mmol Na and chloride/d, which is more than three times the daily requirement.

A postal survey of consultant surgeons in the UK was subsequently conducted (Lobo *et al.* 2002c). On the whole, the 710 who responded felt that present practice in peri-operative fluid management is unsatisfactory. Junior staff are given written guidelines in 22% of instances. Only 16% felt that their pre-registration house officers are adequately trained in the subject and 35% felt that fluid balance charts are not accurately maintained, nursing shortages being the commonest reason for inaccuracies. Only 30% felt that post-operative patients are receiving appropriate amounts of water, Na and K.

Better training and education of doctors and nurses is the key to improvement in the management of fluid and electrolyte balance. Consultants and specialist registrars

should play a more active role in the management of fluid and electrolyte balance in patients undergoing major surgery and in the training of junior staff in this subject.

A recent paper (Shafiee *et al.* 2003) and the accompanying editorial (Sterns & Silver, 2003) provide reminders that errors in fluid prescription are common in hospital practice and are dangerous, particularly at the extremes of life. These articles emphasise that both salt and water are frequently given in excess and that salt-containing solutions are mainly for volume replacement or to replace known losses, which are often overestimated.

Conclusions

Moore & Shires (1967) were right in emphasising the importance of prescribing fluid and electrolytes in a way that optimises physiological function. It is clear that even modest deficits or excesses can cause physiological derangement and hence adverse clinical consequences in terms of complications, outcome and rate of recovery from disease. When prescribing fluid and electrolytes, it is important, therefore, to understand the relationship between internal and external balance and the effects of starvation and injury in order to prevent the adverse physiological and clinical consequences of errors in treatment. Attention to detail and better education are the key to better prescribing.

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