Physiological Aspects of Fluid and Electrolyte Balance

by

Dileep N. Lobo

MB, BS, MS, Dip. NB, FRCS (Gen Surg)

Submitted to the University of Nottingham for the degree of Doctor of Medicine, October 2002

Table of Contents

Abstract

Brevity makes counsel more portable for memorie and readier for use.

Joseph Hall
Characters of Virtues and Vices

The intake of water and electrolytes is inseparable from feeding by natural or artificial means and careful attention to salt and water balance is a vital component of perioperative care and of nutritional support.

Nutritional support with water and sodium restriction in post-intensive care patients with oedema, dilutional hypoalbuminaemia and fluid excess of 10 L, cleared oedema over 7-10 days, with a 1 g/L rise in serum albumin for every kg loss in weight. Return of gastrointestinal function was also observed.

Accordingly, 20 patients, undergoing colonic surgery, were randomised to receive standard ($\geq$3 L water and 154 mmol sodium/day) or restricted postoperative fluids ($\leq$2 L water and 77 mmol sodium/day). Solid (72.5 vs 175 min) and liquid phase (73.5 vs 110 min) gastric emptying times were significantly longer in the standard group on the 4th postoperative day and associated with a three day longer hospital stay.

In volunteers receiving 2 L of 0.9% saline and 5% dextrose infusions, on separate occasions over one hour, haematocrit and serum albumin concentration fell, mainly due to dilution. While dextrose was rapidly excreted, two-thirds of the saline was retained after 6 h. Following 1 L infusions, plasma renin and angiotensin concentrations decreased more after saline than dextrose (P<0.04). Responses of aldosterone, atrial natriuretic peptide and vasopressin were not significantly different. Comparing 2 L infusions of saline and Hartmann's solution, volunteers excreted more water (median 1000 vs 450 mL) and sodium (122 vs 73 mmol) after Hartmann's. Hyperchloraemia and reduced bicarbonate were noted after saline alone.

Whereas fluctuations in water balance are dealt with efficiently through osmoreceptors and vasopressin, and sodium deficiency by volume receptors and the renin angiotensin aldosterone system, the mechanism for dealing with sodium and chloride excess appears relatively inefficient. Natriuretic peptide responds to volume expansion rather than sodium gain.

Declaration

Except where acknowledged in the acknowledgements and text, I declare that this dissertation is my own work and is based on research that was undertaken by me in the Section of Surgery, School of Medical and Surgical Sciences University of Nottingham Medical School from 1 April 1999 to 31 March 2002.

Dileep N. Lobo

Acknowledgements

This thesis has reached fruition because of the collaboration and help I have received from a number of individuals to whom I am most grateful. I am particularly indebted to the following.

- To my guide and supervisor, Professor Simon P. Allison for having taken a personal interest in this project. His office has had open doors and he has been an inspiration at every stage of the thesis. His capacity for lateral thinking is second to none and the manuscript has been greatly enriched by his criticism.
- To Professor Brian J. Rowlands for providing me with the opportunity to undertake this research and for being a pillar of support all through.
- To Dr. Keith R. Neal for providing statistical advice and help with statistical calculations and interpretation of results.
- To Kate Bostock for her help with the gastric emptying studies, administration and management of accounts.
- To Professors Ian A. Macdonald, Alan C. Perkins and Fiona Broughton Pipkin for providing ideas, constructive criticism and laboratory facilities.
- To Deborah Myhill, Dr. Jose M. Latre, and Andrew Mackenzie for the radioimmuno assays of the hormones.
- To David Foster and Simon Lawes for their help with the laboratory tests for the measurement of body water compartments and transcapillary escape rate of albumin.
- To Sandy Brown and Dr. Gerry Dolan for their help with the biochemical and haematological tests.
- To Mukul Dube for helping with the two surveys.

- To Zeno Stanga, for being a friend and helping with the studies in normal subjects.
- To John Anderson, Alastair Simpson and Fiona Reid, whose BMedSci projects I was a co-supervisor of, for their help with the studies in normal subjects, especially for enthusiastically recruiting volunteers.
- To the Special Trustees of Queen's Medical Centre for awarding me a two-year fellowship that helped fund my salary.
- To the European Society of Parenteral and Enteral Nutrition, the Intensive Care Society, Nutricia Clinical Care and the British Journal of Surgery Society for the award of grants and fellowships that funded the running costs of the various studies.
- To the patients and volunteers studied, for selflessly agreeing to participate in the studies and help improve our understanding of the pathophysiology of fluid and electrolyte balance.
- Finally, to Annie Lobo for tolerating an untidy and disorganised writer. I am sure she is relieved that the mounds of paper cluttering the house have disappeared, albeit temporarily!

Presentations arising from this thesis

Invited Lectures

1. Allison SP, Lobo DN, Stanga Z. **The treatment of hypoalbuminaemia.** European Society of Parenteral and Enteral Nutrition Annual Congress, Madrid, September 2000.
2. Lobo DN. **Resuscitation fluids in the 21st century.** Association of Surgeons of India Annual Conference, Chandigarh, November 2000.
3. Lobo DN. **Salt and water: Getting the balance right.** British Pharmaceutical Nutrition Group Annual Conference, Nottingham, June 2001.
4. Lobo DN. **Salt and water balance and serum albumin: Dilution or escape?** Nutricia Clinical Care Fellowship Lecture, British Association for Parenteral and Enteral Nutrition Annual Conference, Harrogate, November 2001.
5. Lobo DN. **The importance of perioperative fluid management on outcome in surgery.** University Hospital, Berne, Switzerland, February 2002.
6. Lobo DN. **Guidelines on resuscitation of the shocked patient.** Royal College of Surgeons of England, London, March 2002.
7. Lobo DN. **The pathway back to recovery: Fluid and electrolytes.** The Moynihan Chirurgical Club, Nottingham, September 2002.

Platform Presentations

1. Lobo DN, Bjarnason K, Field J, Rowlands BJ, Allison SP. **Fluid balance status of patients referred for nutritional support.** British Association for

Parenteral and Enteral Nutrition Annual Conference, Bournemouth, December 1998.

2. Lobo DN, Neal KR, Dube MG, Simpson J, Rowlands BJ, Allison SP. **Problems with solutions: Drowning in the brine of an inadequate knowledge base.** Association of Surgeons of Great Britain and Ireland Annual Conference, Cardiff, May 2000.
3. Lobo DN, Bostock K, Neal KR, Perkins AC, Rowlands BJ, Allison SP. **The effect of postoperative salt and water restriction on recovery of gastrointestinal function and outcome in patients undergoing elective colonic resections: a prospective, randomised controlled study.** Association of Surgeons of Great Britain and Ireland Annual Conference, Birmingham, April 2001.
4. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. **Effect of salt and water balance on recovery of gastrointestinal function and outcome after abdominal surgery: a prospective randomised controlled study.** European Society of Parenteral and Enteral Nutrition Annual Congress, Munich, September 2001.
5. Lobo DN, Dube MG, Neal KR, Allison SP, Rowlands BJ. **A national survey of consultant surgeons on perioperative fluid and electrolyte management.** Association of Surgeons of Great Britain and Ireland Annual Conference, Birmingham, April 2001.
6. Myhill DJ, Lobo DN, Broughton Pipkin F, Allison SP. **The effect of blood volume expansion on the renin angiotensin system (RAS). A randomised, double-blind, cross-over study.** 13th World Congress of the

International Society for the Study of Hypertension in Pregnancy, Toronto, June 2002.

Poster Presentations

1. Lobo DN, Neal KR, Dube MG, Simpson J, Rowlands BJ, Allison SP. **Problems with solutions: Drowning in the brine of an inadequate knowledge base.** European Society of Parenteral and Enteral Nutrition Annual Congress, Madrid, September 2000.
2. Lobo DN, Bostock KA, Bush D, Perkins AC, Rowlands BJ, Allison SP. **Reproducibility and normal ranges for gastric emptying in volunteers using a test meal designed for postoperative patients.** European Society of Parenteral and Enteral Nutrition Annual Congress, Madrid, September 2000.
3. Simpson JAD, Lobo DN, Anderson JA, Perkins AC, Macdonald IA, Rowlands BJ, Allison SP. **Body water compartment measurement using bioelectrical impedance analysis, tritium and sodium bromide: a validation study.** European Society of Parenteral and Enteral Nutrition Annual Congress, Madrid, September 2000.
4. Lobo DN, Stanga Z, Simpson JAD, Anderson JA, Rowlands BJ, Allison SP. **Dilutional hypoalbuminaemia: myth or reality?** British Association for Parenteral and Enteral Nutrition Annual Conference, Harrogate, November 2000.
5. Lobo DN, Stanga Z, Simpson JAD, Anderson JA, Rowlands BJ, Allison SP. **Changes in serum albumin concentration, other biochemical and haematological parameters, and bioelectrical impedance following**

crystalloid infusions in normal subjects. Association of Surgeons of Great Britain and Ireland Annual Conference, Birmingham, April 2001.

6. Lobo DN, Simpson JA, Stanga Z, Allison SP. **Oral glucose loading does not alter urinary sodium or water excretion after a saline load in normal subjects.** European Society of Parenteral and Enteral Nutrition Annual Congress, Munich, September 2001.
7. Lobo DN, Dube MG, Neal KR, Allison SP, Rowlands BJ. **Perioperative fluid and electrolyte management: a survey of senior surgeons in the UK.** European Society of Parenteral and Enteral Nutrition Annual Congress, Munich, September 2001.
8. Lobo DN, Myhill DJ, Stanga Z, Broughton Pipkin F, Allison SP. **The effect of volume loading with 1 litre intravenous infusions of 0.9% saline and 5% dextrose on the renin angiotensin system and volume controlling hormones: A randomised, double-blind crossover study.** European Society of Parenteral and Enteral Nutrition Annual Congress, Glasgow, September 2002.
9. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. **(Ab)normal saline and physiological Hartmann's solution (Ringer's lactate): A randomised, double-blind crossover study.** European Society of Parenteral and Enteral Nutrition Annual Congress, Glasgow, September 2002.
10. Anderson JA, Lobo DN, Lawes SC, Rowlands BJ, Allison SP. **Sequential changes in serum albumin, C-reactive protein and transcapillary escape rate of albumin in patients undergoing major abdominal surgery.**

European Society of Parenteral and Enteral Nutrition Annual Congress, Glasgow, September 2002.

Publications arising from this thesis

Abstracts

1. Lobo DN, Bjarnason K, Field J, Rowlands BJ, Allison SP. **Fluid balance status of patients referred for nutritional support.** *Proc Nutr Soc* 1999; **58**: A114.
2. Lobo DN, Dube MG, Neal KR, Simpson J, Rowlands BJ, Allison SP. **Problems with solutions: Drowning in the brine of an inadequate knowledge base.** *Br J Surg* 2000; **87** (S1): 53.
3. Lobo DN, Dube MG, Neal KR, Simpson J, Rowlands BJ, Allison SP. **Problems with solutions: Drowning in the brine of an inadequate knowledge base.** *Clin Nutr* 2000; **19** (S1): 42.
4. Lobo DN, Bostock KA, Bush D, Perkins AC, Rowlands BJ, Allison SP. **Reproducibility and normal ranges for gastric emptying in volunteers using a test meal designed for postoperative patients.** *Clin Nutr* 2000; **19** (S1): 39-40.
5. Lobo DN, Bostock K, Neal KR, Perkins AC, Rowlands BJ, Allison SP. **The effect of postoperative salt and water restriction on recovery of gastrointestinal function and outcome in patients undergoing elective colonic resections: a prospective, randomised controlled study.** *Br J Surg* 2001; **88** (S1): 25-6.
6. Lobo DN, Dube MG, Neal KR, Allison SP, Rowlands BJ. **A national survey of consultant surgeons on perioperative fluid and electrolyte management.** *Br J Surg* 2001; **88** (S1): 46-7.

7. Lobo DN, Stanga Z, Simpson JAD, Anderson JA, Rowlands BJ, Allison SP. **Changes in serum albumin concentration, other biochemical and haematological parameters, and bioelectrical impedance following crystalloid infusions in normal subjects.** *Br J Surg* 2001; **88** (S1): 80-1.
8. Lobo DN, Stanga Z, Simpson JAD, Anderson JA, Rowlands BJ, Allison SP. **Dilutional hypoalbuminaemia: myth or reality?** *Proc Nutr Soc* 2001; **60**: 113A.
9. Lobo DN, Dube MG, Neal KR, Allison SP, Rowlands BJ. **Perioperative fluid and electrolyte management: a survey of senior surgeons in the UK.** *Clin Nutr* 2001; **20** (S3): 16.
10. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. **Effect of salt and water balance on recovery of gastrointestinal function and outcome after abdominal surgery: a prospective randomised controlled study.** *Clin Nutr* 2001; **20** (S3): 35-6.
11. Lobo DN, Simpson JA, Stanga Z, Allison SP. **Oral glucose loading does not alter urinary sodium or water excretion after a saline load in normal subjects.** *Clin Nutr* 2001; **20** (S3): 37.
12. Myhill DJ, Lobo DN, Broughton Pipkin F, Allison SP. **The effect of blood volume expansion on the renin angiotensin system (RAS). A randomised, double-blind, cross-over study.** *Hypertens Pregnancy* 2002; **21** (S1): O037.
13. Lobo DN, Myhill DJ, Stanga Z, Broughton Pipkin F, Allison SP. **The effect of volume loading with 1 litre intravenous infusions of 0.9% saline and 5% dextrose on the renin angiotensin system and volume controlling**

hormones: A randomised, double-blind crossover study. *Clin Nutr* 2002; **21** (S1): 9-10.

14. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. **(Ab)normal saline and physiological Hartmann's solution (Ringer's lactate): A randomised, double-blind crossover study.** *Clin Nutr* 2002; **21** (S1): 9.
15. Anderson JA, Lobo DN, Lawes SC, Rowlands BJ, Allison SP. **Sequential changes in serum albumin, c-reactive protein and transcapillary escape rate of albumin in patients undergoing major abdominal surgery.** *Clin Nutr* 2002; **21** (S1): 29.

Papers

1. Lobo DN, Bjarnason K, Field J, Rowlands BJ, Allison SP. **Changes in weight, fluid balance and serum albumin in patients referred for nutritional support.** *Clin Nutr* 1999; **18**: 197-201.
2. Allison SP, Lobo DN. **Debate: Albumin administration should not be avoided.** *Crit Care* 2000; **4**: 147-50.
3. Allison SP, Lobo DN, Stanga Z. **The treatment of hypoalbuminaemia.** *Clin Nutr* 2001; **20**: 275-9.
4. Lobo DN, Neal KR, Dube MG, Simpson J, Rowlands BJ, Allison SP. **Problems with solutions: Drowning in the brine of an inadequate knowledge base.** *Clin Nutr* 2001; **20**: 125-30.
5. Simpson JAD, Lobo DN, Anderson JA, Macdonald IA, Perkins AC, Neal KR, Allison SP, Rowlands BJ. **Body water compartment measurements: a**

comparison of bioelectrical impedance analysis with tritium and sodium bromide dilution techniques. *Clin Nutr* 2001; **20**: 339-43.

6. Lobo DN, Stanga Z, Simpson JAD, Anderson JA, Rowlands BJ, Allison SP. **Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study.** *Clin Sci (Lond)* 2001; **101**: 173-9.
7. Lobo DN, Bostock KA, Bush D, Allison SP, Rowlands BJ, Perkins AC. **Reproducibility and normal ranges for gastric emptying in volunteers using a test meal designed for postoperative patients.** *Nucl Med Commun* 2002; **23**: 97-101.
8. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. **Effect of salt and water balance on gastrointestinal function and outcome after elective colonic resection: A randomised controlled trial.** *Lancet* 2002; **359**: 1812-8.
9. Lobo DN, Dube MG, Neal KR, Allison SP, Rowlands BJ**. Peri-operative fluid and electrolyte management: A survey of consultant surgeons in the UK.** *Ann R Coll Surg Engl* 2002; **84**: 156-60.
10. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. **(Ab)normal saline and physiological Hartmann's solution: A randomized, double-blind crossover study.** *Clin Sci (Lond)* 2003; **104**: 17-24.
11. Lobo DN, Simpson JAD, Stanga Z, Allison SP. **The effect of an oral glucose load on sodium and water excretion after rapid intravenous infusion of 0.9% (w/v) saline.** *Clin Nutr* 2003 (In press).

Papers submitted for publication

1. Myhill DJ, Lobo DN, Stanga Z, Broughton Pipkin F, Allison SP. **The effect of volume loading with 1 litre intravenous infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on the renin angiotensin aldosterone system and volume controlling hormones: A randomised, double blind, crossover study.**
2. Lobo DN, Anderson JA, Lawes SC, Rowlands BJ, Allison SP. **Sequential changes in serum albumin, C-reactive protein and transcapillary escape rate of albumin in patients undergoing major abdominal surgery.**

Editorials by peers on publications arising from this thesis

1. Sitges-Serra A. **Water and sodium balance: a nutritional goal.** *Clin Nutr* 1999; **18**: 191-2.
2. Kramer GC, Svensen CH, Prough DS. **To bolus or not to bolus — is that the question?** *Clin Sci (Lond)* 2001; **101**: 181-3.
3. Heyland DK, Paterson WG. **Fluid restriction for postoperative patients?** *Lancet* 2002; **359**: 1792-3.
4. Wilkes NJ. **Hartmann's solution and Ringer's lactate: targeting the fourth space.** *Clin Sci (Lond)* 2003; **104**: 25-6.

1. Introduction

Only a man who is familiar with the art and science of the past is competent to aid in its progress in the future.

Theodor Billroth

This thesis describes studies of fluid and electrolyte physiology encountered by patients undergoing surgery or receiving nutritional support, as well as studies in normal subjects to elucidate some of the problems observed in patients. Many of the problems encountered in patients are iatrogenic in origin, owing in some cases to inadequate knowledge and standards of practice in fluid and electrolyte management. This aspect is highlighted by a regional survey conducted among junior doctors and a national survey conducted among senior surgeons.

Intravenous fluids are the most commonly prescribed treatment in hospital, yet there is paucity of studies on crystalloid infusions in normal subjects, as a basis for understanding the changes which occur with illness. Accordingly, studies were undertaken, infusing commonly used crystalloids into normal subjects. The implication of the results of these studies for clinical practice is discussed.

Disease is accompanied not only by changes in the balance of water and electrolytes between the body and its environment (external balance) but also by changes in the relationship between the fluid compartments within the body and the fluxes between them (internal balance). Disease also influences the cardiovascular and renal responses to fluid and electrolyte intake through autonomic and neuroendocrine mechanisms. In this introductory chapter, the physiological background and previous literature in the field will be discussed.

1.1 Anatomy and physiology of body fluids in health and disease

The clinical management of fluid and electrolyte problems requires an understanding of both the distribution of body water and the factors affecting internal and external balance of fluid and electrolytes. The broad physiological principles governing these issues are discussed in this section.

1.1.1 Body water compartments and internal fluid balance

In the average normal subject, the body water comprises 60% of the body weight and 73% of the lean mass (Moore 1959). Fat and bone being relatively anhydrous, fatter individuals have a lower percentage of body water.

Body water is functionally divided into the extracellular fluid (ECF) and the intracellular fluid (ICF), separated from each other by the cell membrane, which through its sodium potassium ATPase pump, maintains the equilibrium between the two compartments, so that sodium is the main extracellular and potassium the main intracellular cation, the latter balancing the negative charges on protein and other molecules within the cell.

The cell membrane is freely permeable to water, although not to large molecules such as proteins, whose negative charges help retain potassium within the cell (Gibbs-Donnan equilibrium). It is not possible to alter the tonicity of the ECF without altering that of the ICF because uniform osmotic pressure is maintained by shifts of water into or out of the cell depending on the osmotic gradient between the ECF and the ICF. If salt is added to the ECF or water subtracted from it, tonicity is increased. Water then shifts from the ICF to the ECF resulting in cellular dehydration, stimulation of thirst and arginine vasopressin

(AVP) secretion. On the other hand, if salt is lost from or water added to the ECF, tonicity is reduced, water shifts from the ECF to the ICF, and results in increased cellular hydration, suppression of AVP and reduction of thirst.

Although there are methods available to measure total body water and plasma and ECF volume, there is no direct method for measuring ICF volume. It must therefore be calculated by subtracting the ECF volume form the total body water. Plasma volume may be measured by determining the early volume of distribution of a substance which binds to plasma proteins and does not leave the circulation rapidly. Vital red, Evan's blue (T 1824) and ^{125}I or ^{131}I labelled albumin have been used. ECF volume is measured using a substance that distributes itself throughout the ECF, but does not enter the cells. It should equilibrate rapidly, so that urinary loss and metabolic degradation do not necessitate too large a correction. Although the ideal substance has not been found, thiocyanate, inulin, sucrose, bromide and radiolabelled sulphate have all been used. Total body water is measured by determining the volume of distribution of substances such as urea, thiourea, antipyrine, deuterium and tritium which diffuse evenly throughout the body water.

The ECF has been likened to the continuous phase of an emulsion and the ICF to the disperse phase, emphasising the function of the ECF as a transport medium penetrating all tissues while the ICF provides the anatomical basis for differentiation of cellular chemical function (Edelman and Leibman 1959; Robinson and McCance 1952). It was Claude Bernard who suggested that the ECF provided an internal environment (*milieu interieur*) of virtual constancy in which the tissue cells might safely graze and it is only by such an arrangement

that the body can digest the tissue of other animals, or form acidic urine, without damage to its own cells (Black 1960).

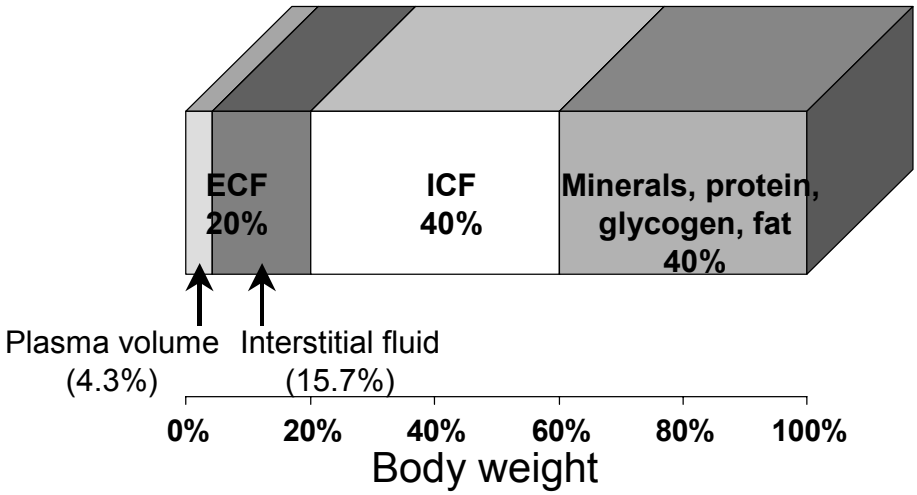


Fig. 1.1: *Body water compartments expressed as a percentage of body weight. (ECF=extracellular fluid, ICF=intracellular fluid)*

The ECF is further divided by the capillary membrane into its intravascular and interstitial compartments (Fig. 1.1), the equilibrium between these 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). Starling's equation, now known as the Law of the Capillary indicates that the extravascular flux of water is inversely related to capillary oncotic pressure as long as other factors in the equation remain constant.

$$F_{H2O} = KC \times SA\ [(P_c - P_i) - (OP_i - OP_c)]$$

where F_{H2O} is the flux of water across the capillary, KC the capillary hydraulic conductivity, SA the capillary surface area, P_c the capillary hydraulic pressure, P_i

the interstitial hydraulic pressure, OP_i the interstitial oncotic pressure and OP_c the capillary oncotic pressure.

Under normal circumstances, 5-7% of the intravascular albumin escapes from the circulation into the interstitial space every hour (transcapillary escape rate of albumin – TER_{alb}) and is returned into the circulation via the lymphatic system. Since this flux is ten times the albumin synthesis rate it is understandable that changes in serum albumin and fluid distribution are more rapidly and profoundly affected by physical distribution or dilution than by metabolic or nutritional factors.

Intravascular and ECF volumes are essentially preserved by the factors controlling the body sodium content. Appropriate ingestion or excretion of sodium protects the constancy of both volumes. The kidney is capable of conserving large amounts of sodium, but as this thesis will show, the capacity to excrete an excess of sodium may be limited, possibly due to the fact that during mammalian evolution there has been little or no exposure to this circumstance.

As body tissue is lost during starvation the ECF is relatively expanded depending on salt and water intake (Keys, Brozek *et al.* 1950). This may give rise to so called "famine oedema" which is exacerbated during refeeding (Winick 1979). This process is even more marked with surgery, trauma or acute illness which all impair the capacity to excrete an excess salt and water load (Le Quesne and Lewis 1953; Moore 1959; Wilkinson, Billing *et al.* 1949). Apart from severe catabolic illness, e.g. burns, pancreatitis or sepsis, the rate of tissue loss during starvation is relatively slow, so that rapid changes in weight reflect fluid rather

than protein-energy balance. The changes in body water in response to starvation and injury are discussed in detail in section 1.2.

1.1.2 Content and concentrations

The concentrations of electrolytes and minerals in the body water compartments are summarised in Table 1.1 and Fig. 1.2.

The total body sodium is between 3000-4000 mmol, of which 44% is in the ECF, 9% in the ICF and the remaining 47% in bone. A little more than half the bone sodium requires acid for its solution and is osmotically inactive; the rest is water soluble and therefore, exchangeable. The daily sodium intake is variable, but on an average amounts to 1 mmol/kg, which is equivalent to the amount excreted in the urine and faeces. Sodium loss in the sweat is negligible, except in individuals not acclimatised to heat. The large sodium stores readily compensate for abnormal losses.

Table 1.1: Electrolyte and mineral concentrations in body water compartments

Electrolyte	ECF (mmol/L)	ICF (mmol/L)	Total in body (mmol)
Sodium	140-155	10-18	3000-4000
Potassium	4.0-5.5	120-145	3000-4000
Calcium	2.2-2.5		25000-27000
Ionised calcium	0.9-1.3		
Magnesium	0.7-1.2	15-25	900-1200
Chloride	98-106	2-6	3000-4000
Phosphate	0.7-1.3	8-20	30000-32000

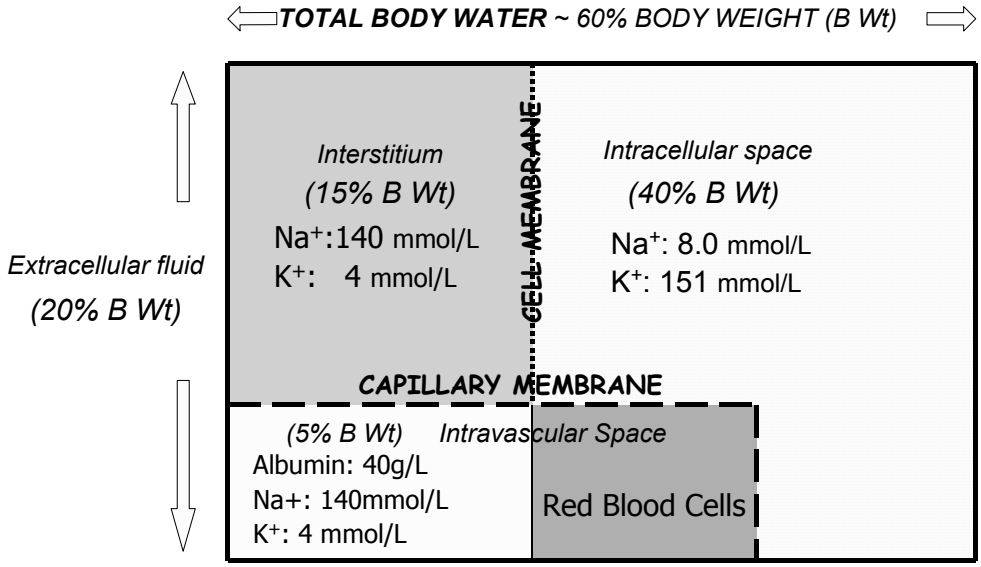


Fig. 1.2: *Distribution of body fluids and the sodium and potassium concentrations in the body water compartments.*

Almost 98% of potassium is intracellular and 75% of the body potassium stores is in skeletal muscle. Potassium and nitrogen are mobilised when the body needs endogenous protein as an energy source, as in conditions of starvation and stress. This mobilised potassium enters the ECF, but the serum potassium concentration usually remains unchanged as healthy kidneys rapidly excrete the excess. The normal daily intake of potassium, like sodium is 1 mmol/kg, and is matched by the urinary excretion.

1.1.3 Fluid balance fluxes: Intake and turnover

External balance and the kidney

In a state of equilibrium, water intake must equal water output and the daily water balances are summarised in Table 1.2.

Table 1.2: Daily water balance in health. Modified from (Rose and Post 2001)

	Intake (mL/day)			Output (mL/day)	
	Obligatory	Elective		Obligatory	Elective
Water from beverages	400	1000	Urine	500	1000
Water from solid food	850		Skin and respiratory tract	900	
Water from oxidation	350		Stool	200	
Total	**1600**	**1000**	**Total**	**1600**	**1000**

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 sodium concentration. If the plasma osmolality is decreased, AVP secretion is inhibited and this results in excretion of dilute urine and return of the plasma osmolality to normal. When the plasma osmolality is increased AVP release and thirst are stimulated and the combination of decreased urinary water loss and increased water intake results in water retention and a decrease in plasma osmolality. The obligatory renal water loss is directly related to the solute excretion and if 800 mOsm of solute have to be excreted per day to maintain the steady state, and the maximum urinary osmolality is 1200 mOsm/kg, a minimum of 670 mL/day of urine will be required to excrete the 800 mOsm solute load (Rose and Post 2001). The renal handling of water and electrolytes is summarised in Table 1.3. The normal kidney responds to water or sodium excess or deficit, via osmo and volume receptors, acting through AVP and the renin-angiotensin system to restore normal volume and osmolality of the ECF. Maintenance of volume

always overrides maintenance of osmolality if hypovolaemia and hypoosmolality coincide.

Table 1.3: Renal handling of water and electrolytes. Modified from (Rose and Post 2001)

Substance	Filtered	Excreted	Net reabsorption (%)
Water	180 L	0.5-3 L	98-99
Na^+	26,000 mmol	100-250 mmol	>99
Cl^-	21,000 mmol	100-250 mmol	>99
HCO_3^-	4,800 mmol	0 mmol	~100
K^+	800 mmol	40-120 mmol	85-95
Urea	54 g	27-32 g	40-50

Sodium is the principal cation and osmotic agent in the ECF. Although the body sodium content may be up to 4000 mmol, only half of this is exchangeable. The kidney filters about 22,400 mmol sodium per day, with 22,300 mmol being reabsorbed, and the daily sodium requirement is therefore between 1-1.2 mmol/kg. The renal countercurrent mechanism, in conjunction with the hypothalamic osmoreceptors that control the secretion of AVP maintains a finely tuned balance of water to maintain the serum sodium concentration between 135-145 mmol/L despite the wide variation in water intake.

Just as sodium salts account for most of the extracellular osmoles and hold water in the ECF, potassium accounts for almost all the intracellular cationic osmoles holding water in the ICF. The daily potassium requirement is about 1 mmol/kg with the total body potassium stores are approximately 3000-4000 mmol, with 98% being intracellular.

Internal balance and fluxes

a) Across the cell membrane

Regulation of the internal distribution of potassium must be extremely efficient as the movement of as little as 2% of the ICF potassium to the ECF can result in a potentially fatal increase in the serum potassium concentration. The sodium-potassium ATPase pump is the most important determinant of potassium distribution and the activity of the pump itself is increased by catecholamines and insulin. Critically ill patients may develop defects in cell membrane function leading to an accumulation of sodium within the cells or the so called "sick cell syndrome" (Campbell, Green *et al.* 1998; Flear and Singh 1973).

b) Across the capillary membrane

This is discussed in detail in Section 1.2.2

c) Through the gastrointestinal tract

Although 8-9 L of fluid cross the duodenum, only about 150 mL are excreted in the faeces (Fig. 1.3). The reabsorptive capacity of the gut may fail in diarrhoeal diseases and in patients with intestinal fistulae or the short bowel syndrome. In patients with ileus or intestinal obstruction as much as 6 L of water may be pooled in the gut and therefore be 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 1.4).

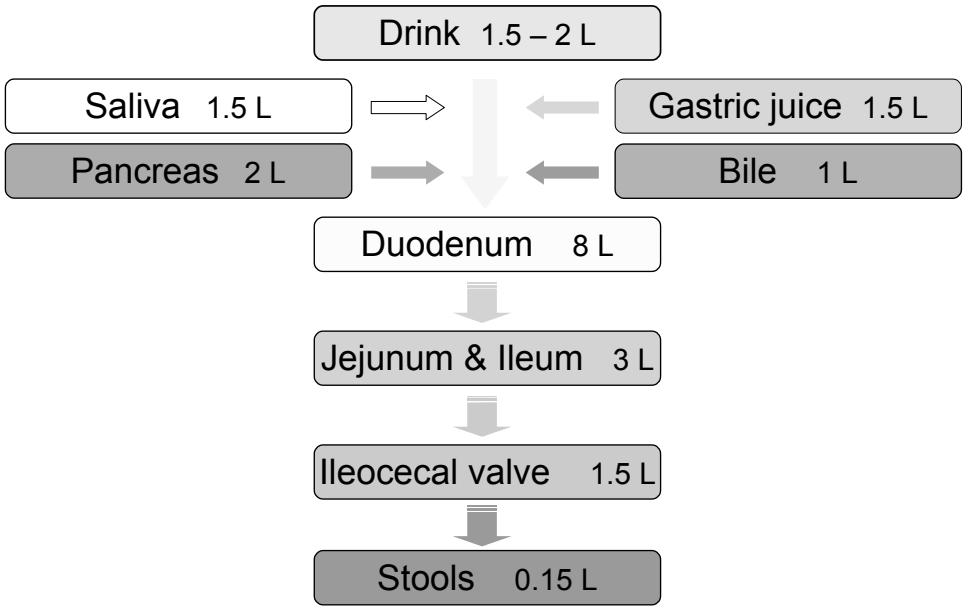


Fig. 1.3: *Flux of fluid across the gastrointestinal tract.*

Table 1.4: Approximate electrolyte content of gastrointestinal secretions.
Modified from (Allison 1996).

Secretion	**Na^+ (mmol/L)**	**K^+ (mmol/L)**	**Cl^- (mmol/L)**
Saliva	44	20	
Gastric	70-120	10	100
Bile	140	5	100
Pancreas	140	5	75
Small intestine	110-120	5-10	105
Diarrhoea (adult)	120	15	90

1.2 Fluid and electrolyte balance: Effects of starvation and injury

Life began in the sea and the intracellular environment of early life forms was isotonic with the external environment, as these unicellular organisms had no means of regulating the internal osmotic pressure (Thompson 1968). As life evolved, organisms became more complex and left the marine environment. John Gamble summarised this beautifully when he wrote, "Before our extremely remote ancestors could come ashore to enjoy their Eocene Eden or their Palaeozoic Palm Beach, it was necessary for them to establish an enclosed aqueous medium which would carry on the role of sea water".

This transition required four main areas of adaptation: nutrition, gas exchange, thermoregulation, and fluid and electrolyte balance. The development of complex interacting organ systems required osmotic and volume stability, the *milieu interieur* of Claude Bernard, which was achieved universally by balancing the intake of salt and water with excretion. As early terrestrial life forms had to cope mostly with nutrient, salt and water deficiencies rather than excess, the mechanisms to cope with salt and water lack or loss appear more efficient than those to cope with excess. Many diseases and pathological states are associated with or caused by derangements in the body water compartments which impair normal physiology. In clinical practice treatment should be directed towards maintaining normal balance and it is essential, therefore, to understand the effects of starvation and injury on both external and internal balance of water and electrolytes.

1.2.1 Effects on external balance

The response of the human body to starvation, stress and trauma is teleologically designed to preserve vital functions. John Hunter, in 1794, perceived that although these responses were designed to provide some advantage in the recovery process, when taken to the extreme, they could threaten survival, when he wrote, "Impressions are capable of producing or increasing natural actions and are then called stimuli, but they are likewise capable of producing too much action, as well as depraved, unnatural action, or what we commonly call diseased action" (Hunter 1794).

Sir David Cuthbertson, in his classic studies on tibial fractures (Cuthbertson 1930; Cuthbertson 1932), recognised two phases in the response to injury — the ebb phase and 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. This subsequently leads either to death or to the flow phase when metabolism is increased, protein catabolism is maximal and salt and water are retained. Moore 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 (Moore 1959).

As well as having the above response to injury, patients may also be exposed to starvation and weight loss. Famine and refeeding oedema have been described by several authors (Keys, Brozek *et al.* 1950; Shizgal 1981; Winick 1979). In a detailed study of the effects of semistarvation and refeeding in normal volunteers, Keys *et al*. (Keys, Brozek *et al.* 1950) showed that although the fat

and lean compartments of the body shrink, the ECF volume remains either at its prestarvation level or decreases very slightly (Fig. 1.4). In relative terms, therefore, the ECF volume occupies an increasing proportion of the body mass as starvation progresses. The degree of oedema may be related to access to sodium and water and may be exacerbated by refeeding (Figs. 1.4 and 1.5). Sodium 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.

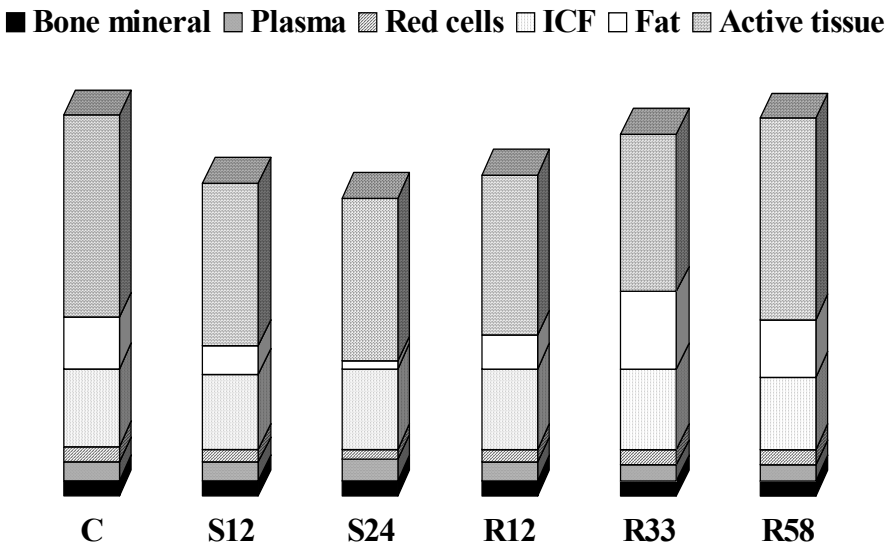


Fig 1.4: *Major body compartments, as body weight, in young men in the state of normal nutrition, semistarvation and subsequent rehabilitation. C = control (pre-starvation); S12 and S24 = 12 and 24 weeks of semistarvation; R12, R33 and R58=12, 33 and 58 weeks of rehabilitation.* Modified from (Keys, Brozek *et al*. 1950).

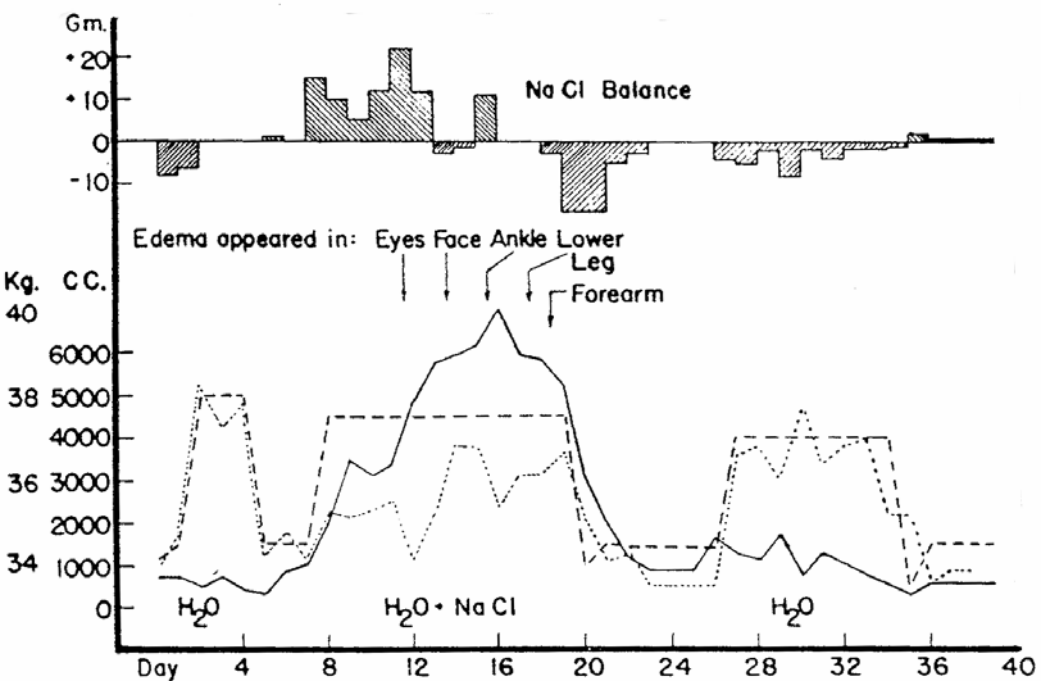


Fig. 1.5: *The influence of addition of water, and salt and water on the body weight of semi-starved subjects.* From (Keys, Brozek *et al*. 1950).

Both starvation and injury therefore lead to a state of sodium and water retention that is mediated by a number of complex neuroendocrine mechanisms in response to a perceived diminution in intravascular volume (Figs. 1.6 and 1.7) which will be discussed in some detail in section 1.2.3.

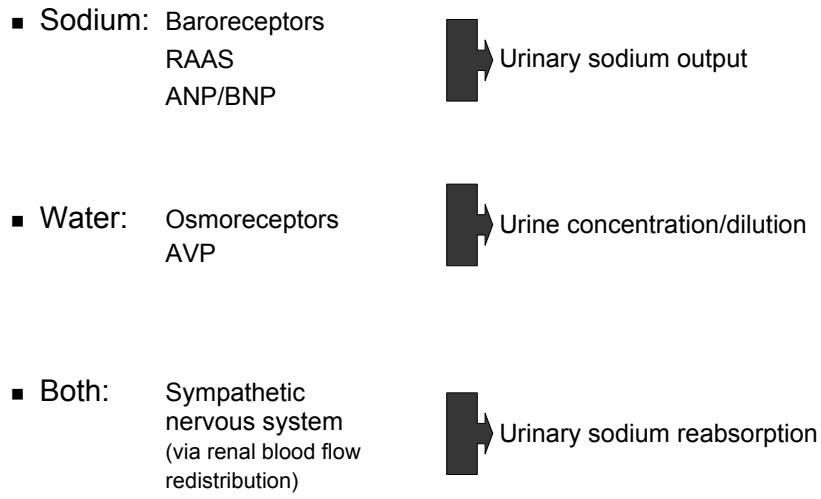


Fig. 1.6: *Pathways for response to changes in water and sodium in the ECF.*

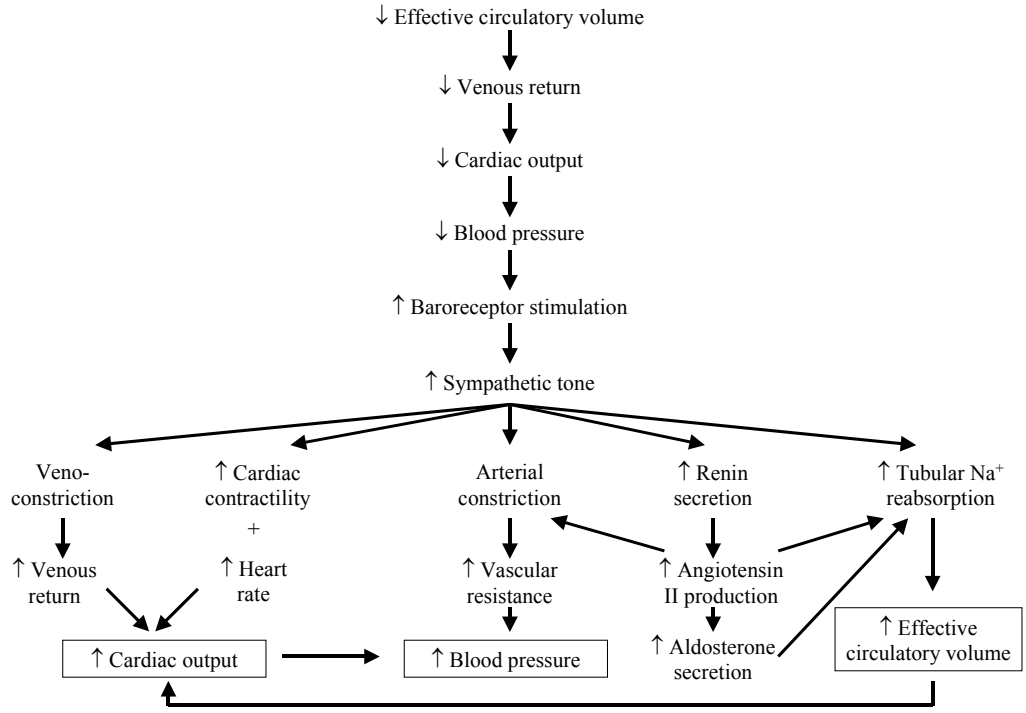


Fig. 1.7: *Haemodynamic responses to hypovolaemia.* Modified from (Rose and Post 2001).

Table 1.5: Properties of commonly prescribed crystalloids

	Plasma	0.9% NaCl	Hartmann's	0.18% NaCl /4% dextrose	5% dextrose
Na^+ (mmol/L)	135-145	154	131	31	0
Cl^- (mmol/L)	95-105	154	111	31	0
$[Na^+]$:$[Cl^-]$ ratio	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

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 1.5.

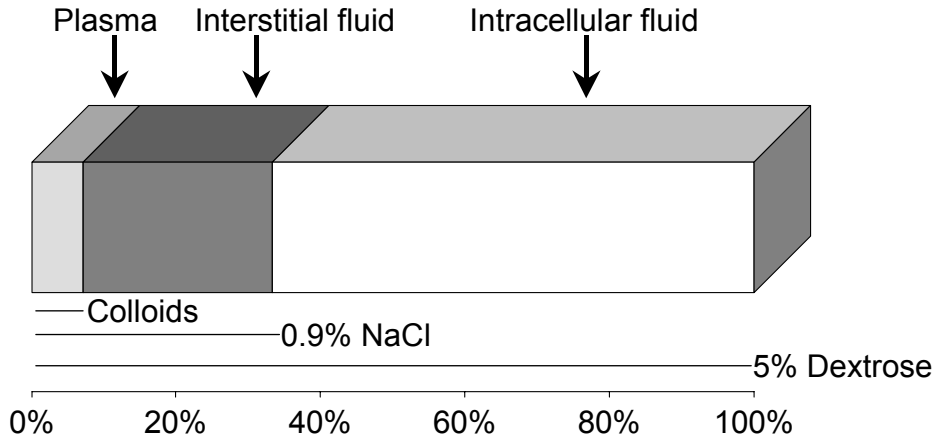


Fig. 1.8: *Distribution of infused fluids in the body water compartments*

The ability of a solution to expand the plasma volume is dependent on the volume of 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 blood volume expanding capacity (Fig. 1.8, Table 1.6). Isotonic sodium-containing crystalloids are distributed throughout the whole extracellular space (including the plasma) and textbook teaching classically suggests that such infusions expand the blood volume by 1/3rd the volume of crystalloid infused (Kaye and Grogono 2000). In practice, however the efficiency of these solutions to expand the plasma volume is only 20 and 25%, the remainder being sequestered in the interstitial space (Lamke

and Liljedahl 1976; Svensen and Hahn 1997). Although these solutions are used successfully for this purpose the price paid for adequate intravascular filling is overexpansion of the interstitial space and tissue oedema.

Table 1.6: Volume of infusion required to expand the plasma volume by 1 L

	Infused volume (mL)	Δ Interstitial volume (mL)	Δ Intracellular volume (mL)
5% albumin	1000		
25% albumin	250	-750	
5% dextrose	14000	+3700	+9300
Hartmann's solution/0.9% saline	4700	+3700	

1.2.2 Effects on internal balance

Internal balance concerns the relationship and equilibrium between the body fluid compartments. 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 due to a gradual loss of plasma into inflamed tissue or from the bowel or due to a generalised increase in capillary permeability.

As described in section 1.1, the integrity of the intravascular volume is maintained by the oncotic pressure of the plasma proteins and the integrity of the capillary membrane. In health, albumin escapes across the capillary membrane at the rate of 5-7 %/h, which is 10 times the rate of albumin synthesis. The albumin that escapes into the interstitial space is then returned into the intravascular

compartment via lymphatic channels into the thoracic duct and a steady state is thereby maintained (Fig. 1.9).

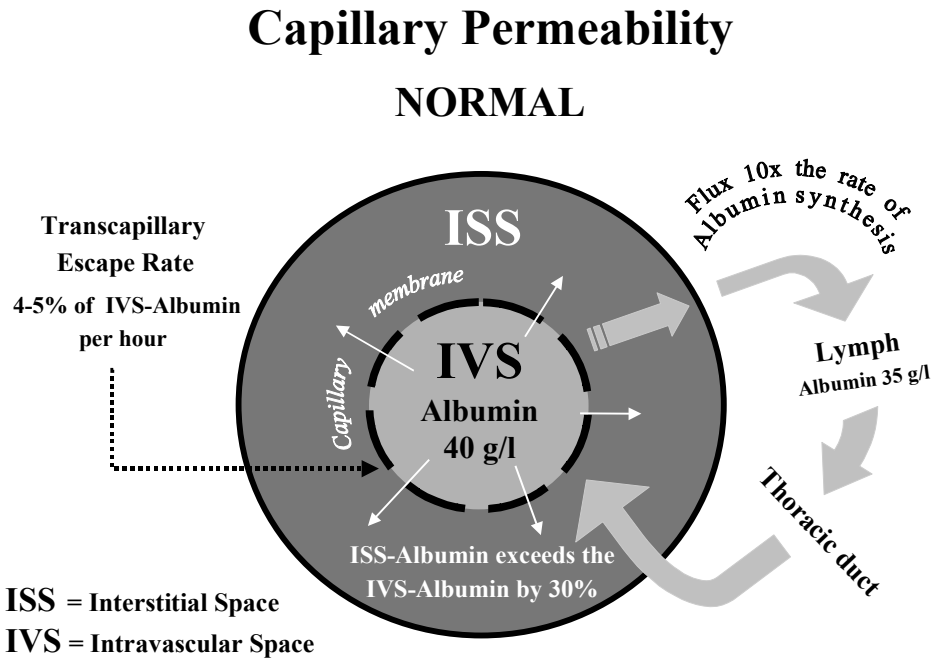


Fig. 1.9: *Capillary permeability and albumin flux in health*

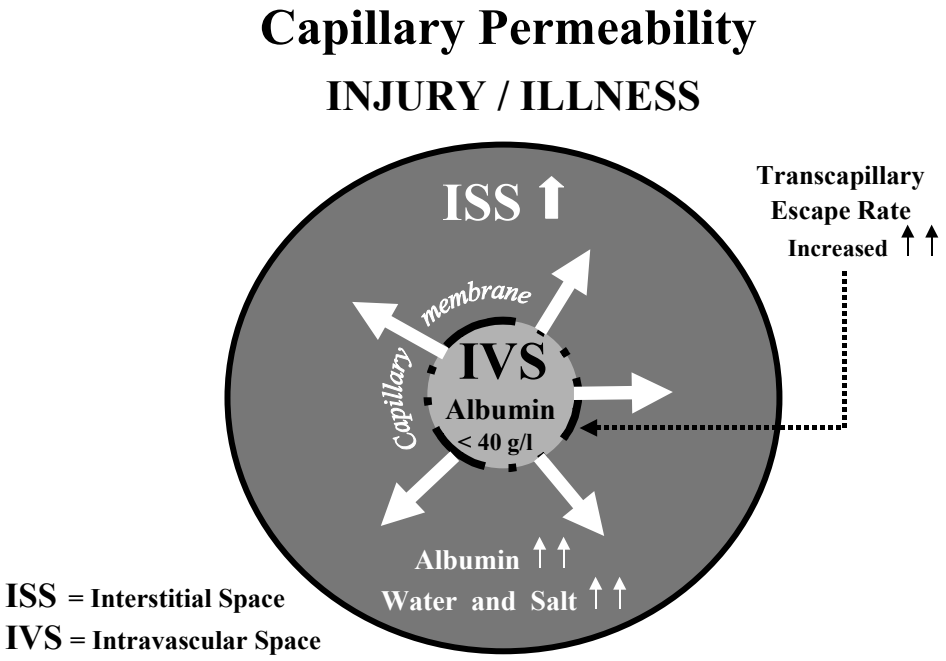


Fig. 1.10: *Capillary permeability and albumin flux in illness and after injury and stress.*

In the early postoperative phase and in patients with sepsis, the transcapillary escape of albumin may increase by three-fold (Fleck, Raines *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, therefore, accumulates in the interstitium. This results in an increased interstitial oncotic pressure causing salt and water to accumulate in the interstitium at the expense of the intravascular volume (Fig. 1.10).

As mentioned in Section 1.1.3, critical illness may also disturb the normal balance across the cell membrane (Allison 1996; Campbell, Green *et al.* 1998; Flear and Singh 1973; Flear and Singh 1982) resulting in a rise in intracellular sodium and reduced intracellular potassium and electrical potential across the cell membrane. This leads to the so called "sick cell syndrome" and ultimately to cell death. In support of this hypothesis, the data from Campbell *et al*. (Campbell, Green *et al.* 1998) on the measurements of glycogen, sodium, potassium and creatine in muscle cells of patients with multiple organ failure are shown in Table 1.7.

Table 1.7: Changes in muscle glycogen, sodium, potassium and creatine in patients with multiple organ failure. From (Campbell, Green *et al.* 1998).

	Glycogen (μmol/100μmol creatine)	**Sodium (μmol/100μmol creatine)**	**Potassium (μmol/100μmol creatine)**	**Total creatine (μmol/g dry weight)**
Patients: Median (Range)	164 (78-407)	201 (125-507)	274 (175-485)	95 (43-121)
Normal range	151-383	40-132	319-415	18-159

A knowledge of the electrolyte content of various gastrointestinal fluids (Table 1.4) at different levels of the gastrointestinal tract is also essential so that fluid prescriptions in patients with losses from fistulae and stomas may be adjusted accordingly.

1.2.3 Clinical relevance

As described above, the metabolic response to trauma also includes retention of water and sodium and loss of potassium. Pringle *et al*. (Pringle, Maunsell *et al.* 1905) demonstrated that both anaesthesia and surgery produced a reduction in urine volume. The use of intravenous hydration gained acceptance in surgical practice (Coller, Dick *et al.* 1936) when it was recognised that the intravenous infusion of saline to patients recovering from major surgery lessened both morbidity and mortality, mainly from renal failure. These authors recommended that patients should receive a litre of isotonic saline on the day of the operation, in addition to the replacement of abnormal losses with equivalent volumes of isotonic saline (Coller, Bartlett *et al.* 1938). However, they subsequently withdrew their guidelines because of the high incidence of postoperative oedema and electrolyte imbalance. They found that postoperative patients were less able to excrete a salt and water load than those who had not undergone surgery (Coller, Campbell *et al*. 1944), describing this as postoperative "salt intolerance" and suggesting that isotonic sodium containing solutions should be avoided on the day of the operation and during the subsequent two days. They recommended replacement of water losses with dextrose solutions over this period.

Other authors also found postoperative oedema to be common in patients receiving sodium containing intravenous fluids. A study published in 1942 suggested that the administration of sodium chloride and water was satisfactory therapy for patients in good or fair condition who had suffered acute gastrointestinal fluid losses (Power, Pedersen *et al.* 1942). However, these authors also found that patients with chronic illness and those in a poor general condition commonly accumulated the administered salt and water in the extravascular compartment and developed oedema.

Wilkinson *et al*. studied the effects of surgery on the excretion of sodium and chloride and found that the excretion of both ions was reduced for the first six days after surgery (Wilkinson, Billing *et al.* 1949). They initially thought that this may have been a result of lack of salt intake during the usual period of postoperative starvation. However, the findings persisted even when the salt intake was maintained by the intravenous or oral routes, leading to the conclusion that the decrease in sodium and chloride excretion is "an expression not merely of a failure of intake but also of some active process leading to a retention of sodium and chloride. A year later the same authors documented an increase in urinary potassium excretion in the early postoperative period in spite of a reduction in the potassium intake (Wilkinson, Billing *et al.* 1950). This resulted from the fact that potassium and protein exist in muscle in a ratio of 3:1 so that when protein is catabolised, potassium passes from the ICF to the ECF and is excreted by the kidneys (Allison 1996). Potassium is similarly linked to glycogen, being released during glycogenolysis and taken up during glycogen synthesis. These effects and the action of mineralocorticoids account for the increase in potassium excretion.

There is often no fall in serum potassium concentration despite a reduction in total body potassium since potassium is only lost in proportion to protein and passes continuously into the ECF (Allison 1996). Once refeeding commences, the cells begin to take up potassium as glycogen and protein are resynthesised, resulting in a sudden fall in the serum potassium concentration, revealing the underlying potassium deficit.

These findings of Wilkinson *et al*. were confirmed by Le Quesne and Lewis (Le Quesne and Lewis 1953) who attributed them to the fusion of three separate events — primary water retention, early sodium retention and late sodium retention. They found that primary water retention is independent of sodium 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 arginine vasopressin. Early sodium retention also occurs in the first 24 h and is largely adrenocortical in origin. Late sodium retention starts 24-48 h after surgery and lasts several days. The authors suggested that potassium deficiency may augment late sodium retention and concluded that all three phases combine to produce continuous postoperative sodium and water retention.

Postoperative patients may excrete only 100 mmol of sodium during the first four or five days after surgery without postoperative fluids (Clark 1977). In patients given intravenous saline, the amount of sodium retained is proportional to the quantity infused. Intakes of 300 and 1000 mmol sodium during the first four days after surgery were associated with retention of 200 and 600 mmol respectively (Clark 1977).

In further studies, Tindall and Clarke (Tindall and Clark 1981) observed the effects of two different postoperative fluid regimens on postoperative antidiuresis. The group of patients who received high sodium intakes (450 mmol sodium in 3000 mL water/day) did not develop hyponatraemia, but had marked sodium (+1023 mmol) and water retention (+3509 mL) by day 4. Patients who were given 3 L dextrose/day became hyponatraemic on day 1, but subsequently excreted the excess water with normalisation of the plasma sodium concentration.

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. Moore (Moore 1959) coined the terms "the sodium retention phase" and the "sodium diuresis phase of injury" to describe these two periods in the response to trauma or acute illness. At one time it was considered likely that the change in renal function could be related to an alteration in renal haemodynamics secondary to loss of fluid, but these are unlikely to be directly responsible for the continued retention of sodium and water which may persist for four or five days after uncomplicated surgery. Shires *et al*. (Shires, Brown *et al.* 1960; Shires, Williams *et al.* 1961) suggested that these changes were a response to a deficit in functional ECF postoperatively, although Roth *et al*. (Roth, Lax *et al.* 1969) later showed that Shires' data were based on a methodological error and that, in fact, most patients have an expanded ECF during the postoperative period. In contrast Moore (Moore 1959) suggested that sodium and water retention may be part of the obligatory reaction mediated directly by the hormonal response to injury itself. Increased secretion of AVP, mineralocorticoids and catecholamines are described even in the presence of positive fluid balance. The renin-angiotensin aldosterone system (RAAS) is also stimulated by injury.

Angiotensin is a powerful vasoconstrictor and promotes adrenal production of aldosterone, which in turn enhances sodium conservation by the kidneys and the gastrointestinal tract (Dick, Dasta *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.

Although these responses occur despite salt and water excess, they are exacerbated by intravascular hypovolaemia in cases of blood or plasma loss. In the severely injured and critically ill, with a major inflammatory response there is leucocyte activation and increased microvascular permeability (Ballmer-Weber, Dummer *et al.* 1995; Fleck, Raines *et al.* 1985; Plante, Chakir *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 response may be protective in that 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 sodium containing crystalloids to maintain intravascular volume and oxygen delivery to the cells, although, as described above, artificial colloids allow the use of lower volumes. Resuscitation is therefore achieved, but at the expense of overexpansion of the interstitial space (Table 1.8). 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 balance. Moore and Shires (Moore and 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, according to them, can never be achieved by inundation.

Table 1.8: Mechanisms of sodium and water retention in the critically ill and its associated complications. Modified from (Gosling 1999).

Mechanism	Clinical Complication
Increased capillary permeability Iatrogenic positive fluid balance Vasopressin release	Hypovolaemia due to protein and water leak Interstitial and pulmonary oedema Fluid retention
Iatrogenic sodium overload Hyperaldosteronism Suppression of atrial natriuretic peptide release	Hypernatraemia develops with fluid restriction and/or increased insensible losses Fluid retention
Reduced cardiac output	Interstitial and pulmonary oedema Fluid retention
Compromised renal concentrating ability	Urea and sodium retention Fluid retention

.

The average ECF overload after the first two days of resuscitation of patients with sepsis has been shown to be in excess of 12 L and it takes about three weeks to mobilise this excess (Plank, Connolly *et al.* 1998; Plank and Hill 2000). The association of increased capillary permeability and profound positive fluid balance with multi-organ failure is being recognised (Alsous, Khamiees *et al.* 2000; Arieff 1999; Gosling 1999; Plante, Chakir *et al.* 1995) and attempts to limit interstitial oedema have shown benefit (Alsous, Khamiees *et al.* 2000; Mitchell, Schuller *et al.* 1992).

1.3 Fluid and electrolyte prescriptions: Training and practice

Fluid and electrolytes are the most often prescribed substances in hospital practice and 0.9% (w/v) sodium chloride (NaCl) solution has been the mainstay of intravenous fluid therapy ever since Thomas Latta reported that intravenous saline infusions saved cholera victims from almost certain death (Latta 1832).

Stoneham and Hill (Stoneham and Hill 1997) conducted a survey of postoperative fluid therapy over a four-week period and found that 0.9% saline was the most often prescribed fluid. They also emphasised that there was a wide variability in the prescriptions with patients receiving a median of 3000 mL water and 242 mmol sodium per day. Fluid balance charts were incomplete in 42% of patients and only 37% of patients received potassium supplements. The tendency to over prescribe saline is not a new phenomenon, and dates back to the days when fluid replacement was achieved by rectal infusions, as evidenced by Evans' statement from 1911: "One cannot fail to be impressed with the danger…(of) the utter recklessness with which salt solution is frequently prescribed, particularly in the postoperative period…" (Evans 1911). Very little has changed over the years. Rhoads made the following comment in 1957, "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." (Rhoads 1957) and three decades later, these sentiments were echoed by Veech, "The use of fluid and electrolyte therapy has become such a familiar part of medicine that it is rarely scrutinised." (Veech 1986). The 1999 report of the UK National Confidential Enquiry into Perioperative Deaths (Callum, Gray *et al.* 1999) has emphasised that fluid imbalance leads to serious postoperative

morbidity and mortality, and estimated that 20% of the patients studied had either poor documentation of fluid balance or unrecognised/untreated fluid imbalance. It was suggested that some doctors and nurses lack awareness of the central role of good fluid management. Recommendations included 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.

1.4 Consequences of salt and water excess

0.9% saline is constituted by dissolving 9 g NaCl in 1 L 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 mole (i.e. 58.5 g NaCl) per litre of water. So, "normal" saline is, in fact, 1/6.5 normal saline. Although the solution is described as isotonic, its osmolality, at 308 mOsm/kg, is slightly higher than that of plasma. Moreover, each litre of the solution contains 154 mmol of sodium and chloride, which exceeds both the sodium (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 $[Na^+]$:$[Cl^-]$ in human plasma is 1.38, while it is 1.0 in normal saline (Veech 1986). It has been suggested that the low $[Na^+]$:$[Cl^-]$ ratio 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 may be because the permeation of the chloride ion 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 may, to some extent, account for the decrease in morbidity in infants treated for diarrhoea when Hartmann replaced some of the chloride in normal saline with lactate (Hartmann 1934).

The toxicity of large amounts of saline was recognised when proctoclysis was used as a route for fluid replacement and Trout (Trout 1913) wrote, "It is true that sodium chloride is the least toxic of the group of similar metal chlorides, but even at that it 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, it has long been believed that retention of as much as 600 mmol of sodium in the postoperative 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-expansible capsule, thereby slowing micovascular perfusion, increasing arterio-venous shunting and reducing lymphatic drainage, all of which facilitate further oedema formation (Stone and Fulenwider 1977).

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

Starker *et al*. (Starker, Lasala *et al.* 1983) 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% postoperative complication rate compared to 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*. (Gil, Franch *et al.* 1997) compared a group of patients receiving a standard feed containing 70% of non-protein energy as glucose, 140 mmol of sodium/day and 45 mL water/kg/day with a group receiving a modified feed containing 70% of non-protein energy as fat, no sodium and 30 mL water/kg/day. Weight gain with positive sodium and water balance and lowering of serum albumin concentration were noted in the standard group while a negative sodium and water balance was noted in the modified group. Four patients in the latter group developed prerenal failure because of insufficient fluid intake, but after excluding these, there was a significant reduction in overall complications and postoperative stay in the modified group.

Other attempts to limit interstitial oedema have also been beneficial. Mitchell *et al.* (Mitchell, Schuller *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) and found that the latter group showed less than half the cumulative fluid balance, had reduced interstitial oedema and spent significantly fewer days on the ventilator and in the intensive care unit.

The records of 36 patients admitted to the intensive care unit with septic shock, excluding those who needed dialysis, were reviewed and it was found that while all of 11 patients who achieved a negative fluid balance of >500 mL on one or more of the first three days of admission survived, only 5 of 25 patients who failed to achieve this state of negative fluid balance by the third day of treatment survived (Alsous, Khamiees *et al.* 2000). The authors concluded that at least one day of net negative fluid balance on the first three days of treatment strongly predicted survival.

Postoperative mobility may also be impaired by oedema of the limbs, along with susceptibility to pulmonary oedema, as shown by Guyton (Guyton 1959) who 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 postoperative pulmonary oedema is more likely within the initial 36 h when net fluid retention exceeds 67 mL/kg/day (Arieff 1999). Increased postoperative morbidity and prolonged hospital stay in patients receiving perioperative salt and water excess have also been reported in a recent audit of a homogeneous group of patients undergoing colorectal resections (Frost, Wakefield *et al.* 2001).

Although some of these studies are retrospective and others have small numbers of subjects, they show that salt and water excess is not without consequence and suggest that more attention should be paid to sodium and water replacement in postoperative and critically ill patients if clinical outcomes are to be improved.

1.5 Fluid balance and gastrointestinal function

There are few studies on the effects of perioperative 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.* (Mecray, Barden *et al.* 1937) 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 0.9% sodium chloride equal to the amount of blood withdrawn on each occasion. None of these animals underwent surgery and eight survived more than a month. Mean gastric emptying time in the survivors, as measured by fluoroscopic observation of the transit of a barium meal, was inversely proportional to the serum protein concentration (Fig. 1.11).

The authors then studied three dogs subjected to a pylorectomy after having been rendered hypoproteinaemic. Gastric emptying time was prolonged soon after the operation when the serum protein concentration was low and progressively shortened as the serum protein concentration was restored to normal by a combination of a high protein diet and fluid restriction (Fig. 1.12). 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 days, subsequent to which an infusion of 800 mL 0.9% sodium chloride resulted in a fall in serum protein concentration and retardation of gastric emptying (Fig. 1.13).

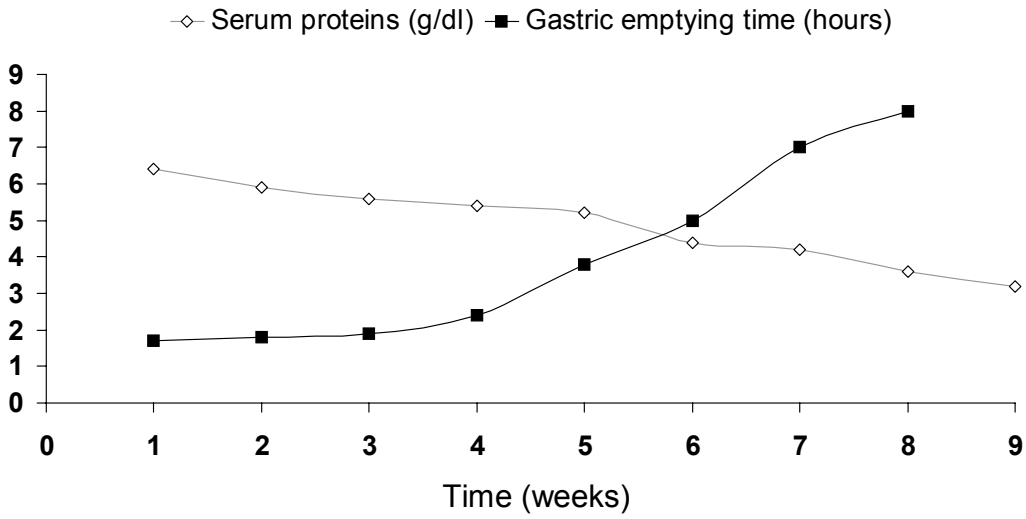


Fig. 1.11: *Inverse relationship between serum protein concentration and gastric emptying time in a group of eight unoperated dogs rendered hypoproteinaemic by a combination of a low protein diet, repeated plasmapheresis and infusions of 0.9% sodium chloride.* Redrawn from (Mecray, Barden *et al.* 1937).

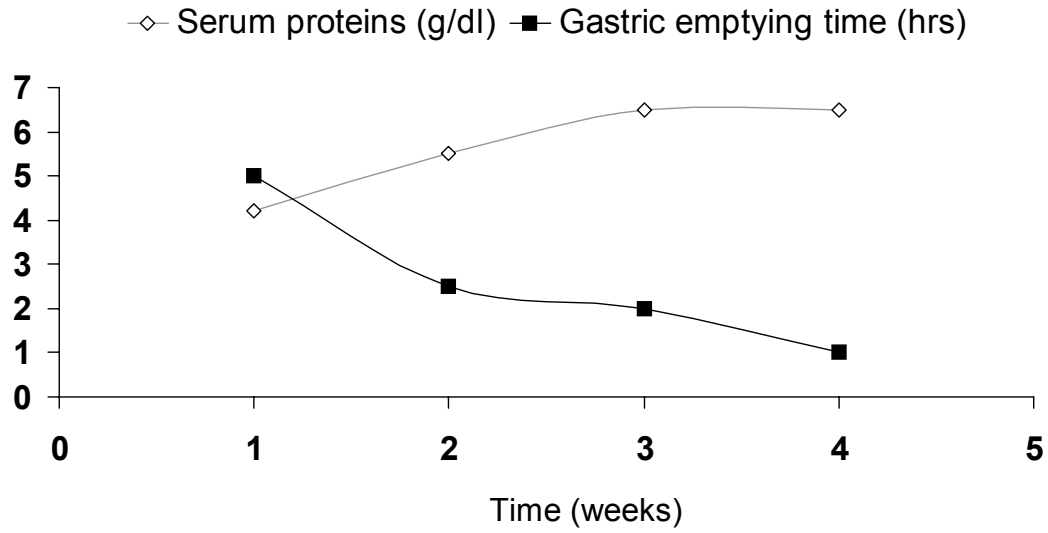


Fig. 1.12: *Return of gastric emptying time to normal as serum protein concentration was restored to normal postoperatively by a combination of a high protein diet and fluid restriction.* Redrawn from (Mecray, Barden *et al*. 1937).

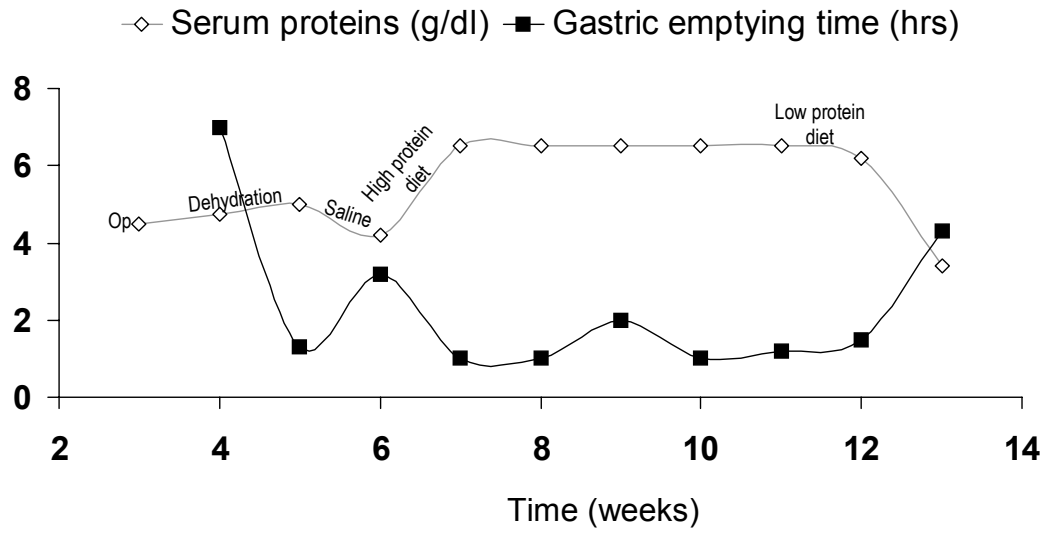


Fig. 1.13: *Effect of dehydration, saline infusion and high and low protein diets on serum protein concentration and gastric emptying time.* Redrawn from (Mecray, Barden *et al.* 1937).

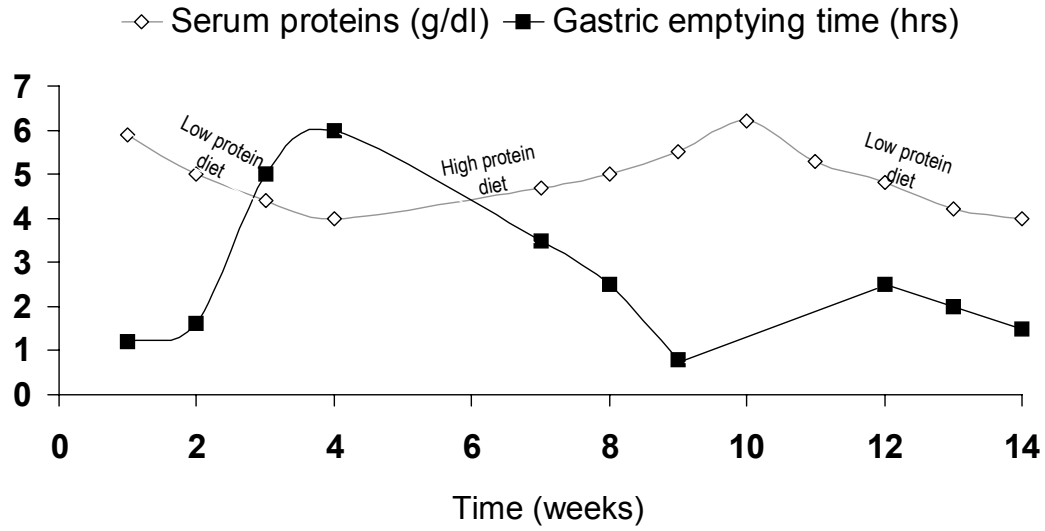


Fig. 1.14: *Changes in serum protein concentration and gastric emptying time with protein content of diet in two dogs subjected to a polya gastrectomy one year previously. The low protein diet was combined with plasmapheresis and infusions of 0.9% sodium chloride.* Redrawn from (Mecray, Barden *et al.* 1937).

Finally, the authors were able to confirm the inverse relationship between serum protein concentration and gastric emptying time over several weeks in two dogs subjected to a polya gastrectomy a 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 0.9% sodium chloride (Fig. 1.14).

Mecray *et al*. (Mecray, Barden *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 was 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 significant quantities of 0.9% sodium chloride infusions at varying stages of the studies and it is impossible to determine whether these effects are due to fluid gain, hypoalbuminaemia or both, since the two are inseparable.

A year later, in 1938, the same group of workers, used a similar model to study the effects of serum protein concentration on small intestinal motility (Barden, Thompson *et al.* 1938). The authors were, once again, able to demonstrate an inverse relationship between both gastric emptying time and small bowel transit, further strengthening their hypothesis. These findings were subsequently reviewed by Ravdin who recommended that during the period of impaired gastric emptying the administration of fluid and salt must be carefully controlled (Ravdin 1938). He opined, “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 postoperatively was related to hypoalbuminaemia led Woods and Kelly (Woods and Kelley 1993) to test the hypothesis that raising the serum albumin concentration to >35 g/L with albumin infusions would result in shortening of the duration of postoperative ileus. They selected patients undergoing elective repair of abdominal aortic aneurysms or aortoiliac or aortofemoral bypass grafts and randomised them either to receive or not to receive postoperative 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. Duration of ileus was defined as the time taken to first pass flatus or stool (or the postoperative day on which the patient was able to tolerate an oral intake. Postoperative hospital stay and complications were also recorded. Of the 83 patients identified, 69 were randomised to either receive albumin replacement (n=37) or no albumin replacement (n=32). Although serial serum albumin concentrations were significantly higher in the albumin replacement group, the authors were not able to demonstrate a significant difference in either the duration of ileus (albumin 4.06 *vs*. no albumin 4.16 days) or the time to resume an oral intake (4.0 *vs*. 3.75 days). Postoperative hospital stay and complication rates were also similar in the two groups.

These authors (Woods and Kelley 1993), however, did not record the fluid balance status of these patients and a similar degree of hydration (or overhydration) in the two groups could explain the almost identical results when

the endpoints were compared. If patients in both groups were infused with similar volumes of crystalloids, the albumin group ran the risk of a greater expansion of intravascular volume (Lucas, Weaver *et al.* 1978), a factor that could explain the lack of difference in the end points. This lends credence to the theory that salt and water balance and not the serum albumin concentration *per se* is a determinant of recovery from postoperative ileus.

The critically ill are another group of patients 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*. (Heyland, Tougas *et al.* 1996) were able to demonstrate, using the paracetamol absorption test, that gastric emptying time was significantly prolonged in a group of 72 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, Woolf *et al.* 2001), and both respiratory and metabolic acidosis have been associated with impaired gastric motility in pigs (Tournadre, Allaouchiche *et al.* 2000).

1.6 Hypoalbuminaemia: Causes and treatment

Albumin is the most abundant protein in plasma and within the intravascular space it provides up to 75% of oncotic pressure. Compared to other plasma proteins, albumin is a relatively small molecule with a radius of 7.5 nm and a molecular weight of about 69 kDa. The contribution of albumin to the oncotic pressure is greater than anticipated because of the Gibb-Donnan equilibrium which predicts that a difference in the concentration of large charged molecules such as albumin on either side of a semipermeable membrane prevents the migration of small diffusible ions. Oncotic pressure is an important determinant of the distribution of ECF between the intravascular and extravascular compartments and the Starling forces involved have been discussed in Section 1.1.1.

Albumin is synthesised in the liver and the average synthesis rate is 12-25 g/day. Albumin synthesis is not sensitive to the serum albumin concentration *per se*, but to the colloid oncotic pressure near the synthetic site, i. e., the hepatocyte (Rothschild, Oratz *et al.* 1972). In health the plasma contains about 140 g albumin and the interstices about 165 g (Lucas 2001). Under normal circumstances, albumin does not freely distribute within the interstitial space and this distribution is modified by the state of hydration of the interstitial hyaluron glycosaminoglycan and collagen gel matrix (Mullins and Bell 1982). The physical space occupied by the interstitial matrix is partially excluded for albumin distribution, and the state of hydration of this matrix is proportional to the space available for the distribution of albumin within its molecular structure (Fig. 10.15) (Sitges-Serra and Franch-Arcas 1998). Since hyaluron is responsible for part of

the albumin exclusion in the interstitial matrix, it is possible that the washout of the interstitial hyaluron contributes to the increase in interstitial space available for albumin (Franch-Arcas 2001). Each hour about 10 g of albumin leaves the plasma through the capillary membrane, enters the interstitial space and returns back to the plasma via the lymphatic channels. This phenomenon has been discussed in detail in Section 1.2.2.

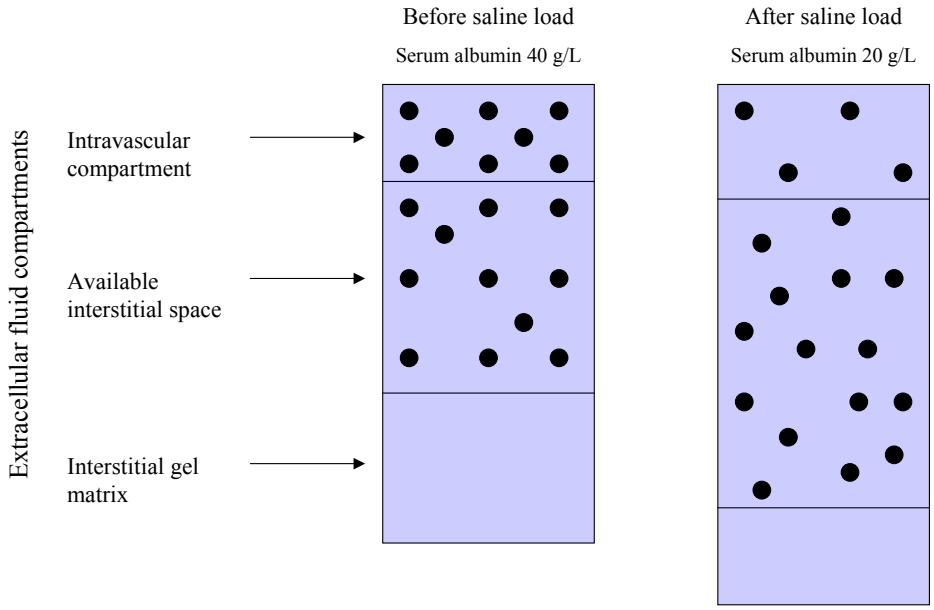


Fig. 10.15: *Diagrammatic model showing how an increase in ECW after acute saline infusion produces a decrease in serum albumin concentration b a distribution-related mechanism. The excluded interstitium represents the glycosaminoglycan and collagen interstitial gel matrix and the dots represent units of albumin mass.* Modified from (Sitges-Serra and Franch-Arcas 1998).

In hypoalbuminaemic states, the decreased plasma oncotic pressure disturbs the equilibrium between plasma and interstitial fluid with the result that there is a decrease in the movement of the interstitial fluid back into the blood at the venular end of the capillaries. The accumulation of interstitial fluid is seen clinically as oedema. The relative decrease in plasma volume results in a fall in

renal blood flow. This stimulates the secretion of renin, and hence of aldosterone through the formation of angiotensin (secondary aldosteronism). The results is sodium retention and an increase in ECF volume which further potentiates the oedema.

Albumin is a high capacity, low affinity transport protein for many substances, such as thyroid hormones, calcium and fatty acids. Albumin binds unconjugated bilirubin and hypoalbuminaemia increases the risk of kernicterus in infants with unconjugated hyperbilirubinaemia. Salicylates, which displace bilirubin from albumin, can have a similar effect. Many drugs are bound to albumin in the blood stream and a decrease in albumin concentration can have import ant pharmacokinetic consequences, for example, increasing the concentration of free drug and thus the risk of toxicity.

Table 1.9: Causes of hypoalbuminaemia

Decreased synthesis
Malnutrition
Malabsorption
Liver disease
Increased volume of distribution
Overhydration
Increased capillary permeability
Sepsis
Hypoxia
Trauma
Increased excretion/degradation
Nephrotic syndrome
Protein-losing enteropathy
Burns
Haemorrhage
Catabolic states
Sepsis
Fever
Trauma
Malignant disease

Hypoalbuminaemia is a result of a number of influences during the natural history of disease (Table 1.9). It is, therefore, a pathophysiological marker and not a disease entity for which there is any specific treatment. Indeed those with congenital analbuminaemia may be symptom free and remain in perfect health (Baldo-Enzi, Baiocchi *et al.* 1987; Russi and Weigand 1983).

Hypoalbuminaemia is not a specific nutritional marker, since it is possible to die of starvation with a normal serum albumin. On the other hand, if disease is present, the serum albumin concentration falls in proportion to the severity and time span of that disease. It is not surprising, therefore, that there is a good correlation between a low serum albumin and poorer outcome (Gibbs, Cull *et al.* 1999), as shown in many of the so-called 'predictive nutritional indices' (Clark and Karatzas 1988; De Jong, Wesdorp *et al.* 1985; Ingenbleek and Carpentier 1985; Mullen, Buzby *et al.* 1980). This does not imply that simply raising the serum albumin concentration by albumin infusion will improve outcome. Indeed the opposite may be true (1998; Boldt 2000). Addressing the causes of and associations with hypoalbuminaemia is more logical and successful. The treatment of hypoalbuminaemia should be considered in relation to its three main causes, i. e. inflammation with redistribution, dilution by crystalloids and changes in metabolism; along with the problem of its association with a low plasma volume in the post-acute phase of illness.

1.6.1 Inflammation — albumin distribution

In health, there is a continual flux of albumin which leaks slowly from the intravascular space across the capillary membrane and is returned via the

lymphatic system (Fleck 1988). This flux is ten times the rate of albumin synthesis, and the total intravascular albumin is exchanged every one to two days. The cytokine response to injury, infection, inflammation or cancer increases vascular permeability and accelerates the escape rate of albumin from the circulation (Ballmer, Ochsenbein *et al.* 1994; Ballmer-Weber, Dummer *et al.* 1995; Fleck, Raines *et al.* 1985), causing not only local swelling, wheal and flare, but also a generalised redistribution of albumin from the circulation to the interstitial space. These changes also contribute to the drop in circulating volume and the shock associated with acute trauma and sepsis. They also explain why acute changes in albumin distribution have a far more rapid and profound effect on its concentration than any alteration in synthesis or catabolism.

It has been argued, not unreasonably, that the use of albumin solutions for the treatment of circulatory hypovolaemia in acute illness is unjustified because of its rapid leakage from the circulation. Plasma substitutes, which normally have a shorter half-life than albumin in the circulation, may have a longer half in acute illness and injury (Salmon and Mythen 1993), and are generally to be preferred for volume expansion in the acute phase. Alternatives are crystalloid or a combination of crystalloid and colloid. The relative effectiveness of these used separately or in combination is much debated (1998; Allison and Lobo 2000; Choi, Yip *et al.* 1999; Pulimood and Park 2000; Schierhout and Roberts 1998; Webb 1999) and outside the scope of this review. The primary concern is to maintain the intravascular volume and preserve the circulation, rather than to address the albumin concentration (Hinton, Allison *et al.* 1973). On the other hand, profound falls in albumin concentration, as Guyton showed (Guyton 1959),

may predispose to systemic and pulmonary oedema unless excessive administration of salt and water is avoided. Albumin solutions are still in widespread use in paediatrics for the treatment of conditions such as shock in meningococcal septicaemia and have proved effective in some adult conditions, including spontaneous bacterial peritonitis associated with liver cirrhosis (Sort, Navasa *et al.* 1999). This area, therefore, requires much more careful thought and study before dogmatic conclusions can be reached.

Treatment of redistributional hypoalbuminaemia in acute inflammatory conditions or in malignant disease should therefore be directed to its cause, i. e. draining the abscess, treating with antibiotics, removing the cancer, or using anti-inflammatory drugs. Once the cause has been resolved, the albumin concentration will return to normal with time and adequate nutrition.

1.6.2 Dilution

Both starvation and the response to illness or injury are associated not only with a reduction in cell mass, but also with a relative expansion of the extracellular fluid volume and an inability to excrete an excess salt and water load (Keys, Brozek *et al.* 1950; Moore 1959; Wilkinson, Billing *et al.* 1949). The return of the ability to excrete excess sodium and water heralds recovery, leading Moore to coin the terms ‘the sodium retention phase’ and ‘the sodium diuresis phase’ of injury (Moore 1959). In those patients with complications, however, spontaneous sodium diuresis is delayed and oedema persists. Administered crystalloids, therefore, cause a cumulative retention of sodium and water, which further dilutes the serum albumin. A low serum albumin concentration, therefore,

may not only be a result of redistribution due to inflammation, but also of dilution from fluid infusions (Marik 1993; Mullins and Garrison 1989; Sitges-Serra and Franch-Arcas 1998).

It is often assumed erroneously that salt and water retention with oedema is innocuous and that the patients soon diurese any excess which has been administered. There is increasing evidence, however, to suggest that excess salt and water is associated with inhibition of gastrointestinal function, pulmonary complications, immobility and prolonged recovery (Arieff 1999; Gil, Franch *et al.* 1997; Mecray, Barden *et al.* 1937; Starker, Lasala *et al.* 1983). Starker and colleagues (Starker, Lasala *et al.* 1983) showed that preoperative administration of intravenous feeds in malnourished individuals, could result in salt and water retention and hypoalbuminaemia, which were associated with increased postoperative complications. On the other hand, in those patients with a return of the ability to excrete salt and water, accompanied by a rise in serum albumin, the postoperative complications were fewer. As Sitges-Serra's group has shown, prevention is better than cure in this situation, since the use of low volume/low sodium feeds under these conditions avoids fluid overload, dilution of albumin and postoperative complications (Franch, Guirao *et al.* 1992; Gil, Franch *et al.* 1997; Guirao, Franch *et al.* 1994; Sitges-Serra 1999).

These considerations emphasise that, in all patients referred for nutritional support, as much care should be taken over fluid balance assessment and the sodium and water content of the feed as other aspects of nutrition. They also highlight the paradox that in the immediate post-acute phase of illness clinical and

functional improvement is associated with weight loss as the accumulated excess of salt and water is cleared.

1.6.3 Post-acute plasma hypovolaemia

Although for resuscitation from shock in the acute stage of most illnesses, albumin infusions are unnecessary and expensive, there may well be a few situations where such infusions are justified, particularly in paediatric practice, although more detailed studies in specific groups of patients need to be undertaken before clear conclusions can be reached.

In the post-acute phase, that is 1-2 weeks after the initial event, the situation may be different. The Nutrition Team at University Hospital, Nottingham is frequently referred patients, for nutritional support, with persistent oedema from previously administered sodium and water. In some cases the jugular venous pressure is elevated or normal and diuretics produce a satisfactory response. In others, particularly those with additional serous losses from wounds or fistulae, the interstitial overload is accompanied by a low jugular venous pressure assessed at the bedside. Since sodium and water diuresis is impossible in the presence of renal underperfusion and assuming that TER_{alb} has returned to normal by this stage, the logical treatment of this situation is 20% salt-poor albumin since further diuretics alone are either ineffective or exacerbate the plasma hypovolaemia. Secondly, salt-poor albumin does not add substantially to the sodium load (in contrast to plasma substitutes) and thirdly it has a longer half life than plasma substitutes (Salmon and Mythen 1993). The return of TER_{alb} to normal at this stage is also supported by our finding that in order to obtain a

diuresis it is only necessary to administer two to four 100 mL doses of 20% salt-poor albumin in the first two days and none thereafter. The consequent diuresis, restored diuretic sensitivity and clearance of oedema suggests a useful therapeutic effect. The use of concentrated salt-poor albumin with or without diuretics in the post-acute period is illustrated in Fig. 1.16. Such infusions, however, must be monitored carefully, since inappropriate or excessive administration can be dangerous. Indeed at least one study (Lucas, Weaver *et al.* 1978) included in the Cochrane report (1998) may well have produced excess mortality, not because of the use of albumin *per se* but of the way it was used and the volume of fluid administered (Allison and Lobo 2000). It should be emphasised that we have used albumin infusions in this situation not to treat hypoalbuminaemia but to repair plasma hypovolaemia in the presence of an interstitial salt and water overload. There is no justification on the evidence, for using such infusions to treat the albumin concentration *per se*.

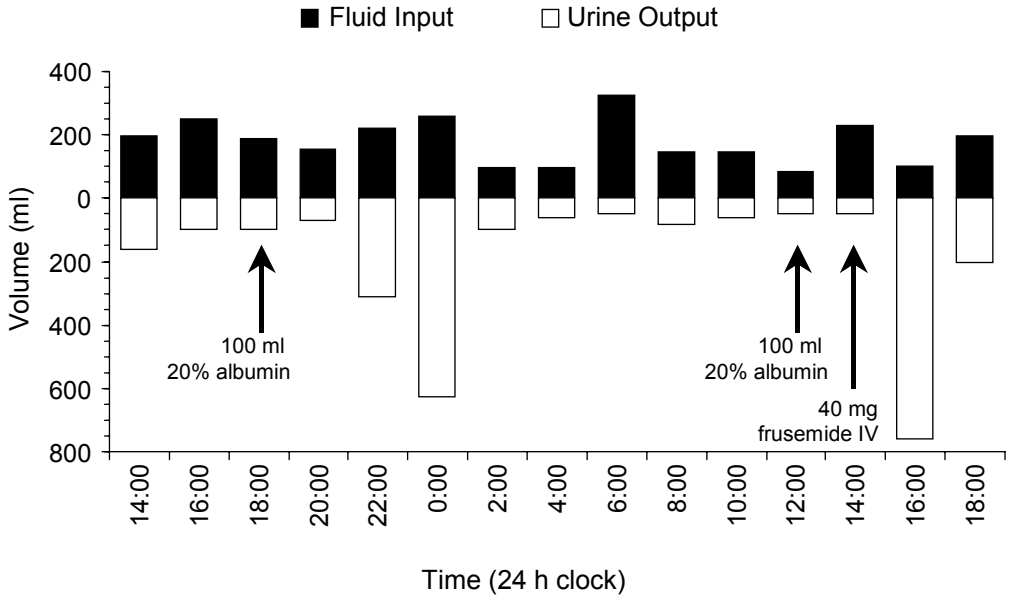


Fig. 1.16: *An illustrative example of the effects of concentrated salt-poor albumin with and without frusemide on urinary output in a patient with fluid overload in the post-acute phase. Fluid balance is charted at two hourly intervals over a period of 28 hours.*

1.6.4 Metabolic

Unless severe prior malnutrition is present, hypoalbuminaemia in the acute phase of illness has no nutritional or metabolic component. Indeed, albumin turnover may be increased, with acceleration of both synthesis and breakdown. Since albumin has a metabolic half-life of 18-20 days, one would expect any metabolic change to have a rather slow effect compared with changes brought about by dilution and redistribution.

In a study of fractured femur patients (Bastow, Rawlings et al. 1983), it has been shown that both well nourished and undernourished patients had a fall in serum albumin concentration acutely, associated with injury, surgery, and dilution, so that albumin concentration had no nutritional discriminatory value during the first few days. However, in the normally nourished or moderately undernourished patients the concentration returned spontaneously to normal over ten days, whereas, in the severely malnourished group such recovery was markedly delayed. Moreover, overnight supplementary nasogastric tube feeding in the latter group restored the recovery rate to that of the other two groups demonstrating clearly a nutritional component to this biochemical change. An isolated measurement of serum albumin concentration may, therefore, be of little value as a nutritional marker, although serial values may reveal a nutritional dimension.

The effect of changes in liver function is also an important consideration since this may be impaired not only in primary liver disease but also with sepsis or the complications of disease and its treatment. In this situation albumin synthesis will clearly be affected. External losses in the nephrotic syndrome, from

protein losing enteropathy or from wounds may also exceed the liver's synthetic capacity. In all these cases protein and energy intake should be optimised and the underlying disease addressed.

1.6.5 Other considerations

Since many drugs, substrates, minerals and hormones are bound to albumin, account must be taken of this factor in the presence of hypoalbuminaemia (Doweiko and Nompleggi 1991a). For example, the doses of warfarin, digoxin, NSAIDs, midazolam and thiopentone need to be reduced. Corrections to serum calcium and magnesium should also be made. The role of albumin as an antioxidant and a free radical scavenger are areas of continuing research.

1.6.6 Conclusions

In conclusion, there is no treatment for hypoalbuminaemia *per se*. Therapeutic options must be directed towards the cause of hypoalbuminaemia, avoiding or treating salt and water overload, instituting prompt medical and surgical treatment of inflammation and sepsis, and providing appropriate nutritional support to enhance recovery. In the presence of interstitial salt and water overload with plasma hypovolaemia in the post-acute phase of illness concentrated salt poor albumin may have therapeutic benefits. The interactions between hypoalbuminaemia and other therapeutic interventions must also be considered.

1.7 The effect of crystalloid infusions in normal subjects

A search through the medical literature reveals that there are few studies on the effects of intravenous crystalloids on the serum and urinary biochemistry of healthy, euvolaemic human subjects. An infusion of 2 L 0.9% saline over 2 h in high risk preoperative patients produced a fall in serum albumin concentration from 34 to 30 g/L) (Mullins and Garrison 1989) and a bolus infusion of 30 mL/kg of 0.9% saline in normal volunteers over 30 minutes has been shown to produce a maximum drop in haemoglobin and haematocrit at 1 h followed by a gradual return to baseline over 8 h (Grathwohl, Bruns *et al.* 1996). This was consistent with earlier work in which 0.9% saline 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/hr (Greenfield, Bessen *et al.* 1989). Haematocrit determined immediately after the bolus infusion decreased by from 4.5, 6.1 and 6.3 points from baseline in the 10, 20, and 30 mL/kg groups, respectively. Twenty minutes into the maintenance infusion, the haematocrit had risen by 1.5, 2.4 and 2.3 points from the post bolus values respectively. The authors also calculated that approximately 60% of infused saline, when delivered as a bolus, diffused from the intravascular space within 20 minutes of administration.

Studies using mathematical models to analyse volume kinetics of Ringer acetate solution in healthy volunteers 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 and Drobin 1998; Hahn and Svensen 1997; Svensen and Hahn 1997) 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 0.9% saline 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, Hildebrand *et al.* 1999). The authors also noted that Hartmann's solution produced small transient decreases in serum osmolality which were not seen after saline. Saline infusions were also associated with a persistent acidosis and delayed micturition. Singer *et al*. (Singer, Shore *et al.* 1987) also reported a slow excretion of saline after a 2 L intravenous load, only 29% having been excreted after 195 min.

In a prospective, randomized double-blind crossover study of 12 healthy male volunteers, Heller *et al*. (Heller, Crocco *et al.* 1996) attempted to determine which of three commonly used intravenous solutions was most effective in establishing urine flow. They rapidly infused 20 mL/kg of 5% dextrose, 5% dextrose-0.45% saline, or 0.45% saline immediately after voiding. They found that the total mean urine volume after 5% dextrose was 1181 mL, significantly greater than after the other two solutions (825 mL and 630 mL respectively), which did not differ between each other, suggesting, as one might expect, that 5% dextrose is more effective than sodium containing solutions in promoting rapid diuresis. These findings suggest, as one might expect, that the manner in which the body handles fluid loads is dependent on both the nature and volume of the infusion.

A comparison of changes in serum electrolyte concentrations and acid-base and haemodynamic status after rapid infusion of 2 L of either 0.9% saline Hartmann's solution in healthy volunteers has revealed that changes within the groups were small and statistically insignificant (Kamp-Jensen, Olesen *et al.* 1990).

Drummer *et al*. (Drummer, Gerzer *et al.* 1992) 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 L 0.9% saline over 25 min and after a 48-h control experiment. Urine flow and urinary electrolyte excretion rates were significantly increased during 2 days after the saline infusion. The largest increase in urinary fluid and electrolyte excretion was observed between 3 and 22 h postinfusion. These long-term changes were paralleled by altered water and sodium balances and also by elevated body weights that returned to baseline values with an approximate half-life of 7 h. The authors suggested that vasopressin, atrial natriuretic peptide, and catecholamines were unlikely to be of major importance for the renal response to this hypervolemic stimulus. The renin-aldosterone system was suppressed during 2 days postinfusion, which correlated with the effects of saline load on sodium excretion. However, the closest relation with Na excretion was observed for the kidney-derived member of the atrial natriuretic peptide family, urodilatin, which was considerably increased during the long-term period up to 22 h postinfusion. Thus, these data show that the human body in supine position requires approximately 2 days to restore normal sodium and water balance after an acute saline infusion and that urodilatin and the renin-aldosterone system might

participate in the long-term renal response to such an infusion and in the mediation of circadian urinary excretion rhythms.

Although these studies, add to our understanding of how the human body handles crystalloid loads in health there are still a number of areas which are unclear, suggesting the need for further studies on the physiological responses of crystalloid responses in normal subjects.

2. Methods

Though this be madness, yet there is method in't.

William Shakespeare,
Hamlet

The methods in this section include only those which have been used for more than one study. Methods which have been used in only one study have been described in the individual chapters.

2.1 Weight and height

Body weight was measured to the nearest 0.1 kg using calibrated Avery 3306ABV scales (Avery Berkel, Royston, UK). Height was measured to the nearest 0.01 m using calibrated wall-mounted measuring rules (Avery Berkel, Royston, UK).

2.2 Bioelectrical impedance analysis

Bioelectrical impedance analysis was performed with single (50kHz) and dual frequency (5 and 200kHz) devices (Bodystat 1500 and Bodystat Dualscan 2005 respectively, Bodystat Ltd., Isle of Man, UK) using tetrapolar distal limb electrodes. The subjects lay supine on a non-conducting surface, with limbs abducted to avoid current shunting. Adhesive aluminium foil electrodes were positioned in the middle of the dorsal surface of the hands and feet just proximal to the metacarpophalangeal and metatarsophalangeal joints; a second set of electrodes was positioned between the distal prominence of the radius and the ulnar styloid and between the medial and lateral malleoli at the ankle. An excitation current was applied to the distal electrodes and the voltage drop was detected by proximal electrodes. The devices use pre-programmed regression equations to determine TBW (Bodystat 1500 and Dualscan 2005) and ECW (Bodystat Dualscan 2005).

Equations for dual frequency bioelectrical impedance analysis

$$ECF(litres) = \left(\frac{0.178458 \times height^2}{impedance(5kHz)} \right) + (0.06895 \times weight) + 3.794$$

$$TBW(litres) = \left(\frac{0.24517 \times height^2}{impedance(200kHz)} \right) + (0.18782 \times weight) + 8.197$$

Equation for single frequency bioelectrical impedance analysis

$$TBW(litres) = \left(\frac{0.3963 \times height^2}{impedance(50kHz)} \right) + (0.143 \times weight) + 8.4$$

where height was measured in cm, weight in kg and impedance in Ω.

2.3 Gastric emptying time

It was initially planned to measure solid and liquid phase gastric emptying time using a dual isotope radiolabelled meal developed and validated in this hospital (Kong, Perkins *et al.* 1998). This meal consists of two 60g pancakes labelled with 3 MBq nonabsorbable $^{99}Tc^{m}$-ion exchange resin (Amberlite IRA 416, size 0.30-1.20 mm) and a 200 mL milkshake labelled with 0.5 MBq nonabsorbable ^{111}In-DTPA. However, it was found that the meal was too bulky for patients in the early postoperative period and the test meal had to be modified and revalidated. This is described in Chapter 5.

2.4 Haematological parameters

Haemoglobin and haematocrit were measured on a Sysmex SE 9500 Analyser (Sysmex UK Ltd., Milton Keynes, UK) using direct current hydrodynamic

focusing and cumulative pulse height detection. The CV for haemoglobin and haematocrit estimation was 1-1.5%.

2.5 Biochemical parameters

Serum and urinary osmolality were measured on a Fiske 2400 Osmometer (Vitech Scientific Ltd., Partridge Green, West Sussex, UK) using a freezing point depression method which has a coefficient of variance (CV) of 1.2%. A Vitros 950 analyser (Ortho Clinical Diagnostics, Amersham, UK) was used to measure serum sodium (CV 0.6%), potassium (CV 1.0%), chloride (CV 1.1%), bicarbonate (CV 4.0%), urea (CV 2.0%), albumin (CV 1.6%) and blood glucose (CV 1.2%). Urinary sodium (CV 1.5%) and potassium (CV 1.5%) were assayed on a Vitros 250 analyser (Ortho Clinical Diagnostics, Amersham, UK). Haematological parameters were measured on a Sysmex SE 9500 Analyser (Sysmex UK Ltd., Milton Keynes, UK) using direct current hydrodynamic focusing and cumulative pulse height detection. The CV for haemoglobin and haematocrit estimation was 1-1.5%. Urinary samples were tested with Combur^{5} Test® D sticks (Roche Diagnostics Ltd., Lewes, UK) for glucose content.

2.6 Ethics and consent

The Ethics Committee of University Hospital, Nottingham approved the study design for all studies involving patients. Volunteer studies were approved by the Ethics Committee of the University of Nottingham Medical School. A licence to administer radiopharmaceuticals was obtained from the Administration of Radioactive Substances Advisory Committee (Department of Health, UK) for

each study requiring the use of radioisotopes. The studies were carried out in accordance with the Declaration of Helsinki of the World Medical Association and informed written consent was obtained from patients and volunteers before enrolment.

2.7 Statistical analysis

Statistical analysis was performed using SPSS® for Windows™ Release 9.0 software (SPSS Inc., Chicago, USA), Confidence Interval Analysis software (BMJ Publishing, London, UK) and Epi Info 2000 software (http://www.cdc.gov/epiinfo). Graphs were created with GraphPad Prism 2 software (GraphPad Software Inc., San Diego, USA), SigmaPlot for Windows™ Version 4.00 (SPSS Inc., Chicago, USA) and Microsoft Powerpoint 2000 software (Microsoft Corporation). Individual statistical tests are listed in the methods section of each chapter. Differences were considered significant at $P<0.05$.

Clinical Studies

3. Changes in weight, fluid balance and serum albumin in patients referred for nutritional support

A chronic malady may develop in patients who collect water under their skin.
Celsus

3.1 Introduction

Both starvation and the response to injury or acute illness impair the ability of patients to excrete an excess salt and water load (Keys, Brozek *et al.* 1950; Moore 1959; Shizgal 1981). Wilkinson *et al*. (Wilkinson, Billing *et al.* 1949) found that chloride excretion was markedly reduced during the first six days following partial gastrectomy, when compared with the preoperative and later postoperative periods. They also demonstrated that the time of reduced chloride excretion corresponded with the catabolic phase described by Cuthbertson (Cuthbertson 1932). These changes were also confirmed by Moore (Moore 1959), who showed not only that sodium retention occurred during the flow phase of injury, but that the capacity to excrete an excess sodium load returned during recovery and convalescence. To describe these phenomena Moore coined the terms “the sodium retention” and “the sodium diuretic” phase of injury.

It is a common, but erroneous, assumption by doctors that moderate salt and water excess has no adverse effects. However, malnourished and acutely ill patients readily accumulate salt and water when given in excess, developing oedema and hypoalbuminaemia, which may impair gastrointestinal, respiratory and other functions. A fluid overload of as little as 2-3 L may be enough to produce oedema and a greater than 10-fold delay in gastric emptying time for example has been demonstrated in hypoproteinaemic dogs given saline (Mecray, Barden *et al.* 1937). Clinical observations (unpublished data) suggest that the return of gastrointestinal function is often delayed in oedematous postoperative patients and this may be corrected by diuretics. A higher incidence of postoperative complications, especially pulmonary, has also been observed in

patients with evidence of fluid overload (Gil, Franch *et al.* 1997; Starker, Lasala *et al.* 1983).

This study was undertaken to audit the fluid balance status of patients at the time of referral for nutritional support, to consider the implications of this for the salt and water content of feed prescriptions and to assess the changes in fluid balance and serum albumin concentration during nutritional support.

3.2 Methods

Daily weighing and regular biochemical measurements with recording on serial data charts have been part of the standard protocol of the Clinical Nutrition Unit (CNU) at University Hospital, Nottingham for many years. The systematic records of all patients receiving nutritional support for $\geq$10 days between January 1997 and September 1998 in the CNU were examined retrospectively. Clinical evidence of the presence of oedema was noted. Patients with oedema were managed using a low volume (2 L/day), low sodium (0-50 mmol/day) feed until oedema resolved or weight plateaued. Most patients received an average of 14 g nitrogen/day and 2000 non-protein Calories (8.36 MJ), including 1000 Calories (4.18 MJ) from fat (20% Intralipid) and 1000 Calories (4.18 MJ) from glucose. In some severe cases with oedema and a low jugular venous pressure as judged clinically, 20% salt-poor albumin was infused within the first 48 h to correct a plasma volume deficit. A diuretic was also given within the first 48 h to some oedematous patients with an elevated jugular venous pressure or in combination with albumin in those with a low jugular venous pressure. Non-oedematous patients were given a standard feed (2.5-3 L) with 80-120 mmol sodium/day to

achieve zero fluid and electrolyte balance. These patients received also received an average of 2000 non-protein Calories (8.36 MJ) and 14 g nitrogen/day. Patients who were fed enterally received similar amounts of water, sodium, energy substrates and nitrogen.

Body weight was recorded before commencement of nutritional support and daily thereafter. The lowest recorded weight after institution of nutritional support and the weight at the time of discharge from the CNU were noted. Serum albumin concentrations were recorded at the corresponding points.

Changes within the oedematous and non-oedematous groups were analysed for statistical significance using the *t*-paired test. The χ^2 test, Fisher's exact test, ANOVA (analysis of variance) and Mann-Whitney *U*-test were used to compare the results of the two groups. Pearson's coefficient of correlation was calculated. A sub-group analysis was performed on oedematous patients who received or did not receive albumin infusions.

3.3 Results

The 21 oedematous patients were well matched with the 23 non-oedematous patients for age, gender and type of artificial nutritional support (Table 3.1). Oedematous patients had a significantly greater body weight and lower serum albumin concentration on transfer to the CNU than non-oedematous patients (Table 3.1). Patients with oedema tended to have acute surgical conditions and complications such as sepsis that necessitated aggressive resuscitation and prolonged intensive care, while non-oedematous patients tended

to have chronic conditions such as gastrointestinal malignancy or Crohn's disease with nutritional depletion (Table 3.2).

Table 3.1: Patient profile at admission to the clinical nutrition unit

	Oedematous group (n=21)	Non-oedematous group (n=23)	*P* value (Test)
Age: Mean (SE) years	56.5 (3.7)	57.7 (3.4)	0.82 (ANOVA)
M:F ratio	11:10	10:13	0.55 (χ^2 test)
Enteral:parenteral nutrition ratio	3:18	7:16	0.28 (Fisher exact test)
Weight at admission: Mean (SE) kg	79.3 (2.9)	61.4 (4.0)	0.001 (ANOVA)
Serum albumin at admission: Mean (SE) g/L	21.9 (1.0)	29.2 (1.2)	0.0001 (ANOVA)

Table 3.2: Diagnoses

Oedematous Group		Non-oedematous Group	
Diagnosis	n	Diagnosis	n
Complications of inflammatory bowel disease	4	Sub-acute intestinal obstruction	6
Acute pancreatitis	4	Carcinoma stomach	4
Intestinal anastomotic dehiscence	4	Chronic pancreatitis	3
Abdominal trauma	3	Small bowel carcinoma	2
Intestinal ischaemia	2	Pancreatic cancer	2
Post-pancreatectomy complications	2	Crohn's disease	2
Acute upper gastrointestinal haemorrhage	2	Benign biliary stricture	1
		Recto-vaginal fistula	1
		Rheumatoid arthritis	1
		Chronic depression	1

Table 3.3: Changes in weight and serum albumin concentration

	Weight at admission (kg)	Lowest weight after nutritional support (kg)	Weight at discharge (kg)	Albumin at admission (g/L)	Albumin at lowest weight (g/L)	Albumin at discharge (g/L)
Oedematous (n=21)	79.3 (2.9)	69.2 (3.2)	70.1 (3.2)	21.9 (1.0)	29.8(1.0)	30.0 (0.9)
	⌊ *P*<0.00001 ⌋⌊ *P*=0.005 ⌋			⌊ *P*<0.00001 ⌋⌊ NS ⌋		
Non-oedematous (n=23)	61.4 (4.0)	60.2 (3.9)	61.2 (3.7)	29.2 (1.2)	30.4(0.9)	31.2 (1.0)
	⌊ NS ⌋⌊ *P*=0.002 ⌋			⌊ NS ⌋⌊ NS ⌋		

All values are Mean (SE)
Significance values calculated by t-paired test

Oedematous patients lost a significant amount of weight after commencement of nutritional support but this weight loss was not significant in non-oedematous patients (Table 3.3). Patients in both groups demonstrated a small but significant gain in weight once the nadir had been reached.

Thirteen of the oedematous patients received albumin infusions and similar changes in weight were noted in these patients when compared with oedematous patients who did not receive albumin infusions (Table 3.4). Duration of artificial nutritional support was similar in both groups (Table 3.5).

The serum albumin concentration measured at the point of lowest weight after commencing nutritional support was significantly higher than the initial concentration in the oedematous patients and tended to rise subsequently, though statistical significance was not attained (Table 3.3). The changes in serum albumin concentration were similar in oedematous patients who received or did not receive albumin infusions (Table 3.4). These trends were also seen in the non-oedematous group even though the differences were not statistically significant (Table 3.3).

Table 3.4: Changes in weight and serum albumin concentration in oedematous patients who received or did not receive albumin infusions

	Weight at admission (kg)	Lowest weight after nutritional support (kg)	Weight at discharge (kg)	Albumin at admission (g/L)	Albumin at lowest weight (g/L)	Albumin at discharge (g/L)
Received albumin infusion (n=13)	78.0 (3.0)	66.4 (3.2)	67.7 (3.3)	21.7 (1.4)	29.0 (1.3)	29.1 (1.2)
	⌊ *P*<0.0001 ⌋⌊ NS ⌋			⌊ *P*<0.0001 ⌋⌊ NS ⌋		
No albumin infusion (n=8)	81.4 (6.1)	73.6 (6.5)	74.1 (6.5)	22.2 (1.1)	31.0 (1.4)	31.6 (1.1)
	⌊ *P*=0.001 ⌋⌊ NS ⌋			⌊ *P*=0.003 ⌋⌊ NS ⌋		

All values Mean (SE)
Significance values calculated by t-paired test

There was no significant difference between the two groups when change in weight and serum albumin concentration (admission-lowest and lowest-discharge) were compared using analysis of variance (ANOVA).

The difference between the admission and lowest weight correlated inversely with the change in serum albumin concentration during the corresponding period (Fig. 3.1). There was no correlation in either group, however, between the post nadir weight rise and the change in serum albumin at that time.

Table 3.5: Duration of artificial nutritional support

	Oedematous (n=21)	Non-oedematous (n=23)	*P* value (Mann-Whitney U-Test)
Total duration	20 (17.5)	20 (18)	0.95
Admission to lowest weight	14 (16.5)	11 (7)	0.07
Lowest to discharge weight	3 (6)	10 (18)	0.06

All values Median (Inter-quartile range) days

All patients with oedema lost weight, some in excess of 20 kg, during nutritional support, a change that was deliberately enhanced by the management protocol. As might be expected, the magnitude of initial weight loss was much less in patients without oedema (Fig. 3.1). Indeed, some patients in this latter group gained weight after the initiation of nutritional therapy. This weight gain in non-oedematous patients coincided with a fall in the serum albumin concentration, suggesting short-term fluid gain and dilution.

Three patients in the oedematous group died while there was one death in the non-oedematous group within thirty days of starting nutritional therapy. This difference was not statistically significant (P=0.27, Fisher exact test).

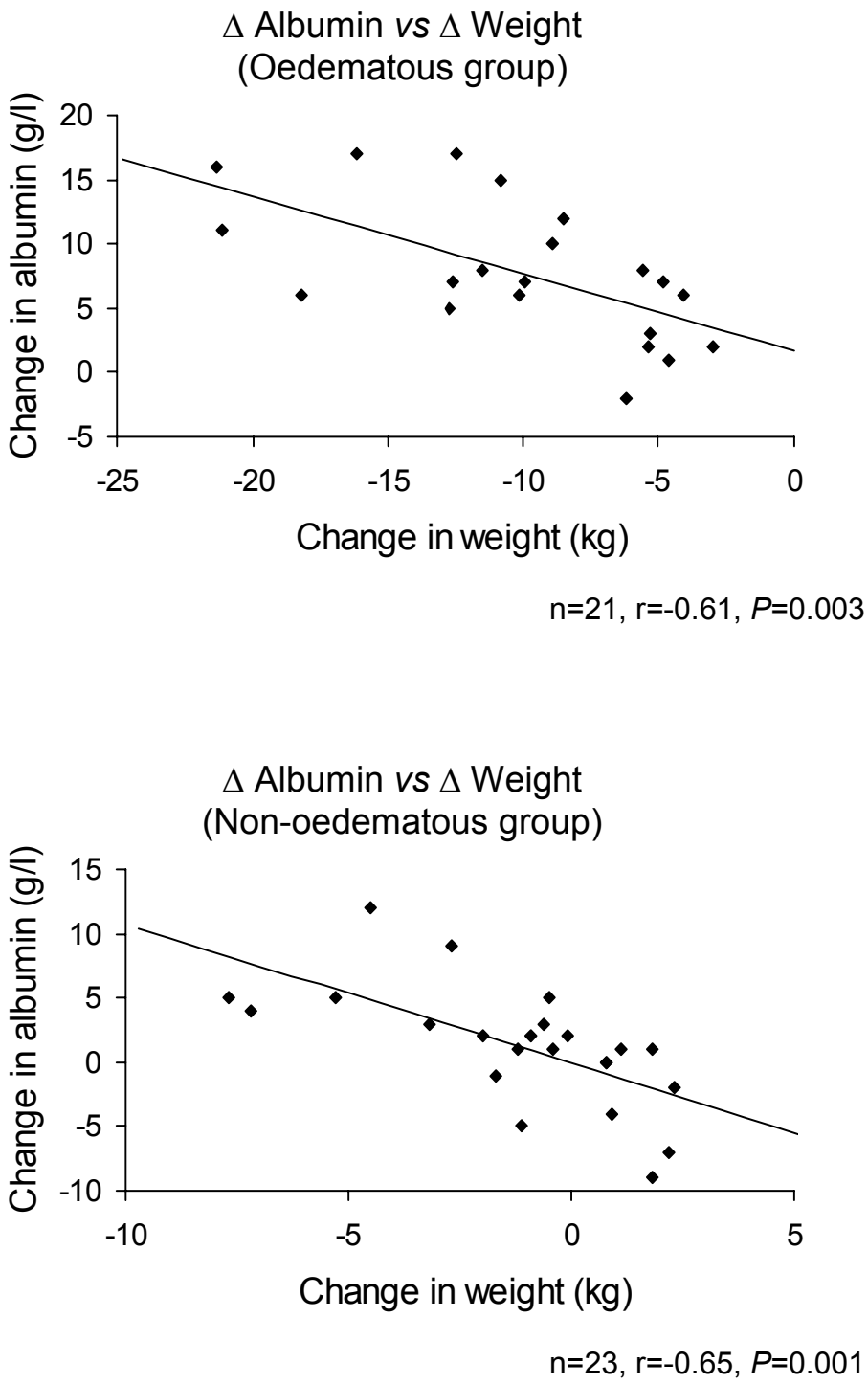


Fig. 3.1: *Correlation between the decrease in weight between the admission record and the lowest record after commencement of nutritional therapy and the change in serum albumin concentration at the corresponding points in oedematous and non-oedematous patients.*

3.4 Discussion

This study has shown that patients presenting to the CNU with chronic nutritional depletion seldom have oedema, whereas those with recent acute illnesses, surgical complications or injury requiring resuscitation often have fluid overload, oedema and hypoalbuminaemia at the time of referral. It has also shown that successful nutritional support may be accompanied by weight loss, as the excess fluid is excreted, and that this process is accompanied by a rise in serum albumin, suggesting that one of the major factors in the initial hypoalbuminaemia was dilution. The conclusions concerning fluid balance, derived from daily weight change are in line with common practice in renal units, since fluid balance measurements derived from intake-output charts are notoriously inaccurate, not least because insensible loss is immeasurable. These changes are compatible with those described in the literature and have implications for the salt and water component of feed prescriptions.

Body composition studies have shown that lean body mass decreases in response to starvation and injury (Hill 1992b). This is accompanied, however, by an absolute or relative expansion of the extracellular fluid compartment and therefore, total body weight does not necessarily decrease in proportion to the loss of lean tissue (Keys, Brozek *et al.* 1950; Moore 1959; Shizgal 1981; Winick 1979). There is also a wide variation, between individuals, in the magnitude of expansion of the extracellular fluid compartment which depends on the prevailing salt and water intake. This expansion is much greater in acutely ill patients (Hill 1992b; Moore 1959; Plank, Connolly *et al.* 1998) than in those subjected to gradual nutritional depletion (Keys, Brozek *et al.* 1950). The increase in body salt

and water may be an inevitable consequence of the resuscitation process in patients with sepsis and trauma as shown by a recent study of patients with bowel perforation and peritonitis (Plank, Connolly *et al.* 1998). These patients gained over 12 L of excess salt and water in the first 2 days of resuscitation and intensive care. If complications persist, the recovery of the ability to diurese this excess is delayed (Hinton, Allison *et al.* 1973; Moore 1959), particularly in the elderly (Cheng, Plank *et al.* 1998), and may result in persistent interstitial oedema many days after the acute event. Some critically ill surgical patients are often described as 'dehydrated' because of low urine output, dry mouth and diminished upper body skin turgor, all of which are signs not specific to dehydration. In reality, however, such patients have an increased total body water with an expanded extracellular and a reduced intracellular compartment. This is often accompanied by an inadequate intravascular volume (Shoemaker, Bryan-Brown *et al.* 1973). Diminished cardiac output (Alleyne 1966; Winick 1979) and impairment of glomerular filtration rate (Klahr and Alleyne 1973), which characterise severe malnutrition, further exacerbate the problem. Administration of more crystalloid in this postacute phase simply results in further accumulation of oedema. On the other hand, the present study has shown that where there is an intravascular volume deficit, the administration of concentrated salt poor albumin restores the normal inter-compartmental balance and promotes diuresis, but has no additional effect on the serum albumin concentration achieved at the nadir of weight loss.

The concentration of albumin in serum at presentation has been used, albeit mistakenly, as a nutritional marker, and its gradual rise to normal as a parameter of response to nutritional therapy. Fleck (Fleck, Raines *et al.* 1985) has

argued that the serum albumin concentration is a marker of disease and acute illness resulting from a combination of capillary leak, redistribution, changes in metabolism and iatrogenic dilution with crystalloid. It may be a valid marker of the risk of complications but not a direct reflection of nutritional state. On the other hand the restoration of serum albumin concentration during recovery from acute illness may be accelerated, in malnourished patients by appropriate nutritional support (Bastow, Rawlings *et al.* 1983). The correlation in oedematous patients between the loss of weight over a few days and rise in serum albumin concentration, after the acute stage of illness, suggests a reversal of previous dilution rather than an anabolic effect or a reversal of the increased capillary escape rate of albumin which is seen in the acute phase of illness (Fleck, Raines *et al.* 1985). Changes in weight and serum albumin have been used to monitor the response to nutritional therapy, expecting a gain in weight and an increase in serum albumin concentration in patients receiving nutritional support. This is a simplistic concept as these changes are more often a reflection of changes in fluid balance rather than nutritional status (Hill 1992b). In a retrospective study Starker *et al*. (Starker, Lasala *et al.* 1983) 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% postoperative complication rate compared to a 4% rate in the remaining patients who were able to diurese their excess salt and water with resulting weight loss and increase in serum albumin concentration. Again, in a randomised study of water and sodium restriction in severely malnourished patients receiving preoperative parenteral nutrition, Gil *et al*. (Gil, Franch *et al.*

1997) compared a group of patients receiving a standard feed containing 70% of non-protein energy as glucose, 140 mmols of sodium/day and 45 mL water/kg/day with a group receiving a modified feed containing 70% of non-protein energy as fat, no sodium and 30 mL water/kg/day. Weight gain with positive sodium and water balance and lowering of serum albumin concentration were noted in the standard group while a negative sodium and water balance was noted in the modified group. Four patients in the latter group developed prerenal failure because of insufficient fluid intake, but after excluding these, there was a significant reduction in overall complications and postoperative stay in the modified group. The work of Gamble (Gamble 1946-1947) also demonstrates the salt and water retaining effect of glucose as an energy substrate compared with fat. These results suggest that, provided sufficient salt and water is given to prevent deficiency, there are clinical advantages in limiting the salt and water content of feeds to avoid overload. Further studies were therefore designed to identify other adverse consequences of salt and water overload. The ten-fold delay in gastric emptying time observed in hypoalbuminaemic dogs given saline (Mecray, Barden *et al.* 1937) has already been mentioned and animal studies (Barden, Thompson *et al.* 1938) suggest that this may also apply to small bowel function prolonging ileus. Unpublished observations in the patients studied in this chapter suggested that resolution of oedema was associated with a return of gastrointestinal function. Postoperative mobility also appeared to be impaired by oedema of the limbs. Susceptibility to pulmonary oedema may also be increased, as shown by Guyton (Guyton 1959) who demonstrated that pulmonary oedema

develops at a lower pulmonary venous pressure in the presence of a lowered serum albumin.

Finally, the implications of these findings for nutritional support prescriptions are clear. The taking of nourishment by whatever route is inseparable from intake of water (including that produced by oxidative metabolism) and salt. As much care needs to be taken over this aspect of the prescription as over substrate content, if clinically adverse derangements of fluid balance are to be corrected, or preferably, prevented.

4. The natural history of changes in transcapillary escape rate of albumin in patients undergoing major abdominal surgery

Entropy is a measure of the degree of chaos in a solution. Increased entropy causes less oedema.

Charles J Diskin

4.1 Introduction

Albumin comprises about 50% of the total plasma proteins, is the principal determinant of plasma colloid oncotic pressure, and is one of the factors which govern the flux of water between fluid compartments. Cuthbertson and Tompsett demonstrated that serum albumin concentration fell and globulin rose in response to orthopaedic trauma and although they could not offer a satisfactory explanation for this phenomenon, they hypothesised that this may have been related to the process of healing (Cuthbertson and Tompsett 1935). Hoch-Ligeti *et al*. (Hoch-Ligeti, Irvine *et al.* 1953) confirmed that serum albumin concentrations fell significantly during the first 24 hours after surgery in 33% of their patients and in 80% of all cases during the first four days.

Our own studies have emphasised the role of dilution by crystalloids on the serum albumin concentration in both normal subjects and patients (Chapters 3, 6, 10, 11 and 12) (Lobo, Bjarnason *et al.* 1999; Lobo, Bostock *et al.* 2002b; Lobo, Stanga *et al.* 2001). Fleck *et al*. (Fleck, Raines *et al.* 1985) studied albumin concentrations and transcapillary escape rate of albumin (TER_{alb}) in controls, in patients undergoing cardiac surgery and in those with sepsis. They concluded that although haemorrhage and other losses may contribute to the postoperative fall in serum albumin concentration, the increase in TER_{alb} is a major contributing factor. Nutritional factors have little part to play in the majority of patients. A continuous and slow escape of albumin from capillaries at the rate of 5%/h is a normal phenomenon. We have been unable to find any data concerning the rate of return of TER_{alb} to normal after uncomplicated major surgery. The aim of this study, therefore, was to measure the timing and extent of these changes.

4.2 Methods

This prospective observational study was conducted in adult patients undergoing major elective abdominal surgery. Patients unable to give consent, those participating in other interventional studies and those with preoperative cardiac, renal or hepatic failure, ascites or metastatic disease were excluded.

Serum albumin concentration, C-reactive protein (CRP), and TER_{alb} were measured preoperatively and on postoperative days 1, 5 and 10, day 0 being the day of the operation.

TER_{alb} was measured with ^{125}I labelled albumin using a modification of the method described by Fleck *et al*. (Fleck, Raines *et al.* 1985). Thyroid uptake of radioactive iodine was blocked by intravenous administration of 180 mg sodium iodide a day before the study. A standard of human ^{125}I albumin (Isopharma AS, Norway) was weighed and a 0.111 MBq dose was delivered intravenously to the patient on each occasion. A 2 mL blood sample was drawn prior to injection to determine background radioactivity counts and 2 mL blood samples were drawn from the opposite arm at 5 min intervals after injection for 60 min. Blood samples were centrifuged and 0.5 mL of plasma was placed into a standard 10 mL counting tube and analysed on a LKB Wallac 1282 Compugamma Universal Gamma Counter for 9000 seconds. These counts were compared with the 0.5 mL standard count and were corrected for background, decay, and error. The corrected counts were plotted semilogarithmically against time. The gradient of the line was calculated with the least squares method after eliminating any grossly deviant points. The gradient, expressed as %/h was the TER_{alb}.

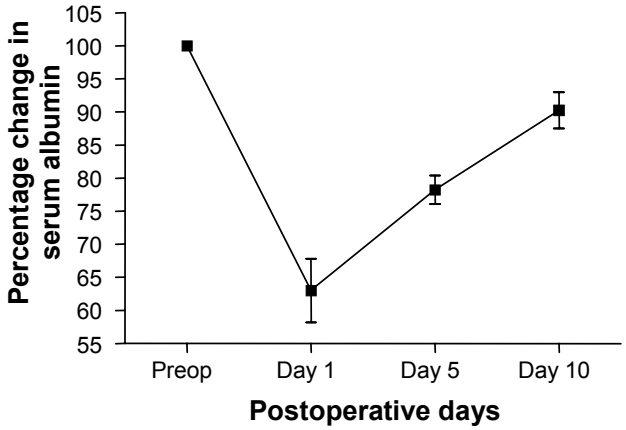
4.3 Results

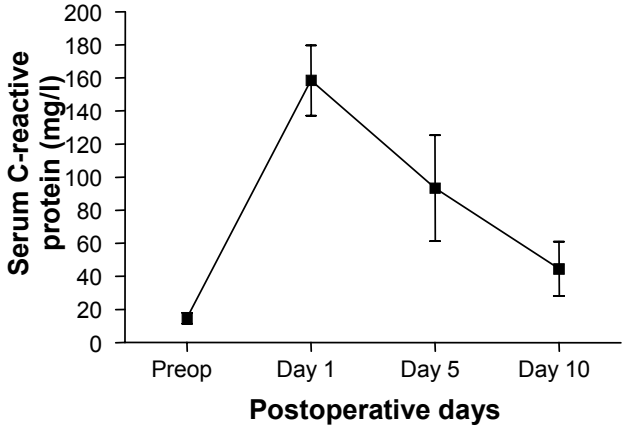
Eight patients were recruited for the study, but two withdrew consent after recruitment. The study was therefore carried out on six patients (three male, three female) with a median (IQR) age of 54.5 (42-69) years and preoperative serum albumin concentration of 36 (34-37) g/L. Percentage changes in serum albumin from baseline (preoperative value taken as 100%), CRP and transcapillary escape rate of albumin (TER_{alb}) are shown in Fig. 4.1. Mean (SE) TER_{alb} was 4.3 (0.8) %/h preoperatively, 13.3 (0.9) on day 1, 11.3 (0.6) on day 5 and 6.6 (0.5) and day 10. These changes paralleled closely the changes in CRP and serum albumin. None of the patients had major postoperative complications and the median (IQR) postoperative stay was 12 (11-12) days.

4.4 Discussion

This study has shown that after uncomplicated major surgery, TER_{alb} rises to about three times normal on the first postoperative day, is still more than twice normal on day 5, but returns nearly to normal by day 10, corresponding to changes in CRP and serum albumin concentration.

The baseline preoperative values for TER_{alb} are similar to those obtained by Fleck *et al*. (Fleck, Raines *et al.* 1985) for both healthy volunteers and preoperative patients, their peak values 7 h after cardiac surgery were only double basal. This difference in peak values may be explained by the fact that the peak inflammatory response takes closer to 24 h than to 7 h to develop, as evidenced by the 100-fold rise serum CRP concentration on the first postoperative day.





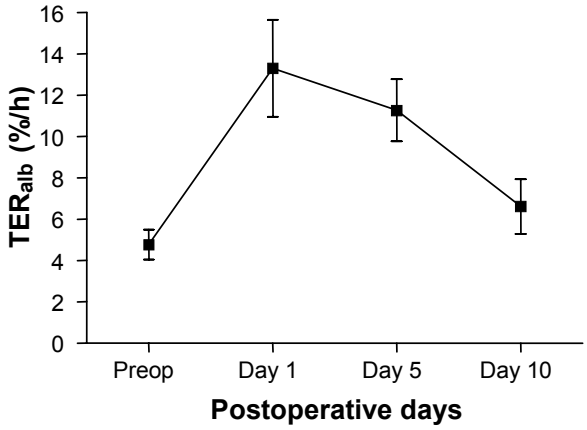


Fig. 4.1: *Percentage changes in serum albumin from baseline (100%), serum C-reactive protein (CRP) and transcapillary escape rate of albumin (TER_{alb}). Measurements were made preoperatively and on postoperative days 1, 5 and 10.*

Like Fleck *et al*. (Fleck, Raines *et al.* 1985) we were also able to show that serum albumin varied inversely with TER_{alb}. As we were unable to accurately monitor fluid balance in this study we are not able to comment on the effect of dilution and its reversal on the serum albumin concentration in this study. However, we have demonstrated in other studies that fluid balance has a significant effect of serum albumin concentration (Chapters 3, 6, 10, 11 and 12) (Lobo, Bjarnason *et al.* 1999; Lobo, Bostock *et al.* 2002b; Lobo, Stanga *et al.* 2001). Fleck *et al*. (Fleck, Raines *et al.* 1985) were unable to show a direct correlation between TER_{alb} alone and serum albumin concentration possibly because of the additional factor of dilution.

It has also been argued that translocation of albumin from the intravascular to the interstitial compartment reduces the transcapillary oncotic pressure difference facilitates the development of oedema. However, the acute inflammatory response secondary to major surgery is associated with an increase in concentration of a number of acute phase proteins including fibrinogen, haptoglobin, caeruloplasmin, complement and CRP, which may compensate, to some extent, for the decrease in plasma oncotic pressure caused by hypoalbuminaemia (Doweiko and Nompleggi 1991b).

From this, and from our previous studies (Chapters 3, 6, 10, 11 and 12) (Lobo, Bjarnason *et al.* 1999; Lobo, Bostock *et al.* 2002b; Lobo, Stanga *et al.* 2001), we conclude that the two major influences on serum albumin concentration postoperatively are redistribution due to an increase in TER_{alb} which following uncomplicated major surgery returns to normal within 10 days, and dilution due to crystalloid infusions, which may often be excessive. In some patients there may

be additional serous losses from wounds and inflamed tissues Nutrition appears to play little part except in cases of extreme malnutrition (Bastow, Rawlings *et al.* 1983).

5. Reproducibility and normal ranges for gastric emptying in volunteers using a test meal designed for postoperative patients

A hungry stomach will not listen.

Jean de La Fontaine

5.1 Introduction

Measurements of gastric emptying and intestinal motility have been employed to study gastrointestinal function in a number of conditions, but results may differ according to the methodology employed (Frier and Perkins 1994).

Scintigraphic techniques are regarded as the gold standard for such studies (Maughan and Leiper 1996; Vantrappen 1994) and a two pancake and milkshake meal was developed in University Hospital, Nottingham (Kong, Perkins *et al.* 1998) following an earlier review of published methodology (Frier and Perkins 1994). This meal was adopted for clinical use following validation in normal volunteers (Kong, Perkins *et al.* 1998). However, when patients were given the meal in the early postoperative period, they found it bulky and were unable to ingest it completely. This meal was therefore modified to make it more suitable for postoperative patients. The aim of this study was to test the reproducibility of gastric emptying and to obtain normal reference ranges using the modified test meal.

5.2 Methods

Gastric emptying time was measured on two occasions each (Test 1 on day 0 & Test 2 at day 7-10) in 10 healthy adult male and 10 healthy adult female volunteers after obtaining informed consent. Female volunteers underwent a pregnancy test on the morning of each study and were only included if this test was negative. Other exclusion criteria included previous abdominal surgery, acute or chronic illness, regular medication and substance abuse.

Each volunteer reported for the study at 0830 h after an overnight fast, having abstained from smoking, alcohol and caffeine for at least 18 h prior to the test. Low activity radioactive anatomical markers (<0.5 MBq $^{99}Tc^{m}$) were attached to the skin, anteriorly and posteriorly at the lower right costal margin.

Test meal A consisted of a single pancake and 100 mL water. The pancakes were made from a supermarket batter mix (Sainsbury's batter mix, J. Sainsbury, London, UK). A total of 128 g of powdered pancake mix was added to 200 mL water and an egg. Before cooking 3 MBq nonabsorbable $^{99}Tc^{m}$-ion exchange resin (Amberlite IRA 416, size 0.30-1.20 mm) was added to a 60 g aliquot of the batter and mixed thoroughly. Each pancake provided 355 kJ (73% carbohydrate, 17% protein and 10% fat). 100 mL water was labelled with 0.5 MBq nonabsorbable ^{111}In-diethylenetriamine pentaacetic acid (^{111}In-DTPA). Volunteers were asked to ingest the meal within 5 min and time zero was defined as the end of the meal. Total radiation exposure for each volunteer amounted to 0.45 mSv.

Gastric emptying data were acquired with 30 s anterior and posterior images of the stomach (Hardy and Perkins 1985) every 20 min using a Scintronix GRC 1 gamma camera (Bartec Medical, Farnborough, UK) equipped with a medium energy (300 keV maximum) general purpose collimator (Fig 5.1). Images of the high-energy ^{111}In photopeak (247 keV) and $^{99}Tc^{m}$ photopeak (141 keV) were recorded using dual energy windows. The gamma camera was linked to a dedicated Sun Sparc 4 nuclear medicine computer system running Smart Soft applications (Bartec Medical). Regions of interest were created around the computer-generated image of the stomach for both anterior and posterior images

and counts were recorded. The geometric mean of the anterior and posterior measurements was calculated and count rates were corrected for background radiation, radionuclide decay and crosstalk between the high and low energy windows. The time-activity curve was expressed as a percentage of the total meal in the stomach against time, from which the time for 50% emptying (T_{50}) was derived from simple interpolation of the data points on the gastric emptying curve (Fig. 5.2) Data obtained from the ten male volunteers were compared with historical data from ten other male volunteers obtained using test Meal B which consisted of two 60 g pancakes labelled with 3 MBq nonabsorbable $^{99}Tc^{m}$-ion exchange resin (Amberlite IRA 416, size 0.30-1.20 mm) and a 200 mL milkshake labelled with 0.5 MBq nonabsorbable ^{111}In-DTPA using a similar technique under identical conditions (Kong, Perkins *et al.* 1998). Meal B had a total energy content of 1.67 MJ (57% carbohydrate, 30% fat and 13% protein).

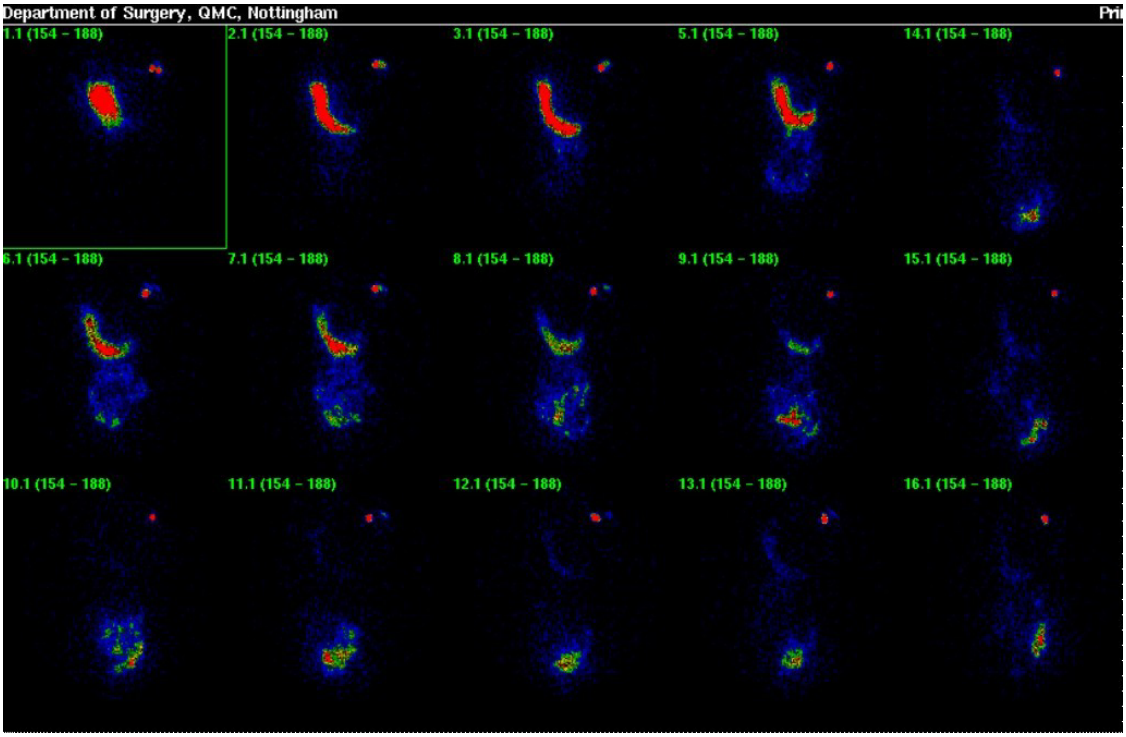


Fig. 5.1: *Sequential anterior gastric images obtained with the gamma camera.*

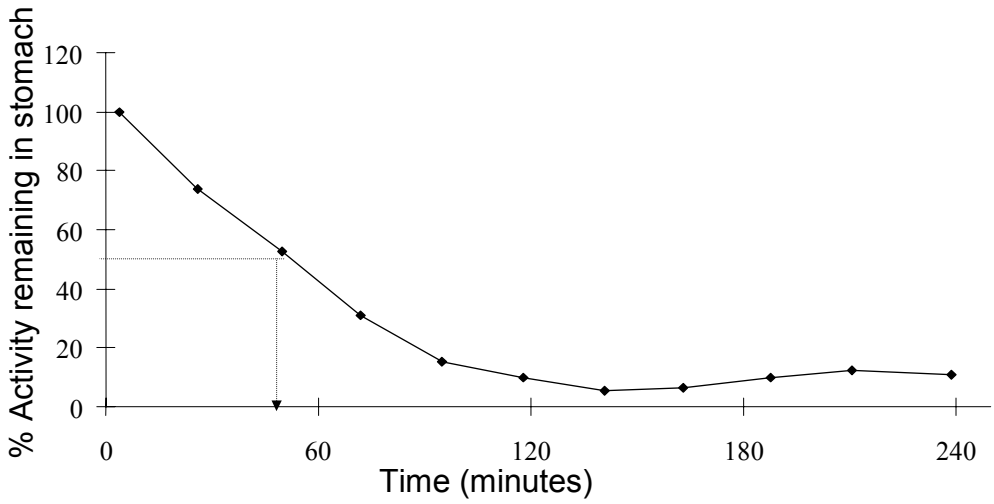


Fig. 5.2: *Calculation of T_{50}*

All results were expressed as mean (95% CI). Normal ranges for males and females were expressed as 95% CI of the average of Tests 1 & 2. Differences between groups were tested for significance using one-way ANOVA and the Mann-Whitney U test. Bland-Altman plots (Bland and Altman 1986) of the difference between the T_{50} results of Tests 1 and 2 against the mean results for each subject for the solid and liquid phases were used to assess agreement and reproducibility.

5.3 Results

The demographic data of the 20 volunteers (age range: 20-57 years) are summarised in Table 5.1. The T_{50} for both the solid and liquid phases of Meal A was greater for female volunteers that males, but this difference was statistically significant only for the liquid phase (Table 5.2). Normal ranges for the T_{50} for the

solid phase were 44-58 min for males and 52-65 min for females. Similar ranges for the liquid phase were 26-40 and 38-62 min for males and females respectively.

Table 5.1: Volunteer profile

	Male	Female	Total	*P**
n	10	10	20	
Age [years]	29.6±2.1	35.6±3.8	32.6±2.2	0.18
Weight [kg]	75.2±2.9	68.2±3.5	71.7±2.3	0.14
Height [m]	1.79±0.02	1.63±0.02	1.72±0.02	<0.001
Body mass index [kg/m^2]	23.3±0.7	25.4±1.1	24.3±0.7	0.11

*Data expressed as Mean ± SE. *One-way ANOVA used to test for statistical significance (male vs. female)*

The Bland-Altman plots for the solid (Fig. 5.3) and liquid phases (Fig. 5.4) for all volunteers demonstrate good agreement and reproducibility of the results obtained using Meal A. The mean difference between Test 1 and Test 2 for the solid phase was 0.4 minutes with all points lying within ±1.96 standard deviations of the mean. The mean difference for the liquid phase was 4.7 minutes with only one point lying outside ±1.96 standard deviations of the mean.

Although liquid phase gastric emptying was not statistically different for the ten males given Meal A when compared with ten historical males given Meal B (Table 5.3), solid phase emptying was twice as long in the latter group.

Table 5.2: Solid and liquid phase gastric emptying time (T_{50}) for Meal A. [Data represented as Mean (95% CI) in minutes]

	Male (n=10)		Female (n=10)		All volunteers (n=20)	
	T_{50} solid	T_{50} liquid	T_{50} solid	T_{50} liquid	T_{50} solid	T_{50} liquid
Test 1	50.9 (39.7-62.1)	34.1 (19.7-48.5)	59.2 (47.8-70.6)	54.0 (39.2-68.8)	55.0 (47.6-62.5)	44.0 (33.6-54.5)
Test 2	51.3 (41.7-60.8)	32.3 (25.1-39.5)	58.0 (50.4-65.6)	46.5 (34.4-58.5)	54.6 (48.9-60.4)	39.4 (32.2-46.6)
Average of Tests 1 & 2	51.1 (44.1-58.1)	33.2 (26.1-40.3)	58.6 (52.7-64.5)	50.2 (38.4-62.1)	54.8 (50.3-59.3)	41.7 (34.3-49.2)

Male vs. female (solid phase): Test 1 P=0.3, Test 2 P=0.2, Average of Tests 1 & 2 P=0.08
Male vs. female (liquid phase): Test 1 P=0.02, Test 2 P=0.1, Average of Tests 1 & 2 P=0.009
Mann-Whitney U test

Table 5.3: Comparison of T_{50} for males using Test Meal A (single pancake + 100 mL water) and Test Meal B (Kong, Perkins *et al.* 1998) (two pancakes + 200 mL milkshake).

	Average of Tests 1 & 2 for Meal A	Average of Tests 1 & 2 for Meal B	*P* (Mann-Whitney U test)
T_{50} Solid phase	51.1 (44.1-58.1)	128.9 (112.8-145.1)	<0.0001
T_{50} Liquid phase	33.2 (26.1-40.3)	30.7 (21.4-39.9)	0.36

Data represented as Mean (95% CI) in minutes

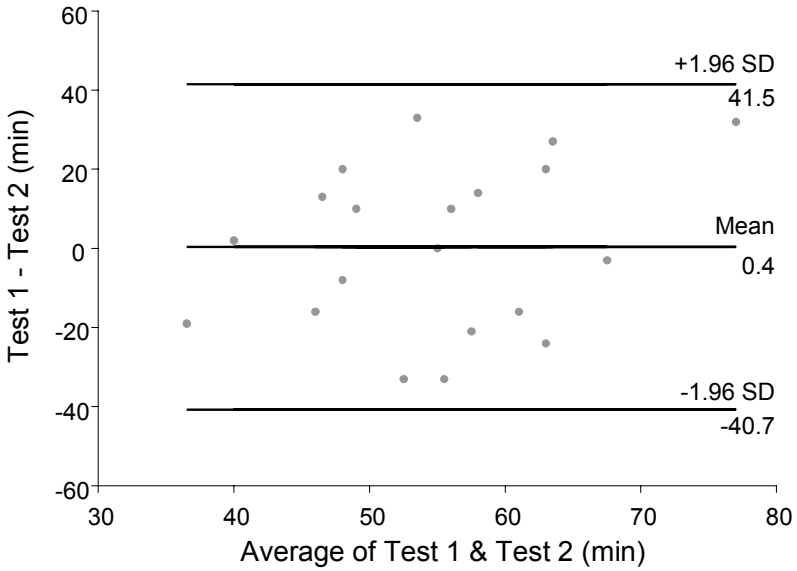


Fig. 5.3: *Bland-Altman plot showing agreement between Tests 1 & 2 for solid phase gastric emptying for the 20 volunteers fed Meal A.*

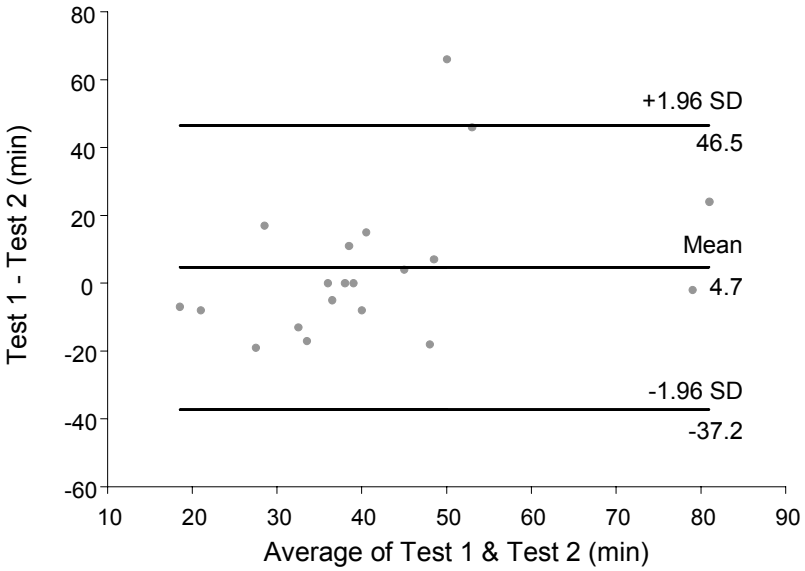


Fig. 5.4: *Bland-Altman plot showing agreement between Tests 1 & 2 for liquid phase gastric emptying for the 20 volunteers fed Meal A.*

5.4 Discussion

The major advantage of scintigraphy lies in its ability to quantify the emptying of solids and liquids separately and simultaneously by using radionuclides of differing energy and a dual channel gamma camera. This study has demonstrated that the modified test meal is suitable for quantifying both the solid and liquid phases of gastric emptying. The test is reproducible in normal volunteers and reference ranges have been obtained for males and females. The meal is palatable and acceptable to most patients. It contains sufficient calories to stimulate nutrient receptors and we have subsequently used it with success in postoperative patients (Chapter 6) (Lobo, Bostock *et al.* 2002b).

Gastric emptying was slower in females than in males for both the solid and liquid phases, but this difference was statistically significant only for the liquid phase, possibly because of the relatively small sample size. These gender differences are consistent with the findings of other workers who used dual-phase scintigraphy (Datz, Christian *et al.* 1987a; Degen and Phillips 1996) and may be due to the relaxational effects of female sex hormones, especially progesterone on gastric smooth muscle (Datz, Christian *et al.* 1987a; Degen and Phillips 1996). Some authors have been able to demonstrate more rapid gastric emptying in females at the time of ovulation (Carrio, Notivol *et al.* 1988), but most others have not shown a significant difference during various stages of the menstrual cycle (Degen and Phillips 1996; Horowitz, Maddern *et al.* 1985). The effect of sex hormones on gastric emptying has been further emphasised by other studies (Datz, Christian *et al.* 1987b; Gryback, Naslund *et al.* 1996) which found that premenopausal women had significantly slower gastric emptying than postmenopausal women and that gastric emptying times in the latter group were

similar to those in men. These data, therefore, emphasise the need for separate reference ranges for premenopausal women and men.

Comparison of gastric emptying times for males using Meals A and B has confirmed the work of others (Christian, Moore *et al.* 1980) that solid phase emptying time increases as the bulk of the meal is increased. In this study, however, there was no difference in liquid phase emptying despite the fact that Meal A comprised 100 mL water and Meal B consisted of a 200 mL milkshake. This result is not surprising since the liquid emptying is considered to be less sensitive than solid emptying (Christian, Datz *et al.* 1983).

In conclusion, the reproducibility of the modified test meal for scintigraphic quantification of solid and liquid phase gastric emptying has been demonstrated, provided inter-individual and intra-individual differences in gastric emptying are appreciated. The normal range data provide an initial validation for the future use of this meal in patients. Although the T_{50} emptying times have been used in this study it is not intended that this will be the sole criterion for determination of gastric emptying. This meal has subsequently been found to be acceptable to patients in the early postoperative phase (Chapter 6) (Lobo, Bostock *et al.* 2002b) and is therefore suitable for the study of gastric emptying in this period.

6. Effect of salt and water balance on gastrointestinal function and outcome after abdominal surgery: A prospective randomised controlled study

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.

Jonathan E. Rhoads

6.1 Introduction

Clinical observations in patients referred to the Clinical Nutrition Unit at University Hopital, Nottingham for postoperative nutritional support have suggested that elimination of oedema resulted not only in an increase in serum albumin concentration (Chapter 3) (Lobo, Bjarnason *et al.* 1999), but in some cases appeared to be associated with earlier return of gastrointestinal function allowing oral or enteral rather than parenteral feeding (unpublished observations). Mecray *et al*. (Mecray, Barden *et al.* 1937) induced hypoalbuminaemia in dogs by a combination of saline administration, plasmapheresis and a low protein intake resulting in a 6-7 fold increase in gastric emptying time, which they ascribed to stomach wall oedema, demonstrated at autopsy. Gastric emptying was restored to normal either by salt and water restriction or a high protein intake. Whether these changes were due to hypoalbuminaemia, to positive sodium balance, or both is unclear. Since then, the same group (Barden, Thompson *et al.* 1938) and others (Durr, Hunt *et al.* 1986; Woods and Kelley 1993) have also associated hypoproteinaemia with prolonged gastric emptying, delayed small bowel transit or ileus.

Such changes in postoperative patients, receiving crystalloid infusions, are exacerbated by their diminished ability to excrete an excess sodium and water load (Coller, Campbell *et al.* 1944; Moore 1959; Wilkinson, Billing *et al.* 1949), although this is sometimes forgotten (Frost, Wakefield *et al.* 2001; Lobo, Dube *et al.* 2001; Stoneham and Hill 1997). Several authors have described an increase in postoperative complications and adverse outcome associated with excess sodium and water administration in the perioperative period (Alsous, Khamiees *et al.* 2000; Arieff 1999; Frost, Wakefield *et al.* 2001; Gil, Franch *et al.* 1997; Moore

and Shires 1967; Starker, Lasala *et al.* 1983). The 1999 report of the UK National Confidential Enquiry into Perioperative Deaths has also identified errors in fluid and electrolyte management as a significant cause of death (Callum, Gray *et al.* 1999).

This study of patients was designed to test whether the phenomenon of delayed gastric emptying postoperatively described by Mecray *et al*. (Mecray, Barden *et al.* 1937) in dogs, could be reproduced in man by positive salt and water balance; and conversely whether restriction of postoperative saline infusion, aimed at achieving near zero salt and water balance, could result in earlier return of gastrointestinal function and better clinical outcome.

6.2 Methods

6.2.1 Study Design

Prospective randomised controlled trial set in a university teaching hospital.

6.2.2 Selection Criteria

Adults undergoing elective hemicolectomies and sigmoid colectomies for cancer were approached for enrolment. Those excluded were patients with preoperative evidence of impaired renal function, congestive cardiac failure, hepatic disease, diabetes mellitus, ascites, peritoneal metastases, or impaired mobility, along with those with significant anaemia (haemoglobin <10 g/dL) and those receiving medications affecting gastrointestinal motility. Hemicolectomy patients were selected as a model for this study only because they were a relatively homogeneous group in which to compare the effects of the two different

fluid regimens upon salt and water balance and gastrointestinal physiology. Patients in this group were also unlikely to require blood or colloid transfusion, or upper gastrointestinal surgical procedures which might have affected the results.

6.2.3 Randomisation, study groups and interventions

Randomisation was performed in blocks of ten using consecutively numbered sealed envelopes that were opened, after patient recruitment, by a person not involved in the study. Patients were randomised to one of two groups:

Standard patient management (standard) group:

Patients were managed on the surgical wards and received standard postoperative fluids, as practised on those wards at our hospital. This regimen contained at least 154 mmol sodium and 3 L water per day (typically, 1 L 0.9% saline and 2 L 5% dextrose). Fluid prescriptions were charted independently by surgical staff and were not influenced by the investigators.

Salt and water restriction (restricted) group:

Patients were managed on the Clinical Nutrition Unit and normally received no more than 77 mmol sodium and 2 L water per day (typically, 0.5 L 0.9% saline and 1.5 L 5% dextrose, or 2 L dextrose [4%] saline [0.18%]). Fluids in this group were prescribed by one investigator (DNL). There was an option to increase fluid input if blood urea concentrations rose or if there were clinical indications of salt or water depletion.

Patients in both groups received between 40 and 60 mmol potassium per day from the 2nd postoperative day onwards, according to the serum potassium concentration.

6.2.4 Clinical Management

Patients were admitted under the care of one of three consultant colorectal surgeons. Patients undergoing right hemicolectomy did not receive bowel preparation. Bowel preparation for the rest of the patients was identical and consisted of two sachets of Picolax® (sodium picosulphate 10 mg/sachet, Ferring Pharmaceuticals, Berkshire, UK). Patients were allowed to drink fluids till four hours before the operation. Intraoperative fluids were prescribed by the anaesthetists involved, who were unaware of the details of the study or the randomisation. Once patients in the restricted group left the operating theatre, the investigators controlled all intravenous prescriptions, while in the standard group fluids continued to be prescribed by the anaesthetic and surgical team responsible. Clinical decisions regarding discontinuation of intravenous fluids, commencement of diet and discharge from hospital were made by the treating surgical team and not by the investigators. None of the patients received artificial nutritional support.

All patients had midline laparotomies and postoperative pain was managed by patient-controlled analgesia devices delivering morphine. The daily total morphine dose was recorded in every case. Epidural analgesia was not used.

6.2.5 End points

The primary end points were solid and liquid phase gastric emptying times (T_{50}) on the 4th postoperative day, comparing the two groups. Secondary end points included duration of postoperative hospital stay, and time to first passage of flatus and faeces, to discontinuation of intravenous fluids, to full mobility and to resumption of a normal diet.

6.2.6 Sample size and power calculation

There is little relevant literature upon which to make this calculation, but based on the canine studies of Mecray *et al*. (Mecray, Barden *et al.* 1937), we expected to find a reduction of at least 30 minutes in mean gastric emptying time in the restricted group when compared with the standard group. This gave a sample size of 20 in each group for a 0·05 difference with a power of 90%. A preliminary analysis on the first 10 patients studied showed that this difference was 74 minutes (effect size = 1·4 standard deviations), and the sample size was recalculated to be 10 in each group, so as to minimise the number of subjects in the study.

6.2.7 Monitoring

The following baseline measurements were recorded preoperatively: weight, height, body mass index, sex, full blood count, liver function tests, serum albumin, urea, creatinine, osmolality, sodium and potassium, and urinary sodium, potassium, urea, creatinine and osmolality.

All measurements on day 0 (day of operation) were made between the start of the operation and midnight. Measurements on subsequent days were taken from midnight to midnight. Postoperative body weight was recorded daily between 0800 and 0900 hours and blood was sampled during the same period.

Intraoperative fluid and electrolyte intake and blood loss were recorded, as were daily intravenous water, sodium, potassium and oral fluid intakes, urine output and other fluid losses from days 0 to 4. Serum concentrations of sodium, potassium, urea, creatinine, and osmolality were measured daily for six days. Daily urinary sodium and potassium excretion and osmolality were measured in

24 h collections from days 0 to 4. Full blood count and serum albumin concentration were measured preoperatively and on postoperative days 1, 2, 4 and 6 (day 5 for those patients who were discharged on that day). Blood samples taken preoperatively and on postoperative days 1, 2, 4 and 6 (or 5) were separated and plasma stored at -70°C for subsequent estimation of concentrations of cholecystokinin, motilin and peptide YY.

Postoperative hospital stay and time to first passage of flatus and faeces, discontinuation of intravenous fluids, full mobility and resumption of a normal diet were recorded. Patients were examined daily for the presence of ankle, conjunctival or sacral oedema. Infectious and non-infectious complications and readmissions during the first 30 postoperative days were also recorded.

6.2.8 Gastric emptying

Gastric emptying was measured on the fourth postoperative day using a test meal developed for patients in the early postoperative period and validated by us (Chapter 5) (Lobo, Bostock *et al.* 2002a).

Patients who were vomiting on the day of the gastric emptying studies, or those who had a nasogastric aspirate >1000 mL over the 24 hrs preceding the test, were assumed to have prolonged gastric emptying in accordance with previously published data (Mackie, Hulks *et al.* 1986). For statistical calculations, these patients were assumed to have a T_{50} = the longest recorded T_{50} + 1 min.

None of the patients received any opiate or antiemetic (except those who were vomiting) during the 6 h preceding the gastric emptying studies.

6.2.9 Assay of gastrointestinal hormones

Plasma cholecystokinin, peptide YY and motilin concentrations were measured in duplicate using commercially available radioimmunoassay kits (Peninsula Laboratories Inc., San Carlos, CA, USA). The assays were based upon the competition between labelled ^{125}I-peptide and unlabelled peptide binding to a limited quantity of specific antibody (2000; Patrono and Peskar 1987). The amount of ^{125}I-peptide bound as a function of the concentration of the unlabelled peptide in standard reaction mixtures (1, 2, 4, 8, 16, 32, 64 and 128 pg/mL) was measured and a standard curve constructed from which the concentration of the peptide in the unknown samples was determined.

6.2.10 Statistical Analysis

The Mann Whitney U-test, the χ^2 test and the Fisher exact test were used to determine significance of differences between groups. Tests of between-subjects effects (standard group *vs*. restricted group) were performed using the general linear model repeated measures procedure. Spearman's rank correlation was used for statistical relationships and linear regression lines were plotted on graphs.

6.3 Results

The progress of patients through the phases of the trial is summarised in Fig. 6.1. The preoperative demographic and biochemical profiles of the patients in the two groups were well matched (Table 6.1).

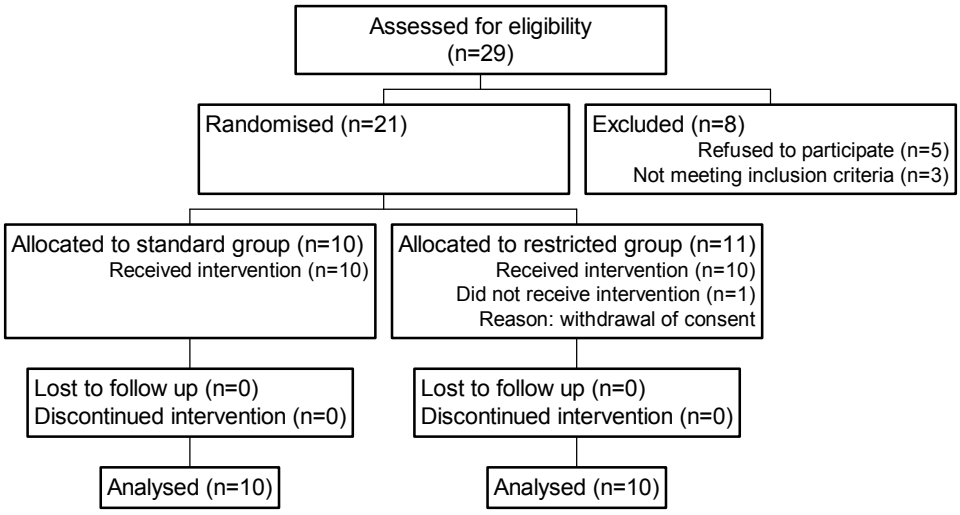


Fig. 6.1: *Trial profile*

Median (IQR) intraoperative blood loss was 275 (169-381) mL in the restricted group and 238 (175-325) mL in the standard group (P=0·79, Mann-Whitney U-test). No patient received blood transfusion and the total operating time was not more than 2 h in any patient. Although mean±SE intraoperative infusions of sodium (385±19 mmol in the standard group and 338±20 mmol in the restricted group, P=0·14, Student t-test) and water (2·8±0·1 L in the standard group and 2·5±0·2 L in the restricted group, P=0·16) were similar, postoperative water and sodium infusions were significantly higher in the standard compared to the restricted group (Fig. 6.2).

Table 6.1: Comparative patient data at entry into the study

	Standard Group (n=10)	Restricted Group (n=10)	*P* value
Age (years)*	58.9 (55.3-66.7)	62.3 (52.5-67.2)	0.70
Sex ratio (M:F)†	6: 4	8: 2	0.63
Height (m)*	1.61 (1.58-1.74)	1.69 (1.56-1.77)	0.38
Weight (kg)*	69.6 (67.9-74.7)	73.3 (61.8-80.3)	0.91
BMI (kg/m^2)*	26.4 (24.3-29.6)	23.6 (22.2-27.5)	0.29
Serum creatinine (mmol/L)*	73.0 (65.8-83.8)	91.0 (72.8-97.8)	0.09
Blood urea (mmol/L)*	5.4 (4.2-6.3)	5.5 (4.1-5.8)	0.65
Serum albumin (g/L)*	38.0 (36.8-40.0)	38.5 (36.5-40.3)	0.82
Serum osmolality (mOsm/kg)*	292.0 (289.8-294.5)	292.5 (287.8-295.5)	0.97
Haemoglobin (g/dL)*	13.6 (12.3-15.3)	13.4 (12.3-14.8)	0.73
Consultant surgeon (A: B: C)‡	4 : 3 : 3	7 : 1 : 2	0.36
Type of operation (R hemicolectomy: L hemicolectomy: sigmoid colectomy)‡	2 : 1 : 7	3 : 1 : 6	0.28

**Figures are median (interquartile range), Mann Whitney U-test applied*

† *Fisher exact test,* ‡ χ^2 *test*

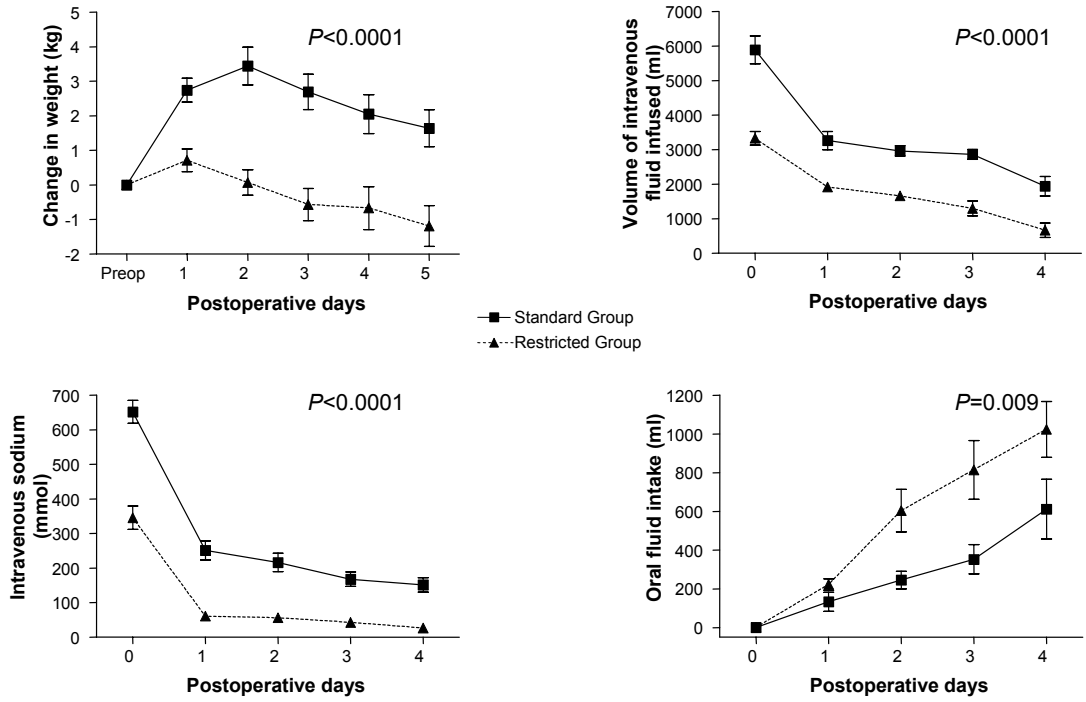


Fig. 6.2: *Weight change and 24 hour water and sodium input. All values are mean ± SE. P values derived using repeated measures testing.*

This was reflected in the higher positive cumulative sodium and water balance (Table 6.2) and weight gain (approximately 3 kg, Fig. 6.2) in the standard group. Patients in the restricted group were able to drink significantly greater quantities of fluids (Fig. 6.2), but total fluid input (intravenous + oral) was greater in the standard group (Fig. 6.3), which also had greater dilution of haematocrit and albumin (Fig. 6.4). Urine volume and urinary sodium and potassium excretion were not significantly different over 4 days in the two groups (Fig. 6.3). None of the patients in the restricted group needed or received extra salt and water over and above the protocol regimen.

Table 6.2: Cumulative sodium and water balance over days 0-4

	Standard group (n=10)	Restricted group (n=10)	*P* value
Total intravenous sodium input (mmol)	1441 (1330-1621)	520 (490-589)	<0.0001
Total urinary sodium output (mmol)	684 (399-938)	489 (314-644)	0.20
Sodium balance (mmol)	747 (492-1091)	82 (-183-230)	0.001
Total water input (mL)	18015 (16454-19320)	11662 (10430-12203)	<0.0001
Total water output (mL)	10478 (8690-11841)	7742 (6371-8559)	0.008
Water balance (mL)	7196 (5882-9308)	3680 (2600-4676)	<0.0001
Estimated insensible losses over 5 days (@ 700 mL/day)	3500	3500	
Net water balance (mL)	3696 (2382-5808)	180 (-900-1176)	<0.0001

All values Median (IQR)

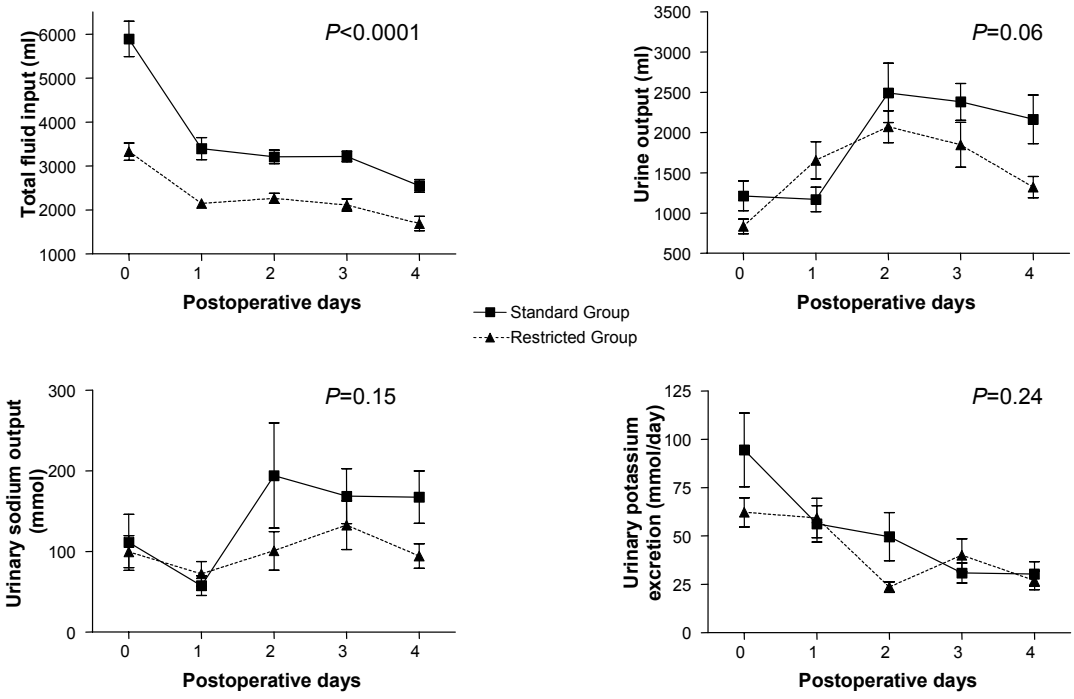


Fig. 6.3: *24 hour total fluid input, urine output and urinary sodium and potassium output. All values are mean ± SE. P values derived using repeated measures testing.*

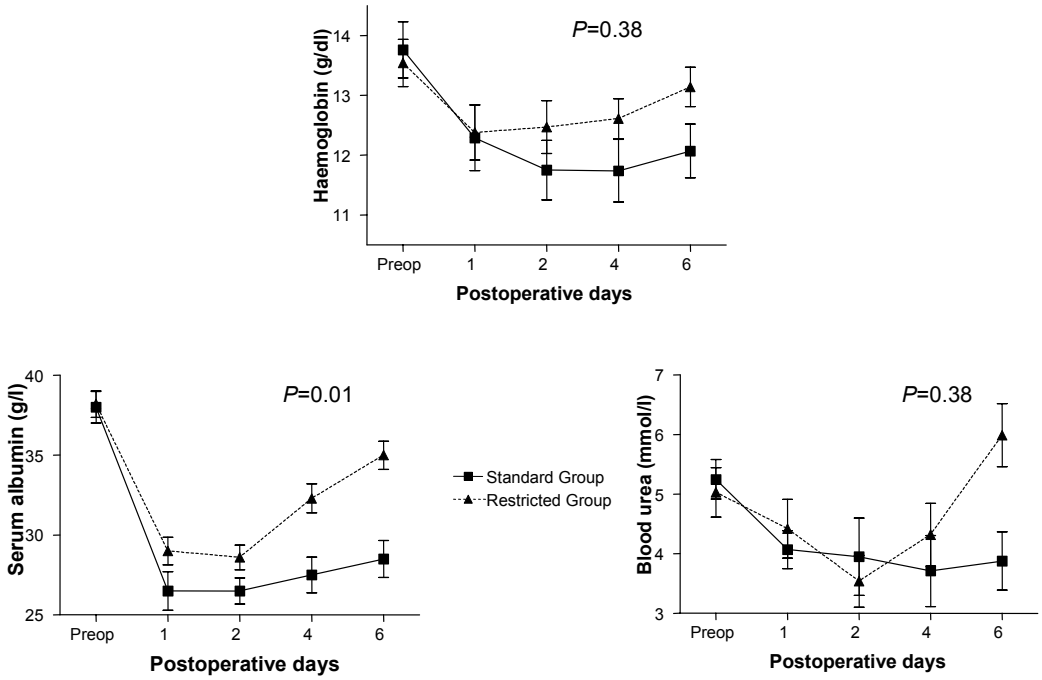


Fig. 6.4: *Sequential changes in haemoglobin, serum albumin concentration and blood urea. All values are mean ± SE. P values derived using repeated measures testing.*

The doses of morphine received by patients in the two groups from days 0-3 were almost identical (Fig. 10.5).

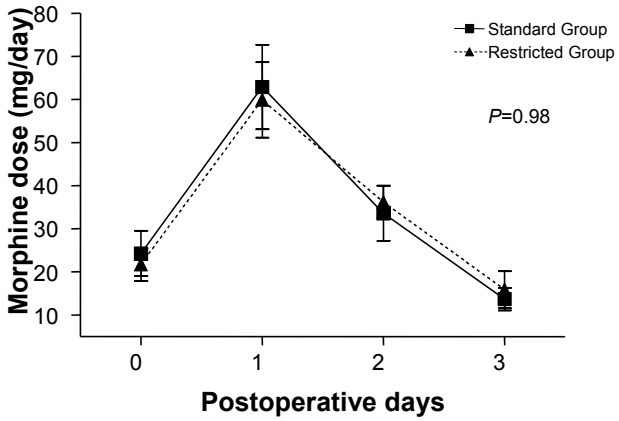


Fig. 6.5: *Morphine dose received on days 0-3. All values are mean ± SE. P values derived using repeated measures testing.*

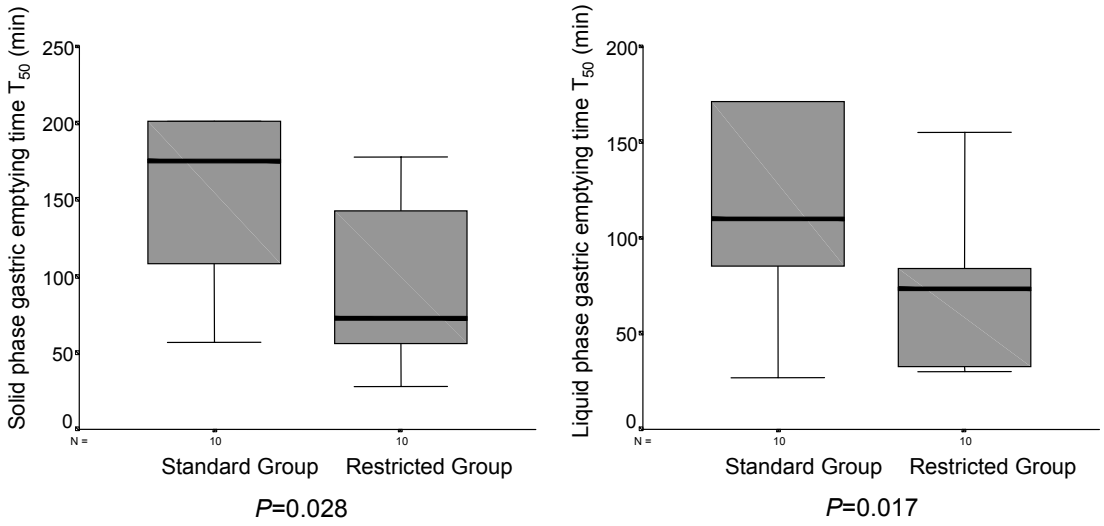


Fig. 6.6: *Solid and liquid phase gastric emptying times (T_{50}). Solid lines represent medians, shaded areas interquartile ranges and whiskers extreme values. P values derived using the Mann-Whitney U-test.*

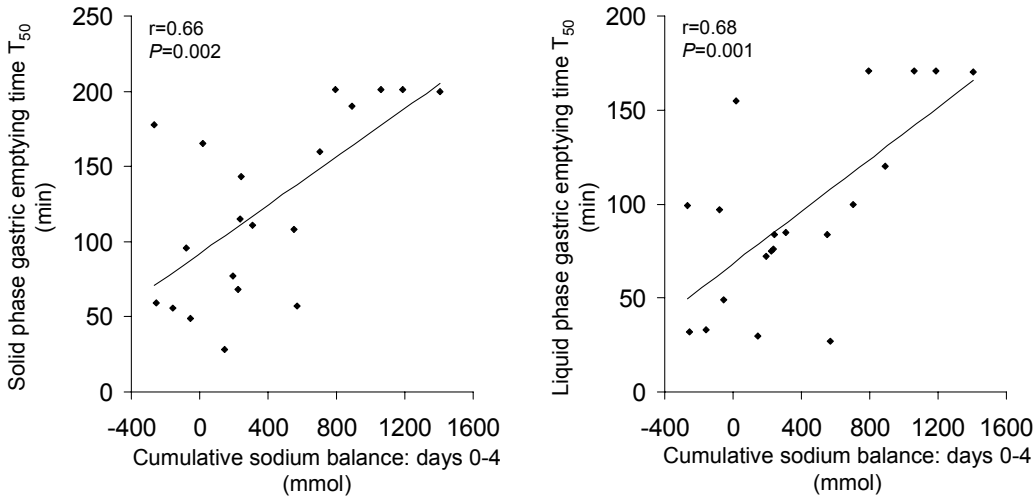


Fig. 6.7: *Linear regression between gastric emptying time and cumulative sodium balance from days 0-4*

Table 6.3: Secondary end points

	Standard group (n=10)	Restricted group (n=10)	*P* value
Day on which flatus first passed	4.0 (4.0-5.0)	3.0 (2.0-3.0)	0.001
Day on which stool first passed	6.5 (5.8-8.0)	4.0 (3.0-4.0)	0.001
Day on which intravenous infusion discontinued	6.0 (4.7-6.3)	4.0 (3.8-4.0)	0.001
Day on which full mobility achieved	5.0 (4.0-6.5)	3.0 (3.0-4.0)	0.003
Day on which patient was eating a normal diet	6.5 (5.5-7.0)	4.0 (4.0-4.3)	0.002
Postoperative hospital stay (days)	9.0 (7.8-14.3)	6.0 (5.0-7.0)	0.001

All figures median (interquartile range), Mann Whitney U-test applied

Table 6.4: Side effects and complications

	Standard group (n=10)	Restricted group (n=10)
Peripheral oedema	7	0
Hyponatraemia (Na ≤ 130 mmol/L), expressed as patient days	4	0
Hypokalaemia (K ≤ 3.5 mmol/L), expressed as patient days	2	1
Vomiting on day 4	3	0
Confusion after day 1	3	0
Wound infection	1	0
Respiratory infection	2	0
Readmission within 30 days	1*	0
Death within 30 days	1*	0
Total no. of patients developing side effects or complications	7**	1**

**Occurred in the same patient. Cause of death: lymphangitis carcinomatosii*
*** P=0.003 Fisher exact test*

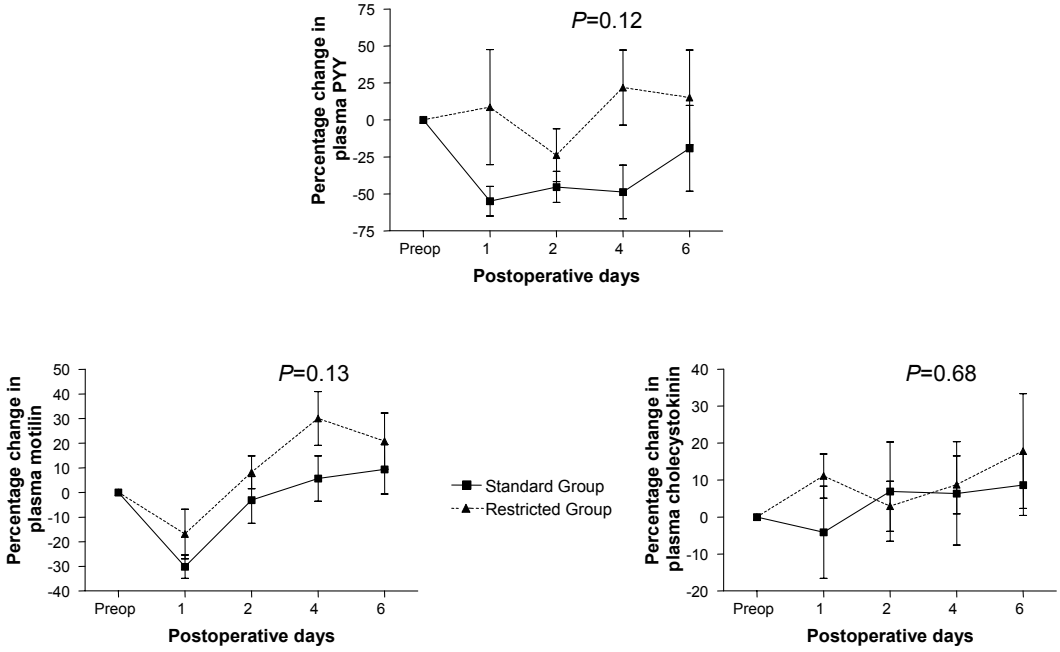


Fig. 6.8: *Sequential changes in plasma cholecystokinin, peptide YY and motilin. All values are mean ± SE. P values derived using repeated measures testing.*

Three patients in the standard group were unable to have gastric emptying measured on the 4th day because they were either still vomiting or had a nasogastric aspirate >1000 mL over the preceding 24 hrs. Median solid and liquid phase gastric emptying times (T_{50}) were significantly prolonged on the 4th postoperative day in the standard group (175 and 110 min respectively), compared to the restricted group (72·5 and 73·5 min respectively) (Fig. 6.6). A linear relationship between gastric emptying time and cumulative sodium balance from days 0-4 was demonstrated (Fig. 6.7). The three patients in the standard group who were vomiting on the 4th postoperative day and unable to have gastric emptying studies done were in the greatest cumulative positive sodium balance. Patients in the restricted group fared better with regard to the secondary end points (Table 6.3) and they also had fewer side effects and complications (Table 6.4). There was no significant difference between the two groups when sequential percentage changes in peptide YY, cholecystokinin and motilin were compared (Fig. 6.8).

6.4 Discussion

This study confirms in man the original observations made in 1937 by Mecray *et al*. (Mecray, Barden *et al.* 1937) in dogs, and shows that even a modest positive salt and water balance causing a 3 kg weight gain after elective colonic resection, is associated with delayed recovery of gastrointestinal function, increased complication rate, and prolonged hospital stay. Whether these effects are due to fluid gain, hypoalbuminaemia or both is impossible to determine since the two are inseparable even in normal subjects in whom striking falls in serum

albumin concentration have been demonstrated with crystalloid infusions (Chapters 10, 11 and 12) (Lobo, Stanga *et al.* 2001). These results have important implications for the management of surgical patients who receive intravenous fluids.

Despite the fact that postoperative patients have a diminished ability to excrete water, sodium and chloride, some centres continue to prescribe 3 L fluid and 154 mmol sodium and chloride per day even to uncomplicated postoperative patients (Chapter 7) (Lobo, Dube *et al.* 2001), failing to separate the requirements for resuscitation and treatment of volume deficit from those required merely for maintenance. The present study has shown that adherence to this regimen leads to a progressive accumulation of salt and water in the early postoperative period, as illustrated by the data in Table 6.2 and the weight change shown in Fig. 6.2. By the end of day 4, after correcting for insensible losses, fluid balance was positive by 3 L in the standard group compared with zero in the restricted group. That serial weighing is the best measure of fluid balance is well known and one we have used previously in normal subjects (Chapters 10-13) (Lobo, Stanga *et al.* 2001) and clinical studies (Chapter 3) (Lobo, Bjarnason *et al.* 1999). Although patients in the restricted group received smaller amounts of salt and water than those in the standard group, there was no significant difference in urine output in the first few days and none of the patients in the restricted group became oliguric or had a blood urea concentration above the upper limit of normal. This accords with previous work showing that, even in normal subjects, excretion of a salt and water load is slow compared with that of water alone (Chapter 10) (Lobo, Stanga *et al.* 2001) and that this is exaggerated in conditions of starvation or stress (Keys, Brozek *et al.* 1950; Moore 1959; Wilkinson, Billing *et al.* 1949). The changes in

serum albumin concentration and haemoglobin (Fig. 6.4) are a reflection of the haemodilutional effects of the two fluid regimes (Chapter 10) (Lobo, Stanga *et al.* 2001), with the changes in albumin being more pronounced than those in haemoglobin since albumin distributes in the plasma and the interstitial compartments, while red blood cells (and haemoglobin) are distributed in the whole blood space (Chapter 10) (Lobo, Stanga *et al.* 2001).

There was no difference between the two groups in the concentrations of the gastrointestinal hormones cholecystokinin, peptide YY and motilin (Fig. 6.8). These findings suggest that the prolongation of gastric emptying and delayed passage of flatus and faeces in the standard group may be a mechanical effect of gastrointestinal oedema produced by the salt and water excess as shown by Mecray *et al*. (Mecray, Barden *et al.* 1937). Seven of the ten patients in the standard group developed peripheral oedema, and it would not be unreasonable to assume that this also involved the viscera.

This was not a study directed to finding the ideal management for patients undergoing hemicolectomies — indeed some surgical centres manage such patients without postoperative intravenous fluids, and others use modest amounts comparable to those in the restricted group. The investigators played no part in the prescription or monitoring of fluids in the standard group. This and all other aspects of management of both groups (except the fluid prescription in the restricted group) were entirely directed by the surgical team concerned and not by the investigators who confined themselves to making measurements and observations. The differences between the two groups in terms of postoperative gastrointestinal function, complications and hospital stay cannot be explained by other clinical differences, e. g. disease severity, time of operation (<2 h in all

cases), blood loss (no blood transfusions required in any patient) or differences in opiate administration.

There is a growing body of evidence suggesting that in surgical patients salt and water excess gives rise to greater problems and complications than fluid restriction (Arieff 1999; Callum, Gray *et al.* 1999; Frost, Wakefield *et al.* 2001; Gil, Franch *et al.* 1997; Lobo, Bjarnason *et al.* 1999; Sitges-Serra and Franch-Arcas 1998; Starker, Lasala *et al.* 1983). Studies of fluid balance in patients receiving nutritional support have suggested that, in the perioperative period, weight gain, indicative of salt and water retention, results in poorer outcome (Gil, Franch *et al.* 1997; Lobo, Bjarnason *et al.* 1999; Sitges-Serra and Franch-Arcas 1998; Starker, Lasala *et al.* 1983). A retrospective study has suggested that postoperative pulmonary oedema is more likely within the initial 36 h when net fluid retention exceeds 67 mL/kg/day (Arieff 1999). Increased postoperative morbidity and prolonged hospital stay in patients receiving perioperative salt and water excess have also been reported in a recent audit of a homogeneous group of patients undergoing colorectal resections (Frost, Wakefield *et al.* 2001). Moderate restriction of salt and water may also benefit some critically ill patients. A review of 36 patients treated on an intensive care unit for septic shock has suggested that at least one day of negative fluid balance ($\leq$ -500mL) achieved by the third day of treatment, may be an independent predictor of survival (Alsous, Khamiees *et al.* 2000). These findings may also be relevant to the impaired gastric emptying observed in mechanically ventilated critically ill patients (Heyland, Tougas *et al.* 1996), a group in which large amounts of fluid are used for resuscitation.

Moore and Shires wrote in 1967 (Moore and Shires 1967), “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 can never be achieved by inundation." The results of this study emphasise the importance of this advice.

Surveys

7. Problems with solutions: drowning in the brine of an inadequate knowledge base

I forget what I was taught. I only remember what I've learnt.

Patrick White

7.1 Introduction

Although the prescription of fluid and electrolytes is an integral part of perioperative care in general surgical patients, this is usually left to the most junior members of the firm who may lack sufficient knowledge and experience to undertake this task competently. This results in poor prescribing practices and suboptimal patient care. A recent editorial in the *British Medical Journal* (Lane and Allen 1999) and the ensuing correspondence (1999) have expressed concerns about the appropriateness of many fluid and electrolyte prescriptions and an earlier audit has emphasised the wide variability in the amount of fluid and electrolytes received by perioperative patients (Stoneham and Hill 1997). This problem has also been highlighted by the 1999 UK National Confidential Enquiry into Perioperative Deaths (NCEPOD) (Callum, Gray *et al.* 1999) and there is an increasing concern about standards of fluid and electrolyte management and the potential complications of excess or inadequate fluid administration. Theoretical and practical training in this subject is probably the key to better practice. This study assesses the present state of knowledge and fluid prescribing patterns among junior doctors and forms a basis for improving undergraduate and postgraduate educational and training programmes.

7.2 Methods

A telephone questionnaire was designed and then piloted among surgical preregistration house officers (PRHOs) in the last month of their PRHO year. Following this, a survey of surgical PRHOs and senior house officers (SHOs) working in 25 teaching and district general hospitals staffed primarily by graduates of three British medical schools was carried out in three phases. In

phase one, 100 PRHOs were surveyed within 10 days of starting their first house job (Group A). In the second phase, 50 other PRHOs from the same hospitals, who had not been previously surveyed, were questioned 6-8 weeks after commencing their job (Group B), to test whether the experience of working on surgical wards improved their knowledge and management skills. In phase three, 50 surgical SHOs were surveyed (Group C) to determine if practical training of a year or more produced a significant difference. One hundred and sixty one PRHOs were identified at the start of the survey from lists obtained from the Postgraduate Deans' offices and by asking the first surveyed in each hospital to name his/her colleagues. One hundred and five of these, selected at random, were approached in the first phase. Three could not be contacted and two declined to respond. The 100 who responded constituted Group A. The remaining 56 PRHOs were approached to constitute Group B. Five of these could not be contacted and one declined to respond. Fifty three SHOs were identified by asking the first surveyed in each hospital to name his/her colleagues. The first 50 who responded comprised Group C.

The questionnaires were administered by one of three investigators and took 6-7 minutes to complete. Respondents had to answer the questions immediately and were asked not to discuss them later with their colleagues.

Questioned asked are shown in the box. Reference ranges were obtained from the metabolic classic of Moore (Moore 1959) and more recent works (Hill 1992a; Shires, Barber *et al.* 1999; Turner 1996).

Fluid and electrolyte questionnaire

1. Who (PRHO, SHO, registrar) is responsible for prescribing fluid and electrolytes on your firm?
2. How confident are you (very confident, reasonably confident, not confident) to prescribe fluid and electrolytes?
3. How would you rate the teaching on fluid and electrolytes in your medical school (excellent, good, satisfactory, unsatisfactory, poor)?
4. Were you given any verbal or written guidelines/teaching on fluid and electrolytes when (or after) you began work on the surgical firm?
5. When are the fluid balance charts checked (on the morning ward round, later, not checked regularly)?
6. What are the daily sodium and potassium requirements for a 70 kg man in health?
7. What is the minimum (obligatory) 24hr urine volume essential to excrete the solute load?
8. What is the sodium and potassium content (in mmol/L) of 0.9% saline, isotonic dextrose saline, Hartmann's solution and Gelofusine® (succinylated gelatin solution, B. Braun Medical Ltd., Sheffield, UK) (answers were considered correct if within ±5% of the actual value)?
9. What is the desired postoperative urine output (mL/hr) in a 70 kg man?
10. What is the best method to calculate daily postoperative fluid requirements?
11. What is the best serial measure of fluid balance?
12. How do urinary sodium excretion (decreases) and osmolality (increases) change in the early postoperative phase when compared to the preoperative phase?
13. How often should serum urea and electrolytes be checked in postoperative patients receiving intravenous fluids?
14. Assuming serum potassium and renal function is normal, how much potassium should be supplemented on days 0 and 1 following a right hemicolectomy?
15. What is your usual fluid and electrolyte prescription for a 70 kg man on the 3rd day after an uncomplicated right hemicolectomy?

Data analysis was undertaken using χ^2 analysis of tables and confidence intervals of proportions.

7.3 Results

Replies from the 200 respondents showed that the responsibility for prescribing fluid and electrolytes lay with the PRHO in 89%, with the SHO in 3%, was shared by the PRHO and the SHO in 6.5% and by the PRHO and registrar in 1.5%.

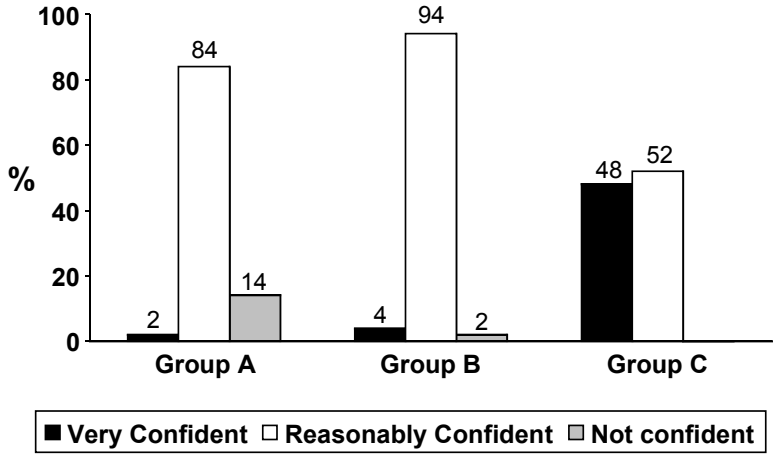


Fig. 7.1: *Level of confidence with prescribing fluid and electrolytes. (Group A vs. B χ^2=5.68, df 2, P=0.06; Group A vs. C χ^2=52.35, df 2, P<0.0001; Group B vs. C χ^2=25.66, df 2, P<0.0001)*

Most of the respondents were reasonably confident with prescribing fluid and electrolytes, with the SHOs being more confident than both groups of PRHOs (Fig. 7.1). The perception of quality of teaching on fluid and electrolyte balance in medical schools was very variable, with 3.5% rating it as excellent, 27.5% as good, 35.5% as satisfactory, 22% as unsatisfactory and 11.5% as poor. There was no difference between medical schools. The majority of respondents had not been given any formal or informal guidelines on fluid and electrolyte prescribing while on the surgical firm (Fig. 7.2). SHOs were less likely to have received guidelines

than PRHOs. 56% of respondents said that fluid balance charts were checked on the morning ward round, 41% said that they were checked later in the day and 3% admitted that the charts were not checked regularly.

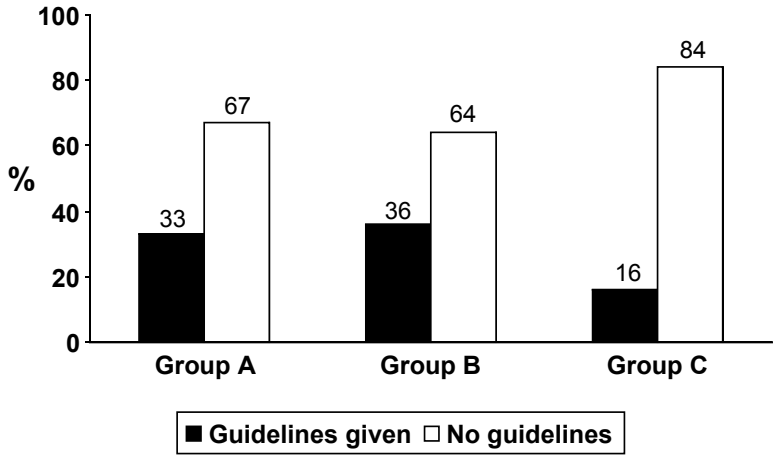


Fig. 7.2: *Respondents who were given formal or informal guidelines on fluid and electrolyte prescribing before or after commencing work on the surgical firm. (Group A vs. B χ^2=0.13, df 1, P=0.71; Group A vs. C χ^2=4.85, df 1, P=0.03; Group B vs. C χ^2=5.20, df 1, P=0.02)*

Responses to the daily sodium and potassium requirement and obligatory 24 h urinary volume are summarised in Table 7.1. A large proportion of all respondents did not know the correct sodium and potassium content of solutions commonly used on surgical wards (Table 7.2).

The answers concerning desired urine output ranged widely between 30-70 mL/h among 85% of respondents in Group A, 94% in Group B, and 98% in Group C. The rest thought that urine output should be more than 70 mL/h. Despite the well known errors in fluid balance charting on general wards, over 90% of respondents in each group felt that the addition of insensible losses to the previous

day's output was the best practical method to calculate daily postoperative fluid requirements. Postoperative weighing was not practised on surgical wards in any of the hospitals surveyed and less than 10% of all respondents knew that regular weighing was the best serial measure of fluid balance (Table 7.3).

Table 7.1: Daily sodium and potassium requirements in health in a 70 kg man and obligatory 24 hour urine output (responses given)

	Group A (%) n=100	**Group B (%) n=50**	**Group C (%) n=50**
Daily sodium requirement			
<60 mmol	-	2	2
60-100 mmol (desired range)	18	10	36
101-150 mmol	26	60	38
151-180 mmol	18	4	4
>180 mmol	1	4	2
Don't know	37	20	18
χ^2=37.4, df 10, P<0.0001. However, for B vs. C, P=0.07			
Daily potassium requirement			
<40 mmol	9	2	8
40-59 mmol	29	20	12
60-80 mmol (desired range)	47	70	70
>80 mmol	1	-	2
Don't know	14	8	8
χ^2=14.1, df 8, P=0.08			
Obligatory 24 h urine volume			
<500 mL	2	2	4
500-750 mL (desired range)	73	66	56
751-1000 mL	6	18	26
>1000 mL	7	8	10
Don't know	12	6	4
χ^2=15.7, df 8, P=0.05 (not significant after multiple testing). However, for A vs. B, P=0.18 and for B vs. C, P=0.78			

Table 7.2: Knowledge of sodium and potassium content of commonly used solutions

	Correct	Incorrect	Don't know	Correct	Incorrect	Don't know	Correct	Incorrect	Don't know	*P* value
Sodium content of 0.9% saline (154 mmol/L)	34	28	38	44	36	20	46	34	20	0.28
Sodium content of dextrose saline (30.8 mmol/L)		18	66	34	22	44	38	22	40	0.005
Sodium content of Gelofusine® (154 mmol/L)	2	6	92	8	38	54	8	38	54	0.15
Sodium content of Hartmann's solution (131 mmol/L)	12	10	78	16	20	64	18	50	32	0.58
Potassium content of 0.9% saline (0 mmol/L)	83	2	15	90	6	4	88	6	6	0.45
Potassium content of dextrose saline (0 mmol/L)	79	1	20	88	2	10	92	4	4	0.09
Potassium content of Gelofusine® (0 mmol/L)	28	1	71	42	8	50	54	8	38	0.007
Potassium content of Hartmann's solution (5 mmol/L)	6	17	77	12	42	46	16	38	46	0.13

Correct answers in parentheses. Margin of error of ±5% allowed

** χ^2 test applied. For calculations, "incorrects" and "don't knows" were considered as one group.*

Table 7.3: Best serial measure of fluid balance

	Group A (%) n=100	Group B (%) n=50	Group C (%) n=50
Blood Pressure	6	4	-
Body weight (desired answer)	7 (3-19)	8 (2-19)	14 (6-27)
Capillary refill	2	-	-
Clinical examination	8	-	4
Central/Jugular venous pressure	15 (9-24)	12 (5-24)	16 (7-29)
Fluid balance charts	8	6	6
Oedema	1	-	-
Postural hypotension	1	-	-
Pulse rate	1	-	2
Skin turgor	7	2	4
Serum urea and electrolytes	4	4	4
Urine output	35 (26-45)	64 (49-77)	48 (34-63)
Urinary osmolality	-	-	2
Don't know	5	-	-

Figures in parentheses are 95% confidence intervals (%)

Table 7.4: Knowledge of changes in urinary sodium excretion and osmolality in the early postoperative phase

Change in urinary sodium excretion in the early postoperative phase			
	Group A [% (95% CI)] n=100	**Group B [% (95% CI)] n=50**	**Group C [% (95% CI)] n=50**
Correct (Decreases)	37 (28-47)	44 (30-59)	68 (53-81)
Incorrect	32 (23-42)	26 (15-40)	24 (13-38)
Don't know	31 (22-41)	30 (18-45)	8 (2-19)
Change in urinary osmolality in the early postoperative phase			
	Group A [% (95% CI)] n=100	**Group B [% (95% CI)] n=50**	**Group C [% (95% CI)] n=50**
Correct (Increases)	44 (34-54)	48 (34-63)	80 (66-90)
Incorrect	22 (14-31)	26 (15-40)	18 (9-31)
Don't know	34 (25-44)	26 (15-40)	2 (0-11)

Only 39% of PRHOs were aware of the inability of the body to excrete an excess salt and water load in the early postoperative period (Table 7.4). SHOs fared better with these responses. More than 80% in each group agreed that serum urea and electrolytes should be measured daily in postoperative patients receiving intravenous fluids. There was some variation in potassium supplementation, but most supplements were appropriate (Tables 7.5 and 7.6). While 89% of all respondents thought that 3 L/day was an ideal postoperative fluid prescription, over a quarter were prescribing much more sodium (and, therefore, chloride) than desirable (Table 7.6).

Table 7.5: Postoperative potassium supplements (assuming serum potassium is normal)

	Group A (%) n=100		Group B (%) n=50		Group C (%) n=50	
	Day 0	Day 1	Day 0	Day 1	Day 0	Day 1
0 mmol/day	64	46	72	60	78	60
1-20 mmol/day	8	18	4	4	6	4
21-39 mmol/day	1	2	4	6	2	2
40-59 mmol/day	10	20	10	14	6	26
60-80 mmol/day	6	9	10	16	8	8
Don't know	11	5	-	-	-	-

Desired ranges:
Day 0: 0 mmol; Day 1: 0-20 mmol

Table 7.6: Usual 24 hour fluid prescription for a 70 kg man on the 3rd day after an uncomplicated right hemicolectomy

	Total volume of fluid					Volume of 0.9% saline						Potassium supplements (mmol)				
	4L	3L	2.5L	2L	Don't know	3L	2L	1.5L	1L	0.5L	Don't know	0	1-39	40-59	60-80	>80
Group A (%) n=100	3	96	-	-	1	3	29	-	67	-	1	8	6	32	52	2
Group B (%) n=50	-	86	14	-	-	2	10	-	86	2	-	6	6	32	54	2
Group C (%) n=50	-	78	20	2	-	-	20	6	70	4	-	6	6	34	50	4

Acceptable ranges:
Total fluid volume: 2.5-3L/day; volume of 0.9% saline: 0.5-1L/day; potassium supplements: 60-80 mmol/day

26% (95% CI: 20%-32%) of all respondents prescribed more saline than necessary and the potassium prescriptions of 48% (41%-55%) were outside the acceptable range

7.4 Discussion

This survey has shown that PRHOs, who were not ideally equipped either by experience or knowledge, were given the major responsibility for fluid and electrolyte prescribing, without much guidance or supervision. Most were reasonably confident in their ability to do this job, although their level of knowledge did not seem to justify this confidence. Instruction on the subject in medical schools was rated as unsatisfactory or poor by over a third of respondents and clearly did not prepare them adequately for the task. About two-thirds stated that they were not given any formal or informal guidelines on fluid and electrolyte prescribing either before or after commencing work on the surgical firm. Equally worrying was that 41% of PRHOs had to chart fluids later in the day, in the absence of seniors, and that 3% admitted that fluid balance charts were not checked regularly.

While most respondents knew the daily potassium requirements and were prescribing approximately the right amount of potassium, this was not the case with sodium and patients were being prescribed far greater amounts of sodium than necessary or, perhaps, safe. This may be a result of the tendency to tailor fluid prescriptions to achieve an "adequate flow of urine", and treat every dip in the urine output with a bolus of a salt containing solution irrespective of its cause, e.g. lack of water, or even when the reduced urine volume is just physiological and of no clinical significance. Less than 50% of respondents knew the sodium content of 0.9% saline, and even fewer that of dextrose saline, Hartmann's solution or Gelofusine®. Ignorance of the limited ability to excrete sodium in the early postoperative phase and the fact that plasma substitutes such as Gelofusine®

contain the same amount of sodium as 0.9% saline compound the problem. Almost all fluid prescriptions were based on the previous day's urine output, which is not necessarily best practice. Regular postoperative weighing, which is the best clinical measure of fluid balance was not practiced on any of the surgical wards in the hospitals surveyed and less than 10% of respondents were aware of the value of this measure. The net result is that postoperative patients receive much more water, sodium and chloride than necessary. Previous work (Stoneham and Hill 1997) has shown that some surgical patients may receive up to 5 L of water and 740 mmol each of sodium and chloride in a day. In the absence of major complications most surgical patients eventually excrete this overload. However, postoperative oedema, impaired wound healing, prolonged ileus, confusion, respiratory complications and delayed mobility may all be consequences of injudicious and excessive salt and water administration (Gil, Franch *et al.* 1997; Starker, Lasala *et al.* 1983). Moreover, patients with a positive fluid balance in excess of 67 mL/kg/day within the first 36 postoperative hours are more prone to develop pulmonary oedema (Arieff 1999). The latest NCEPOD report (Callum, Gray *et al.* 1999) has recorded that 20% of the patients sampled had either poor documentation of fluid balance or had unrecognised/untreated fluid imbalance and that this could contribute to serious postoperative morbidity and mortality. The report (Callum, Gray *et al.* 1999) recommended that fluid prescription should be accorded the same status as drug prescription and that medical and nursing staff should be trained in this area of care to increase awareness and spread good practice.

In most cases, there was no significant difference in responses between PRHOs early or late in their first jobs, nor between PRHOs and SHOs, indicating failure to learn from experience and/or a lack of in service training in this subject.

Errors in fluid balance have the same potential for toxicity and harm as the prescription of drugs. Protocols for management need review and fluid and electrolyte prescription by junior doctors requires closer supervision. In addition, undergraduate and postgraduate education and training of this basic patient management skill needs improvement, with emphasis on the practical applications.

8. Perioperative fluid and electrolyte management: A survey of consultant surgeons in the United Kingdom

The use of fluid and electrolyte therapy has become such a familiar part of medicine that it is rarely scrutinised

Richard L. Veech

8.1 Introduction

The 1999 UK National Confidential Enquiry into Perioperative Deaths report (Callum, Gray *et al.* 1999) has found that fluid imbalance contributes to serious postoperative morbidity and mortality and has recommended that "training in fluid management, for medical and nursing staff, is required to increase awareness and spread good practice". An earlier retrospective study (Stoneham and Hill 1997) showed that perioperative fluid prescriptions are extremely variable, with some patients receiving as much as 5 L fluid and 740 mmol sodium per day. A recent telephone questionnaire survey on 200 junior surgical doctors in the UK (Chapter 7) (Lobo, Dube *et al.* 2001) showed that pre-registration house officers (PRHOs), who are not ideally equipped either by experience or knowledge, are given the major responsibility for fluid and electrolyte prescribing, without much guidance or supervision. Perioperative fluid and electrolyte therapy in the UK is, therefore, an area of concern in terms of practice and training.

This survey was designed to assess the attitudes of consultant surgeons to fluid and electrolyte prescribing and to garner suggestions for improvement in education and training in the subject in order to promote better practice.

8.2 Methods

A postal questionnaire was designed and piloted. The questionnaire was then sent to 1091 British Fellows of the Association of Surgeons of Great Britain and Ireland in May and June 2000, after obtaining approval from the Secretary of the Association. Reminders were sent to non-responders after two months. The questionnaire was printed on an optically readable form (Formic Scanning

Systems, UK. http://www.formic.co.uk) and responses were exported into a Microsoft® Access 2000 database (Microsoft Corporation). The χ^2 and χ^2 for linear trend tests were used to determine statistical significance.

8.3 Results

Of the 1091 questionnaires sent, two were returned because of an incorrect address. 587 replies (54%) were received initially and a further 143 questionnaires were returned after sending 502 reminders, an overall response rate of 67% (730/1089). Of the responders, 14 did not complete the questionnaire because they had retired, one declined to answer and five felt the questionnaire was inappropriate because they had no junior staff working with them. 710 (65%) questionnaires were therefore analysed.

Respondents had been consultants for a median (interquartile range) of 12 (6-18) years, with 147 (21%) having been in post for < 5 years. The primary subspecialty interests (n, %) of the respondents were colorectal surgery (186, 26%), vascular surgery (132, 19%), general surgery (117, 16%), upper gastrointestinal surgery (101, 14%), breast surgery (89, 13%), hepato-pancreaticobiliary surgery (41, 6%), endocrine surgery (12, 2%), transplant surgery (11, 2%), and others (21, 3%). 424 (60%) respondents were based in district general hospitals, 180 (25%) worked in main teaching hospitals, 99 (14%) in associated teaching hospitals and 7 (1%) worked exclusively in the private sector.

While 383 (54%) consultants stated that the PRHO was the primary prescriber of fluid and electrolytes, only 204 (29%) thought that this should be the situation in an ideal world (Table 8.1).

Table 8.1: Responses to the questions "who is the primary prescriber of fluid and electrolytes and who should prescribe in an ideal world?"

	Who should prescribe in an ideal world →							
Actual primary prescriber ↓	PRHO	SHO	Specialist registrar	Staff grade	Consul-tant	Mixed juniors	Juniors + consultant	Total (Primary prescriber)
PRHO	189	65	96	1	24	6	2	383
SHO	5	73	45	1	8	3	0	135
Specialist registrar	4	8	85	0	9	0	1	107
Staff grade	0	0	1	2	3	1	0	7
Consultant	1	0	5	0	8	0	1	15
Mixed juniors	3	6	6	0	1	24	5	45
Juniors + consultant	2	0	3	0	2	0	10	17
Total (Who should prescribe)	204	152	241	4	55	34	19	709*

**One respondent did not answer this question.*
Boxed cells indicate a match between replies concerning actual primary prescriber and who should prescribe.
e.g. While 383 consultants stated that the PRHO was the primary prescriber, only 204 thought that this should be the case. In 189 instances, there was a match between PRHOs actually prescribing and consultants who thought this was appropriate.

Responses to questions concerning provision of guidelines or teaching to junior staff on fluid and electrolyte prescribing are summarised in Table 8.2. Consultants in main teaching and associated teaching hospitals were more likely to provide their junior staff with written guidelines than those in district general

hospitals. 38 consultants (4 upper gastrointestinal, 9 colorectal, 8 vascular, 8 breast, 1 endocrine, 5 general and 3 others) did not provide their junior staff with written or verbal guidelines and answered "no" or "don't know" when asked whether fluid and electrolyte balance was included in the induction programme for junior staff.

Table 8.2: Provision of guidelines or teaching on fluid and electrolyte prescribing

	District General Hospital	Associated Teaching Hospital	Main Teaching Hospital	Total
Formal written guidelines P=0.008, χ^2 for linear trend test				
Yes	79 (19)	26 (26)	50 (28)	155 (22)
No	345 (81)	73 (74)	129 (72)	547 (78)
Don't know			1 (0.6)	1 (0.1)
Verbal guidelines P=0.9 (NS), χ^2 for linear trend test				
Yes	368 (87)	87 (88)	156 (87)	611 (87)
No	56 (13)	12 (12)	24 (13)	92 (13)
Induction course P=0.5 (NS), χ^2 for linear trend test				
Yes	257 (61)	68 (69)	112 (62)	437 (62)
No	74 (17)	13 (13)	19 (11)	106 (15)
Don't know	93 (22)	18 (18)	49 (27)	160 (23)

"Don't knows" and "Nos" were grouped together for statistical calculations
All figures are n (%)

Table 8.3: Training of junior staff in fluid and electrolyte prescribing

	PRHOs	SHOs	Specialist registrars
Junior staff with adequate prior training	113 (16)	384 (54)	602 (85)
Received further training	96 (85)	288 (75)	330 (55)
Did not receive much further training	17 (15)	96 (25)	272 (45)
Junior staff without adequate prior training	584 (82)	299 (42)	76 (11)
Received further training	496 (85)	232 (78)	49 (65)
Did not receive much further training	88 (15)	67 (22)	27 (35)

As stated in the responses, 13 consultants did not have PRHOs, 27 did not have SHOs and 32 did not have SpRs.
All figures are n (%)

While the majority of consultants felt that their PRHOs and SHOs were not adequately trained in fluid and electrolyte prescribing before commencing work on the firm, a significant number admitted that juniors were not provided with much training whilst on the firm (Table 8.3). 420 (59%) consultants stated that they always checked fluid balance charts on their business ward rounds, 235 (33%) checked them frequently, 53 (7%) sometimes and 2 (0.3%) never did so. Only 462 (65%) consultants felt that fluid balance charts were accurately maintained (Table 8.4). Charts were more likely to be accurately maintained in main teaching hospitals. The most common reasons cited for inaccuracies were nursing shortages (132, 53%), inadequately trained or inefficient nurses (73, 29%), failure to recognise the importance of fluid balance charts (26, 11%) and

other reasons which included poor form design and partial shifts (10, 4%). 7 (3%) respondents gave no reason.

Table 8.4: Accuracy of fluid balance charts

	District General Hospital	Associated Teaching Hospital	Main Teaching Hospital	Private Hospital	Total
Charts accurate	269 (63)	57 (58)	130 (72)	6 (86)	462 (65)
Charts inaccurate	155 (37)	42 (42)	50 (28)	1 (14)	248 (35)

All figures are n (%)
P=0.04, χ^2 for linear trend test

Table 8.5: Water, sodium and potassium prescribing

	Too much	Too little	About right
Water	267 (38)	82 (12)	361 (51)
Sodium	188 (26)	105 (15)	417 (59)
Potassium	10 (1)	321 (45)	379 (53)

Right amount of water, sodium and potassium = 215 (30)
All figures are n (%)

Most respondents felt that their patients were not receiving appropriate amounts of water, sodium and potassium (Table 8.5). 385 (54%) either agreed (302) or agreed strongly (83) that salt and water overload frequently causes significant complications in postoperative patients while 325 (46%) either disagreed (304) or disagreed strongly (21). While 423 (60%) respondents preferred their juniors to err on the side of under-replacement of fluid in their postoperative patients, and 227 (32%) on the side of over-replacement, 60 (8%) felt that neither was desirable. Respondents who had been consultants for >5 years

were more likely to prefer erring on the side of under-replacement of fluid than those who were consultants for <5 years (63% [354/563] vs. 47% [69/147], $P<0.0005$, χ^2 test).

While 494 (70%) respondents felt that early postoperative fluid balance is best managed by surgeons, 143 (20%) thought this was best left to anaesthetists, 15 (2%) to others (such as specialist nurses) and 58 (8%) felt it should be under the joint care of surgeons and anaesthetists.

Table 8.6: Suggestions to improve educational programmes on fluid and electrolyte management

	Ranked 1st (n)	Ranked 2nd (n)	Ranked 3rd (n)	Total ranks (n)
Problem orientated ward rounds for senior students and new PRHOs	266	189	92	547
Formal written guidelines at the start of each PRHO and SHO job	148	185	146	479
Discussion of patient scenarios and management plans in the final year of medical school	123	156	146	425
Special study module in final year of medical school	121	63	91	275
Inclusion of vivas/OSCEs on fluid and electrolyte management in the MRCS examination	41	97	195	333

OSCEs = objective structured clinical examinations
MRCS = Member of the Royal College of Surgeons

Having been allowed more than one choice, 404 consultants thought hypoalbuminaemia in surgical patients was an indicator of malnutrition, 267 felt that it was a normal response to illness, 211 that it reflected fluid balance status and 39 that it represented other conditions such as sepsis. Two admitted that they did not know what hypoalbuminaemia truly represented. 245 consultants stated

that there was no role whatsoever for the use of salt poor albumin and 25 did not know whether there was any indication. 159 thought that there was a role for salt poor albumin infusion in postacute extracellular fluid overload with plasma hypovolaemia, 140 in hypoalbuminaemia and 30 in the resuscitation of acute hypovolaemia. 153 felt that there were other uses for the infusion.

Finally, the most favoured suggestions for improvement in educational and training programmes on perioperative fluid and electrolyte management are listed in Table 8.6.

8.4 Discussion

The high response rate to this survey indicates that surgical consultants in the UK consider fluid and electrolyte management important. The results of the enquiry highlight present problems and suggest some solutions.

The results of a recent survey of 200 junior doctors suggested that the PRHO was primarily responsible for fluid and electrolyte prescribing in 89% of instances (Chapter 7) (Lobo, Dube *et al.* 2001), although the present enquiry suggests that this was so in only 54% of surgical firms. This may reflect a difference in perception rather than reality. However, only 29% of consultants felt that PRHOs should be the primary prescribers, with 34% and 8% respectively thinking that this should be the responsibility of specialist registrars or consultants.

Only 38 (5.4%) consultants reported that their junior staff were not given any form of guidelines on fluid prescribing. In our junior doctor survey, however, more than 60% of PRHOs and 80% of SHOs said that they had not received any

guidelines on the subject (Chapter 7) (Lobo, Dube *et al.* 2001). This striking discrepancy may be because of differences in interpretation of the term "guidelines", or due to the fact that junior doctors either do not read written guidelines or do not remember verbal ones.

584 consultants felt that their PRHOs had received inadequate previous training in fluid and electrolyte prescribing and 88 of these admitted that this group of PRHOs did not receive much training on the subject whilst working on the firm. Inaccuracies in fluid balance charting appear to be an institutional nursing problem. Respondents felt that this needed to be addressed by improved nurse training and staffing, and increased awareness of the importance of accurate fluid balance charting in surgical patients.

Only 30% of consultants felt that their patients were receiving the required dose of water, sodium and potassium. These results closely match those of our earlier survey (Chapter 7) (Lobo, Dube *et al.* 2001) in which we found that a quarter of junior doctors were prescribing excessive amounts of sodium and only half were prescribing the required amount of potassium.

Although the majority (54%) were aware that even moderate salt and water overload can cause postoperative complications, a substantial minority disagreed. It is interesting to note that consultants appointed more than 5 years ago were more likely to be cautious in prescribing salt and water infusions than those appointed more recently. This may be because the more senior consultants were influenced by authors like Moore who in 1967 (Moore and Shires 1967) concluded, "The objective of (perioperative) care is restoration to normal physiology and normal function of organs, with a normal blood volume,

functional body water and electrolytes. This can never be achieved by inundation." On the other hand the Advanced Trauma Life Support and the Care of the Critically Ill Surgical Patient Courses may have influenced the responses of more recently appointed consultants. While the teachings of these courses are appropriate for hypovolaemic patients or patients with significant measured losses, they are not necessarily true for the uncomplicated elective surgical patient. There is, in fact, a growing body of evidence suggesting that excess salt and water administration is a greater problem than insufficiency and may cause greater morbidity (Arieff 1999; Callum, Gray *et al.* 1999; Frost, Wakefield *et al.* 2001; Gil, Franch *et al.* 1997; Lobo, Bjarnason *et al.* 1999; Lobo, Bostock *et al.* 2002b; Sitges-Serra and Franch-Arcas 1998; Starker, Lasala *et al.* 1983). Studies of fluid balance in patients receiving nutritional support have suggested that, in the perioperative period, an increase in weight, indicative of salt and water gain, results in poorer outcome (Gil, Franch *et al.* 1997; Lobo, Bjarnason *et al.* 1999; Sitges-Serra and Franch-Arcas 1998; Starker, Lasala *et al.* 1983). A retrospective study on patients developing postoperative pulmonary oedema has also suggested that pulmonary oedema can occur within the initial 36 postoperative hours when net fluid retention exceeds 67 mL/kg/day (Arieff 1999). More recently, our group has shown that salt and water overload in postoperative patients results in delayed return of gastrointestinal function and longer hospital stay, when compared to patients receiving a restricted postoperative salt and water regimen (Chapter 6) (Lobo, Bostock *et al.* 2002b). Increased postoperative morbidity and prolonged hospital stay in patients receiving excessive salt and water loads in the perioperative period have also been reported in a recent audit of a homogenous group of patients undergoing

colorectal resections (Frost, Wakefield *et al.* 2001). Moderate restriction of salt and water may also be beneficial in some critically ill patients. A review of 36 patients treated on an intensive care unit for septic shock has suggested that at least one day of negative fluid balance (< -500mL) achieved by the third day of treatment, may be an independent predictor of survival in such patients (Alsous, Khamiees *et al.* 2000).

There was some disagreement among respondents as to who should be responsible for immediate postoperative fluid prescription. Anaesthetists and surgeons both have a role but it needs to be better coordinated, using evidence-based protocols, since wide differences in practice exist based on tradition rather than scientific information.

There were widely differing views concerning the significance of hypoalbuminaemia and the use of salt poor albumin in perioperative patients. This reflects the confusion in current literature (1998; Allison and Lobo 2000; Pulimood and Park 2000).

The management of fluid and electrolyte balance in the perioperative period leaves much to be desired and better training and education of doctors and nurses is the key to improvement. Theoretical lectures on their own are inadequate for training in this essentially practical subject. Problem orientated ward rounds for medical students and PRHOs, with discussion of patient scenarios and management problems, as well as practical apprenticeship and guidance during the PRHO period are also required. Written guidelines were a popular suggestion, but there needs to be some method of ensuring that they are read and followed. Computerised self-learning packages may also be useful. OSCEs/vivas on fluid and electrolyte management are already included in the MRCS examination, but

as the bulk of prescribing is done by PRHOs, this measure is unlikely to have a major influence on patient care. 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.

Appendix

Questionnaire on fluid and electrolyte management after major surgery

Q1 What is your main sub-specialty ? - please tick one box only

UGI ☐ HPB ☐ Colorectal ☐ Vascular ☐

Breast ☐ Endocrine ☐ Transplant ☐ General Surgery ☐

Other ☐ please specify _____

Q2 In which type of hospital do you primarily work ? (please tick one box)

DGH ☐ Associated teaching ☐ Main teaching ☐ Private ☐

Q3 How many years have you been a consultant ? ☐☐

Q4 Who primarily prescribes fluid and electrolytes on your firm ? (please tick one box)

PRHO ☐ SHO ☐ SpR ☐ Staff grade ☐ Consultant ☐

Q5 Who do you think should prescribe fluid and and electrolytes in an ideal world? (please tick one box)

PRHO ☐ SHO ☐ SpR ☐ Staff grade ☐ Consultant ☐

Q6 Are your junior staff provided with formal written guidelines on fluid and electrolyte prescribing ?

Yes ☐ No ☐ if yes, please could you enclose a copy

Q7 Are your junior staff provided with informal verbal guidelines on fluid and electrolyte prescribing ?

Yes ☐ No ☐ if yes, by whom

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Survey : 500 Serial : 1202 Page : 1

Scanning by Formic Ltd

Q8 Is "fluid and electrolyte balance" included in the induction course for junior doctors in your hospital ?

Yes ☐ No ☐ Unsure or don't know ☐

Q9 How often do your junior staff discuss difficult fluid and electrolyte balance management problems with you ?

Never ☐ Rarely ☐ Occasionally ☐ Frequently ☐

Q10 Do you think your junior staff have had sufficient training in fluid and electrolyte prescribing before they come to work on your firm ?

	Yes	No
PRHOs	☐	☐
SHOs	☐	☐
SpRs	☐	☐

Q11 Do they have much training in fluid balance while on your firm ?

	Yes	No
PRHOs	☐	☐
SHOs	☐	☐
SpRs	☐	☐

Q12 Are fluid balance charts inspected on your business rounds ?

Always ☐ Frequently ☐ Sometimes ☐ Never ☐

Q13 Do you think that fluid balance charts on your wards are accurately maintained ?

Yes ☐ No ☐

If no, please suggest why this may be

Survey : 500 Serial : 1202 Page : 2

Scanning by Formic Ltd

Q14 Do you feel that postoperative patients generally receive

	Too much	Too little	About right
Water	☐	☐	☐
Sodium	☐	☐	☐
Potassium	☐	☐	☐

Q15 Do you think that salt and water overload frequently causes significant complications in postoperative patients ?

Strongly Agree ☐ Agree ☐ Disagree ☐ Strongly Disagree ☐

Q16 For most of your postoperative patients, do you think it is better to err on the side of

under replacement of fluid ☐ over replacement of fluid ☐

Q17 In your opinion, early postoperative fluid balance is best managed by

anaesthetists ☐ surgeons ☐ other ☐

if other, please specify

Q18 In your opinion, does hypoalbuminaemia in surgical patients usually reflect ?

nutritional status ☐ fluid balance state ☐ normal response to illness ☐

other ☐ if other please specify

Q19 In your opinion is there any role for salt poor albumin infusion in

acute hypovolaemia ☐

hypoalbuminaemia ☐

post acute extracellular fluid overload with plasma hypovolaemia ☐

none of these but other uses ☐

no role whatsoever ☐

Q20 How do you think educational programmes on fluid and electrolyte balance could be improved ?

(Please rank [1-3] up to three choices in decreasing importance)

☐ Special study module with examination in final year of medical school

☐ Discussion of patient scenarios and management plans in final year of medical school

☐ Problem orientated ward rounds for senior students and new PRHOs with special reference to commonly used fluids and their electrolyte content

☐ Formal written guidelines at the start of each PRHO and SHO job

☐ Inclusion of vivas/OSCEs on fluid and electrolyte management in the MRCS exam

☐ Other

☐ Other

Thank you for completing the questionnaire

Please check you have answered all the questions on all 4 sheets

Please return the questionnaire in the pre-paid envelope provided

Studies in Normal Volunteers

9. Body water compartment measurements: A comparison of bioelectrical impedance analysis with tritium and sodium bromide dilution techniques

A little water clears us of this deed.

William Shakespeare
Macbeth

9.1 Introduction

Water and electrolytes permit the flow of an electrical current and bioelectrical impedance analysis (BIA) utilises this simple principle to measure body water compartments (Nyboer 1972). Most BIA devices use an alternating current at a frequency of 50kHz. This current passes mostly through the extracellular compartment, but some also passes through the cells. At low frequencies (1-5 kHz) the capacitive nature of the cell membranes does not allow the current to penetrate the cell, so impedance is only related to the extracellular compartment. At high frequencies (200-500 kHz) the current penetrates the cell membranes and the recorded impedance is a measure of the combined intracellular and extracellular spaces (Hannan, Cowen *et al.* 1995).

Major shifts in the body fluid compartments occur in patients with malnutrition, cardiac, renal or hepatic failure, and in postoperative and septic patients (Cheek 1953; Lobo, Bjarnason *et al.* 1999; Plank, Connolly *et al.* 1998; Shizgal 1981). The so called gold standards for measuring total body water (TBW) (tritium or deuterium dilution) and extracellular water (ECW) (sodium bromide [NaBr] dilution) are invasive, expensive, labour intensive, time consuming and cannot be applied repeatedly to monitor patients during therapy. On the other hand BIA has the potential benefits of being non-invasive, portable and able to provide instant results. Previous work undertaken by us (Simpson, Anderson *et al.* 2000), however, has shown that although estimates of TBW in healthy volunteers using single frequency BIA (SFBIA) and dual frequency BIA (DFBIA) were consistent and reproducible, there was a systematic difference in estimates obtained using the two devices.

This study was undertaken to assess the comparability of body water compartment estimates in healthy volunteers using SFBIA and DFBIA with established reference methods of tritium and NaBr dilution.

9.2 Methods

Ten healthy medical student volunteers took part in this study after an overnight fast, a 12 h abstinence from caffeine and alcohol, and voiding of the bladder. Subjects were excluded if they had participated in another trial in the last 3 months, they had received radioisotopes in the last 12 months and if any of the female volunteers had a positive pregnancy test on the day of the study.

The height of each volunteer was recorded and weight before BIA was performed using a single frequency (50 kHz) device (Bodystat 1500, Bodystat Ltd; Isle of Man, UK) and a dual frequency (5 and 200 kHz) device (Bodystat Dualscan 2005) as described in Chapter 2.

Subjects then had an intravenous cannula inserted into each forearm; one was used for the administration of pharmaceuticals and the other to sample blood. A 4 mL venous blood sample was taken prior to injection to measure the background concentrations of tritiated water and bromide, which are markers used to assess TBW and ECW respectively. Each patient was given 3.7 MBq (100 μCi) of tritiated water (^3H_2O) in 10 mL sterile water IV from a syringe which was weighed before and after the injection along with 50 mL of a 5% NaBr solution IV.

9.2.1 Tritium Analysis (Vaughan and Boilin 1961)

Repeated 2×4 mL blood samples were taken every 45 min after injection for up to 4.5 h. 4 mL aliquots of all samples were sublimed in vacuum at room temperature. 1 mL of the resultant water and of appropriate standards were analysed for ^3H_2O activity using an LKB Wallac 1215 Rackbeta II counter.

It was found necessary to use a vacuum sublimation method rather than assaying serum directly because of the marked reduction in counting efficiency induced by the presence of bilirubin and other quenching agents in the samples of such subjects.

After correction for the effects of quenching, the specific activity of all samples was expressed in terms of counts/min/g of water and the TBW calculated:

Total count in standard (DPM_{st}, in counts per minute) =.

$$\frac{\text{mean standard counts} \times [\text{total standard volume } (\mu L)]}{\text{standard sample volume } (\mu L)}$$

Total count in dose (DPM_{ds}, in counts per minute) =

$$\frac{[\text{mass of dose (g)}] \times \text{total standard count}}{\text{mass of standard (g)}}$$

Total body water (TBW in litres) =

$$\frac{\text{total dose count} \times \text{dilution factor} \times 0.94 \times 0.96}{(\text{sample count} - \text{background count})}$$

where 0.94 is the correction for the concentration of protein in the plasma and 0.96 corrects for exchange of ^3H with non-aqueous hydrogen in the body.

9.2.2 NaBr Analysis

4 mL blood samples were centrifuged at 2500 rpm for 20 min at room temperature. Protein-free ultrafiltrates of serum were obtained using a Whatman VectaSpin 3 centrifuge filter (Whatman International Ltd, Maidstone, Kent,

England). After centrifugation the supernatant plasma was transferred to the column and recentrifuged at 2000 rpm.

The serum ultrafiltrate was analysed with high-performance liquid chromatography using 75mmol/L KH_2PO_4 as the mobile phase. 30 μL of the clear serum ultrafiltrate was injected onto the chromatograph column (12.5 cm × 4.6 mm ID Whatman Partisphere SAX column) for each test and the column was cleaned using 5 mL of distilled water after each test. The chromatographs of human serum filtrate were measured to produce a value for the height of the bromide peak in comparison with a previously measured standard. These values were used to calculate the post $[Br]_{plasma}$, then the ECW volume was estimated as:

$$\text{ECW (litres)} = \frac{\text{dose} \times 0.90 \times 0.95}{\text{post}[Br]_{plasma} - \text{pre}[Br]_{plasma}}$$

where 0.90 is a correction factor for intracellular bromide (Br) found mainly in red blood cells, and 0.95 is the Donnan equilibrium factor (Cheek 1953; Cheek 1961). Pre and post refer to the bromide levels immediately preceding and at set times following administration of NaBr.

The 3 h 45 min sample was used for the final estimation of ECW and TBW as previous work has shown that 3-4 h is adequate equilibration time for both tritium and sodium bromide (Hannan, Cowen *et al.* 1995; Kim, Wang *et al.* 1999; Schoeller and Jones 1987; Vaisman, Pencharz *et al.* 1987). BIA measurements were repeated at this time point.

9.2.3 Statistical Analysis

The data were analysed using Spearman's coefficient of rank correlation and Bland-Altman plots were used to assess agreement (Bland and Altman 1986). The Wilcoxon signed ranks test was used to test results obtained using different methods for statistical significance and indicative equations were derived using linear regression analysis where systematic differences were demonstrated.

9.3 Results

Ten healthy volunteers (8 male, 2 female) with a mean (SE) age of 21.9 (0.2) years and a mean (SE) BMI of 24.8 (0.9) kg/m^2 participated in the study. There was no difference between the BIA measurements done at the start of the study and at 3 h 45 min. Fig. 9.1a shows that there was good correlation between body weight and estimates of TBW using tritium (r^2=0.73, *P*=0.004), SFBIA (r^2=0.73, *P*=0.011) and DFBIA (r^2=0.71, *P*=0.001). However, the same figure also demonstrates that SFBIA and, to a greater extent, DFBIA, underestimated TBW when compared to tritium. Excellent correlation was also demonstrated between TBW measurements using SFBIA and DFBIA (r^2=0.99, *P*<0.0001), SFBIA and tritium (r^2=0.96, *P*<0.0001), and DFBIA and tritium (r^2=0.96, *P*<0.0001). However the Bland-Altman plots (Fig. 9.1b-d) show that the closest agreement demonstrated was between TBW estimates using tritium and SFBIA, although SFBIA tended to underestimate TBW by ~1 L compared to tritium dilution (Fig 9.1d). On the other hand, DFBIA underestimated TBW by ~5 L compared to tritium dilution (Fig. 9.1c) and ~4 L when compared to SFBIA (Fig. 9.1b). The regression slope in Fig. 9.1b demonstrates a systematic difference

between measurements made using SFBIA and DFBIA, with the magnitude of the difference increasing with higher TBW. These differences are also apparent in Table 9.1.

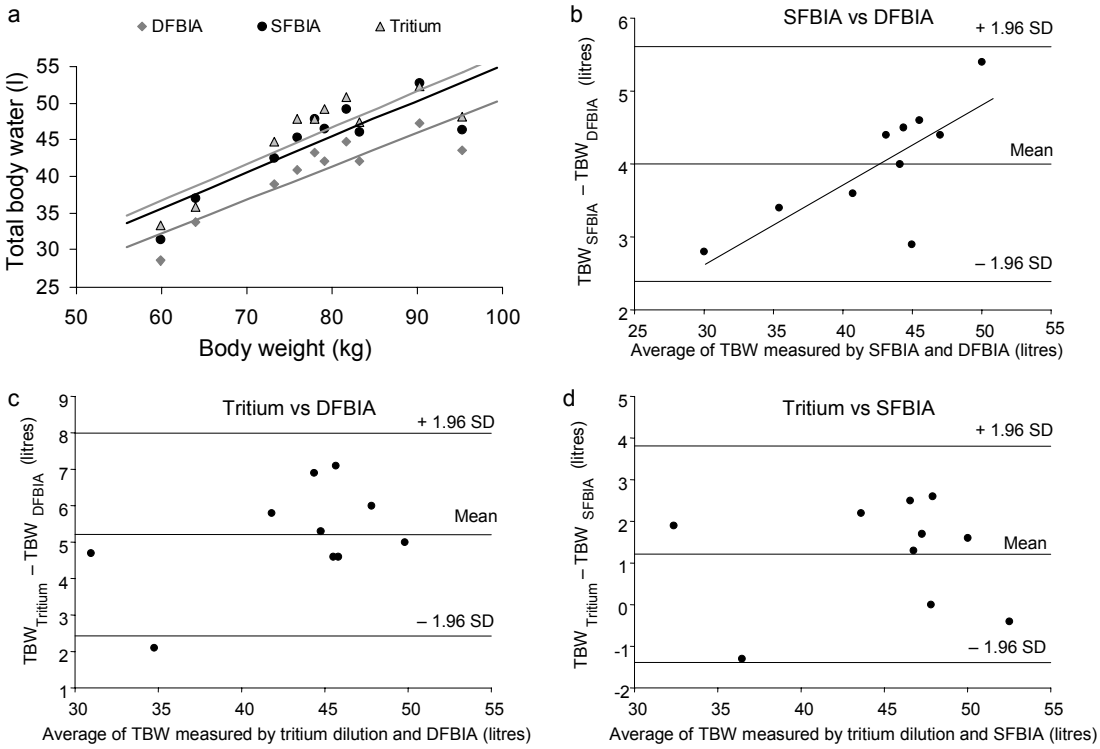


Fig. 9.1: *Correlation between measurements of total body water using single frequency bioelectrical impedance analysis (SFBIA), dual frequency bioelectrical impedance analysis (DFBIA) and tritium dilution with body weight (a). The Bland-Altman plots demonstrate agreement between the methods (b-d). The best agreement was between measurements using tritium and SFBIA (d).*

Table 9.1: Total body water measurements

Method used to estimate total body water	Mean TBW (litres)	Standard error (litres)
Tritium dilution[a]	46.1	2.3
Single frequency bioelectrical impedance[b]	44.5	1.9
Dual frequency bioelectrical impedance[c]	40.5	1.8

a vs. b P=0.29 (NS), a vs. c P=0.009, b vs. c P=0.005
Wilcoxon signed ranks test

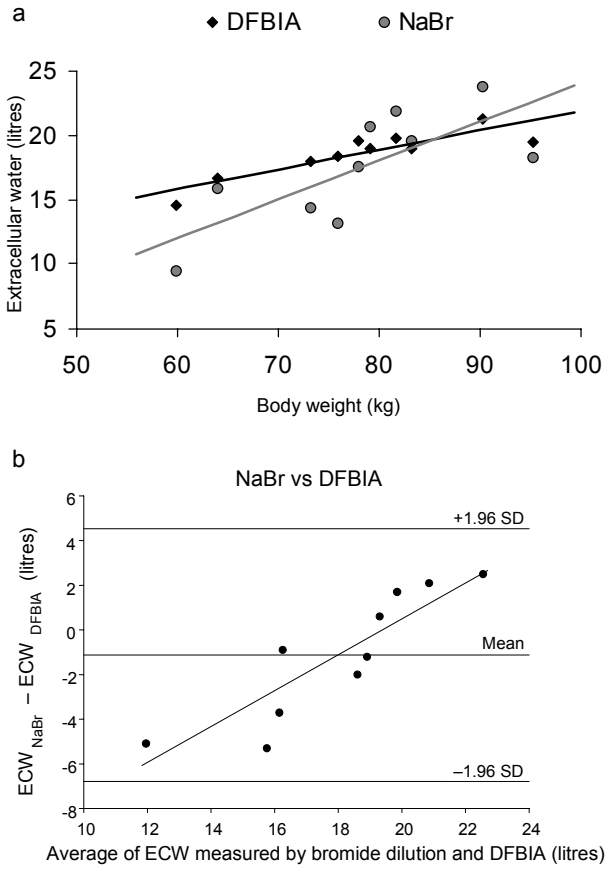


Fig. 9.2: *Correlation between measurements extracellular water using dual frequency bioelectrical impedance analysis (DFBIA) and NaBr dilution with body weight (a). Bland-Altman plot demonstrating agreement between the two methods for estimation of extracellular water (b). The presence of a systematic error is highlighted by the regression line (b).*

There was correlation between body weight and estimates of ECW using DFBIA (r^2=0.77, *P*=0.004) and NaBr dilution (r^2=0.56, *P*=0.006). However, the two lines in Fig. 9.2a intersect at 85 kg, indicating that DFBIA overestimated ECW at weights lower than this and underestimated ECW at higher weights, when compared to NaBr dilution. The Bland-Altman plot in Fig. 9.2b demonstrates that, on the whole, DFBIA underestimated ECW by ~1 L when compared to NaBr dilution, with all the points lying within the limits of

agreement. However, the slope of the regression line in Fig. 2b emphasises the systematic error between ECW measurements using the two methods, and indicates that when compared with NaBr dilution techniques, DFBIA overestimated ECW when the ECW was less than 19 L and underestimated ECW when the ECW was more than 19 L.

Fig. 9.3 demonstrates the excellent correlation (r^2=0.99, P<0.0001) between TBW as measured by SFBIA and DFBIA. As previously shown, DFBIA underestimated TBW by ~4 L when compared to SFBIA; however, the equation of the graph shown in Fig 9.3 (y = 1.1067x – 0.3217) can be applied to the DFBIA result to convert it into the equivalent, accurate SFBIA result:

$$TBW_{SFBIA} = 1.11\ TBW_{DFBIA} - 0.32$$

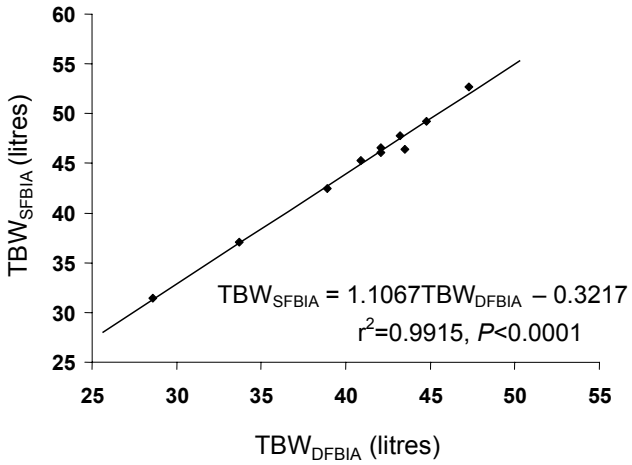


Fig. 9.3: *Correlation between total body water measurements using single frequency bioelectrical impedance analysis (TBW_{SFBIA}) and dual frequency bioelectrical impedance analysis (TBW_{DFBIA}).*

9.4 Discussion

This study demonstrates that in healthy volunteers, SFBIA accurately measured TBW when compared with tritium dilution techniques and that estimates of ECW using DFBIA were comparable with those using NaBr dilution. However DFBIA underestimated TBW by ~4 L and ~5 L compared to SFBIA and tritium dilution respectively, a result consistent with previous work showing that measurements of TBW with SFBIA more closely match measurements made by tritium dilution than those made with DFBIA (Plank, Monk *et al.* 1995).

Direct measurement of body fluid compartments is difficult, if not impossible. Even radioisotope dilution and bromide space techniques are indirect and have themselves to be evaluated against other indirect methods rather than an absolute gold standard. This is very different from calibration, where known quantities are measured by a new method and the result compared with the true value or with measurements made by a highly accurate method (Bland and Altman 1986). The errors in estimates of TBW and ECW depend on the adequacy of the equilibrium time, the losses in urine and the errors in the various assumed correction factors. Hannan *et al.* (Hannan, Cowen *et al.* 1995) investigated the tritium equilibration time in 43 surgical patients and concluded that 3-4 h represented an adequate equilibrium period. They also found that the corrections for losses in the urine during the first 3 h were insignificant and urine collection was not necessary.

The volume occupied by tritiated water is greater than the TBW volume because of exchange with labile hydrogen of protein and other body constituents. Furthermore a correction factor must be introduced to take account of the protein

content of plasma (0.94) and along with the Donnan correction factor these all constitute sources of error when measuring TBW.

ECW was analysed using the 3 h 45 min plasma sample because in accordance with previously published methods (Kim, Wang *et al.* 1999; Schoeller and Jones 1987; Vaisman, Pencharz *et al.* 1987) bromide equilibration is usually achieved within 3-4 h after NaBr administration. Loss of bromide in the urine is negligible and no corrections are necessary for this (Schoeller and Jones 1987).

In conclusion, TBW measurements obtained in healthy volunteers using SFBIA were comparable with those obtained using tritium dilution techniques. There was a systematic difference between measurements of TBW made using SFBIA and DFBIA and this confirms previous work (Simpson, Anderson *et al.* 2000). Application of a correction factor to the regression equations for TBW calculation using DFBIA can make the estimates more accurate. ECW estimates obtained using DFBIA and NaBr dilution were comparable, despite the existence of a systematic error.

The results of this study are also in the BMedSci dissertation of Alastair Simpson, submitted to the University of Nottingham.

10. The dilution and redistribution effects of rapid 2 litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters, serum biochemistry and bioelectrical impedance analysis in normal subjects: a double blind crossover study

Water, water, everywhere,
And all the boards did shrink;
Water, water, everywhere,
Nor any drop to drink.

Samuel Taylor Coleridge,
The Rhyme of the Ancient Mariner

10.1 Introduction

Although intravenous crystalloids are the most commonly prescribed treatment in hospitalised patients, there are remarkably few studies of their effect in normal subjects with which to compare the response in patients, in particular the extent and time scale of their diluting effects on haematocrit and serum albumin and the rate at which they are excreted. An infusion of 2 L 0.9% saline over 2 h in high risk preoperative patients produced a moderate fall in serum albumin concentration (34 to 30 g/L) (Mullins and Garrison 1989) and a bolus infusion of 0.9% saline has been shown to produce a significant decrease in haemoglobin and haematocrit (Grathwohl, Bruns *et al.* 1996). Experimental work on anaesthetised rabbits has demonstrated that acute expansion of the body water by 0.9% saline infusions resulted in a greater dilution of serum albumin than could be explained by expansion of plasma volume alone (Mullins and Bell 1982). Studies using mathematical models to analyse volume kinetics of Ringer acetate solution in healthy volunteers 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 and Drobin 1998; Hahn and Svensen 1997; Svensen and Hahn 1997).

Hypoalbuminaemia is a well-documented sequel to major trauma (Cuthbertson and Tompsett 1935; Frawley, Howard *et al.* 1955), sepsis (Plank, Connolly *et al.* 1998) and surgery (Hoch-Ligeti, Irvine *et al.* 1953; Moore and Clarke 1982). The work of Fleck *et al*. (Fleck, Raines *et al.* 1985) suggested that hypoalbuminaemia, in the acute phase of injury, may be due to redistribution of albumin from the circulation to the interstitial fluid consequent on an increase in

vascular permeability. In these situations, however, patients also receive large volumes of crystalloid infusions. This, coupled with the antidiuretic response to trauma and starvation with inability to normally excrete a salt and water load (Keys, Brozek *et al.* 1950; Moore 1959; Wilkinson, Billing *et al.* 1949), results in oedema and increased total body water (TBW) and extracellular fluid (ECF) volume (Plank, Connolly *et al.* 1998). This dilutes the serum albumin and reduces its concentration further. We have previously demonstrated, in hypoalbuminaemic oedematous postoperative patients, that as excess salt and water is excreted, the serum albumin concentration rises by 1 g/L for every litre of fluid lost (Chapter 3) (Lobo, Bjarnason *et al.* 1999), reflecting reversal of previous dilution.

The present study was conducted to measure the responses of normal subjects to crystalloid infusions as a basis for comparison with those in patients. In particular, the extent and time course of their diluting effects in haematocrit and serum albumin were measured.

10.2 Methods

This double blind, crossover study was conducted on 10 healthy young adult male volunteers after obtaining informed consent. Only those subjects with a body weight of 65-80 kg and a BMI of 20-25 kg/m^2 were included. Those with chronic medical conditions or acute illness in the six-week period preceding the study, on regular medication or with a history of substance abuse, were excluded.

Subjects reported for the study at 0900 hours after a fast from midnight. After voiding of the bladder, height was recorded, weight measured and body mass index calculated. Bioelectrical impedance analysis was performed with

single (50k Hz) and dual frequency (5 and 200 kHz) devices (Bodystat 1500 and Bodystat Dualscan 2005 respectively, Bodystat Ltd., Isle of Man, UK) using tetrapolar distal limb electrodes (Anderson, Simpson *et al.* 2001; Simpson, Lobo *et al.* 2001). TBW and ECF volume were calculated using regression equations programmed into the devices (Chapter 2).

Two venous cannulae were inserted; one in each forearm and blood was sampled for full blood count, haematocrit, serum electrolytes (sodium, potassium, chloride and bicarbonate), albumin, and osmolality, and blood glucose. The urine collected was analysed for osmolality and concentrations of sodium and potassium.

Two litres of 0.9% saline (154mmol/L sodium, 154mmol/L chloride; Baxter Healthcare Ltd., Thetford, Norfolk, UK) or 5% dextrose (Baxter Healthcare Ltd., Thetford, Norfolk, UK) were then infused over 60 min in random order on separate days, with subjects in the supine position. A nurse who was not involved in the study masked all labels on the infusion bags with opaque tape and also performed the randomisation. The infusion started at time 0. Pulse rate and blood pressure were recorded at 15 min intervals for 2 h and then at 30 min intervals for a further 4 h. Subjects were not allowed to eat or drink for the duration of the study and remained supine for most of the time. They stood up to void urine and be weighed, but blood samples were taken after lying supine for at least 15 minutes.

Body weight, bioelectrical impedance analysis and the above blood tests were repeated at hourly intervals for 6 h. Subjects voided their bladders as the need arose and, in all cases, at the end of 6 h. The time of each micturition was

noted and urine volume measured. Urine samples were analysed for osmolality and concentrations of sodium and potassium. Urinary glucose content was assessed using dipsticks.

The experiment was repeated with a 2 L infusion of 5% dextrose in those who received 0.9% saline initially and vice versa 7-10 days later. The randomisation code was broken at the end of the study.

Data were expressed as mean (95% confidence intervals). Data were tested for statistical significance using the t-paired test and tests of between-subjects effects (saline *vs*. dextrose) were performed using the general linear model repeated measures procedure.

10.3 Results

The 10 male volunteers had a mean (SE) age of 22.1 (0.3) years, height of 1.78 (0.01) m, initial weight of 73.6 (1.8) kg and BMI of 23.2 (0.5) kg/m^2. The mean (95% CI) baseline serum albumin concentration, haemoglobin and haematocrit of the volunteers before infusion of saline and dextrose were 44.0 (39.4-48.6) g/L, 14.9 (13.9-15.9) g/dL and 44.8 (43.4-46.2) %, and 43.8 (40.1-47.6) g/L, 15.2 (14.2-16.3) g/dL and 45.1 (43.4-46.9) % respectively (P=NS, t-paired test). Six volunteers received 0.9% saline as the first infusion and four received 5% dextrose initially. All volunteers remained haemodynamically stable throughout the study.

Serum albumin concentration fell significantly (20% after saline and 16% after dextrose) at 1 h after both infusions (Fig. 5.1). The decrease was more pronounced and prolonged after saline (P<0.001). Changes in haematocrit and

haemoglobin were similar, but of a smaller magnitude (7.5% after saline and 6.5% after dextrose) (Fig 5.1). Sequential changes in serum osmolality, sodium, potassium, chloride, bicarbonate, and blood glucose are shown in Fig. 10.2. Despite the changes in serum biochemistry, mean corpuscular volume in each individual subject did not change by more than $\pm$1 fL from baseline during the course of each experiment. Urinary responses are summarised in Table 10.1. All subjects had glycosuria (4+, $\geq$ 55 mmol/L) in the first sample voided after infusion of dextrose. Glycosuria was not detected in pre-infusion or subsequent samples.

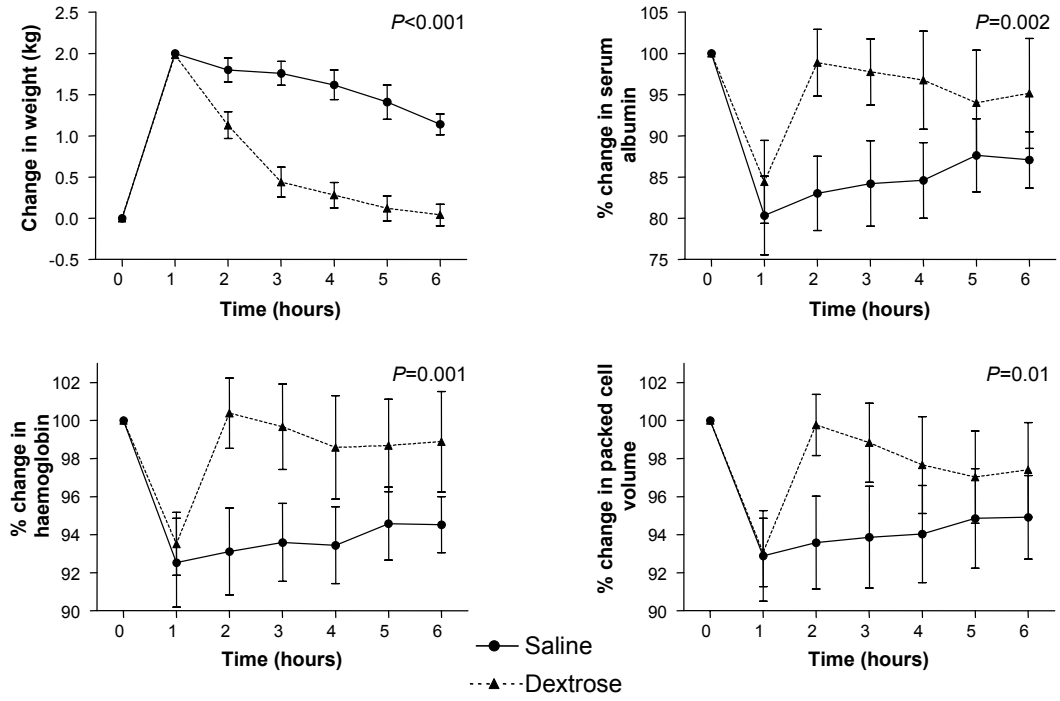


Fig. 10.1: *Changes in body weight, and percentage changes in serum albumin concentration, haemoglobin concentration and packed cell haematocrit after infusion of 2 litres of 0.9% saline and 5% dextrose over 1 hour. All values are Mean (95% CI). P values are for tests of between-subjects effects (saline vs. dextrose) obtained using repeated measures testing.*

Changes in weight were equivalent to the volume of fluid infused and urine excreted (Fig. 10.1 and Table 10.1). Although all volunteers gained 2 kg in weight at the end of each infusion, weight returned to baseline more slowly after saline than after dextrose because of the different rate of excretion of these two solutions.

Table 10.1: Urinary changes

	Saline	Dextrose	*P* value*
Time to first micturition (min)	212 (141-283)	78 (68-88)	0.002
Number of micturitions over 6 h	1.7 (0.9-2.5)	3.4 (2.6-4.2)	0.002
Total post-infusion urine volume over 6 h (mL)	563 (441-685)	1663 (1512-1813)	<0.001
Total post-infusion urinary sodium over 6 h (mmol)	95 (75-116)	26 (15-38)	<0.001
Total post-infusion urinary potassium over 6 h (mmol)	37 (29-45)	10 (8-13)	<0.001
Osmolality of pre-infusion urine (mOsm/kg)	880 (381-1379)	773 (372-1174)	0.87 (NS)
Osmolality of pooled post-infusion urine (mOsm/kg)	630 (540-721)	129 (115-144)	<0.001

*n=10, all values Mean (95% CI). *t-paired test used to calculate statistical significance*

It was interesting to note, however, that measured impedance decreased initially after saline infusions and increased after dextrose infusions. Calculated TBW increased by up to 2 L after a lag period of 1 h in volunteers who received saline infusions, but remained unchanged or decreased after dextrose infusions (Fig. 10.3). The mean increase in TBW after saline infusions was closer to 2 L when measured by single frequency bioelectrical impedance analysis than by the dual frequency device.

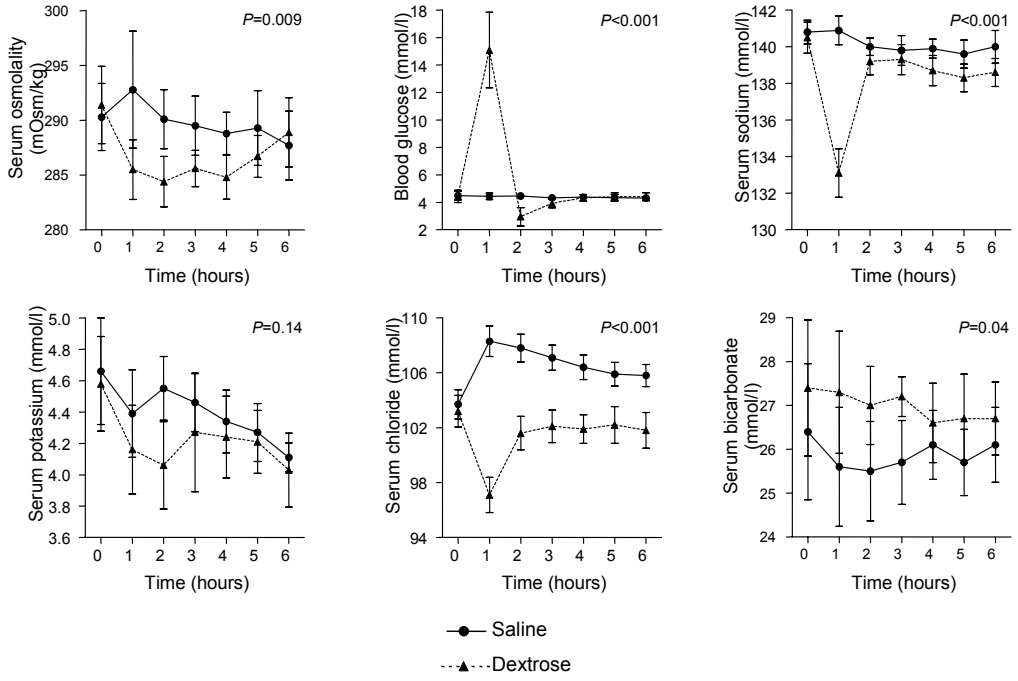


Fig. 10.2: *Changes serum osmolality, blood glucose, and serum concentrations of sodium, potassium, chloride and bicarbonate after infusion of 2 litres of 0.9% saline and 5% dextrose over 1 hour. All values are Mean (95% CI). P values are for tests of between-subjects effects (saline vs. dextrose) obtained using repeated measures testing.*

One subject developed transient periorbital oedema after both infusions, and another developed the same complication after infusion of saline. Five subjects felt light headed for a short duration about 2 h after commencement of the dextrose infusion and this corresponded with the documented reactive hypoglycaemia (Fig. 10.2). No other side effects were observed.

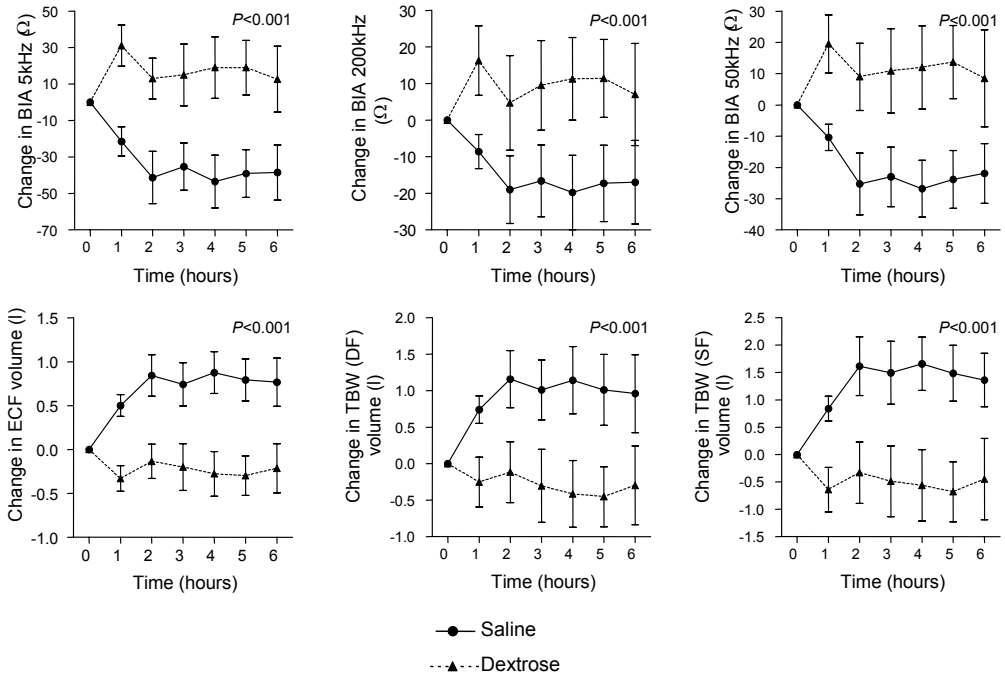


Fig. 10.3: *Changes in measured impedance and calculated body water compartments after infusion of 2 litres of 0.9% saline and 5% dextrose over 1 hour. All values are Mean (95% CI). P values are for tests of between-subjects effects (saline vs. dextrose) obtained using repeated measures testing. BIA = bioelectrical impedance analysis, DF = dual frequency, ECF = extracellular fluid, SF = single frequency, TBW = total body water.*

10.4 Discussion

It is extraordinary that one of the most commonly administered treatments in medical and surgical practice, intravenous crystalloids, has been little tested in normal subjects and that there is so little information concerning normal responses with which to compare those in patients. This study shows that, even in normal subjects, the administration of 0.9% saline precipitated a fall in serum albumin by 20% and haematocrit by 7.5%. This effect was sustained for more than 6 h because only one third to one half of the infused dose of sodium and water had been excreted during this period. This illustrates the contribution of crystalloid infusions to the fall in serum albumin concentration in patients after surgery or

during illness when ability to excrete an excess salt and water load is even less (Keys, Brozek *et al.* 1950; Moore 1959; Wilkinson, Billing *et al.* 1949). The effect of 5% dextrose infusion was more transient, since almost all the water had been excreted by two hours and the volume of distribution was the whole body water rather than just the ECF volume as with saline. The diuretic effect of dextrose was probably partly due to the osmotic effect of hyperglycaemia in the first hour as well as reduced secretion of vasopressin in response to a lower plasma osmolality in the first and second hours after infusion.

Although saline infusion may be expected to induce a diuresis in a patient who is salt and water depleted by excess losses, the mechanism for disposing of a salt and water load in excess of normal (dependent, perhaps, on atrial natriuretic peptide) may be less efficient than that for excreting excess water (changes in osmolality causing reduction in vasopressin secretion). If there is a volume deficit (blood, plasma or salt and water) there is an oliguric response which is reversed by volume repletion with crystalloid or colloid. However, if one administers water or its equivalent (5% dextrose) to a normovolaemic subject, the osmoreceptors switch off vasopressin and there is a diuresis. Similarly, if one administers an isotonic solution with sodium as the osmotic agent holding that fluid in the extracellular space, the water component of saline will only be excreted *pari passu* or secondary to the sodium excretion. This is borne out by our results which suggest that although the mechanisms for adjusting water balance are sensitive and efficient, the mechanisms for disposing of excess sodium, even in normal individuals, are remarkably sluggish by comparison. These observations have

implications for fluid management in clinical situations where the margin of error between adequate fluid replacement and overload is much narrower.

The changes in haematocrit and haemoglobin after saline infusions were very similar to those demonstrated by Grathwohl *et al*. (Grathwohl, Bruns *et al.* 1996) who infused 30 mL/kg of 0.9% saline in normal volunteers over 30 minutes. The greater proportional change at 1 h in serum albumin concentration (20% after saline and 16% after dextrose) compared to that in haemoglobin and haematocrit (7.5% after saline and 6.5% after dextrose) partly reflects the fact that albumin distributes only in the plasma space, while red blood cells (and haemoglobin) are distributed in the whole blood space. Plasma volume expansion is equal to blood volume expansion in absolute terms (mL), but the relative expansion and dilution (%) is greater in the smaller plasma and albumin space. A decrease in haematocrit (or haemoglobin) by 7.5% is the result of expansion of the blood volume by 8.1% $\left(\frac{100\times100}{100-7.5}-100\right)$. With a preinfusion haematocrit of 45% (and plasma volume of 55%), this expansion in total blood volume would result in a 14.7% increase in plasma volume $\left(\frac{(55+8.1)\times100}{55}-100\right)$. Nonetheless, the 20% decrease in serum albumin concentration after saline infusion cannot be explained by dilution alone and suggests a change in albumin distribution as well (Bell and Mullins 1982a; Bell and Mullins 1982b; Mullins and Bell 1982; Mullins and Garrison 1989; Svensen and Hahn 1997). Although it has been suggested that plasma volume expansion may increase the transcapillary escape rate of albumin (Parving, Rossing *et al.* 1974), the greater than expected fall in serum albumin concentration results from a net loss of albumin from the intravascular

compartment in response to the crystalloid infusions (Mullins and Bell 1982; Mullins and Garrison 1989) appears not to be a result of increased capillary permeability (Taylor, Parker *et al.* 1981), but a consequence of increased convective transport of albumin across the microvasculature into the interstitium because of dilution of the plasma colloid oncotic pressure by the infusion (Aukland and Nicolaysen 1981; Mullins and Garrison 1989; Perl 1975). The mechanism of escape of albumin by convection could be used to explain part of the differences noted after saline and dextrose infusions. We speculate that one of the immediate effects of both infusions was to produce a shift of albumin, water and sodium (after saline infusion) into the interstitial space which reverses more slowly with saline because of its slower excretion. The secondary fall in serum albumin and haemoglobin after dextrose could be a result of a return of water from the intracellular to the extracellular compartment following the water diuresis.

All subjects developed hyperchloraemia after saline infusions, and serum chloride concentrations remained elevated even 6 h after the infusion (Fig. 10.2). This is consistent with published data (Williams, Hildebrand *et al.* 1999) and reflects the greater chloride content of 0.9% saline (154 mmol/L) than that of serum (95-105 mmol/L). Bicarbonate concentrations remained normal and, contrary to an earlier study in which subjects received much greater volumes of 0.9% saline (50 mL/kg over 1 h) (Williams, Hildebrand *et al.* 1999), we were unable to demonstrate an acidosis.

Subjects emptied their bladders earlier and more frequently after dextrose than after saline infusions. They also voided greater volumes of urine of low

osmolality, and low sodium and potassium content after dextrose infusions (Table 10.1). Body weight returned to baseline at the end of 6 h following dextrose infusions, while weight at 6 h following saline infusions remained more than 1 kg above baseline (Fig. 10.1), reflecting retention of over half the infused sodium and water. All subjects developed transient hyperglycaemia at the end of the dextrose infusion resulting in an osmotic diuresis. This is borne out by the fact that the first urine sample voided after infusion of dextrose contained $\geq$55 mmol glucose/L. In addition, serum osmolality and sodium concentration decreased substantially at the end of the dextrose infusion (Fig. 10.2).

It was interesting that body impedance at all three measured frequencies decreased after saline infusion and increased after dextrose (Fig. 5.3). This may be because the electrolytes in saline conduct electricity and, therefore, decrease resistance. On the other hand, infusion of dextrose provides electrolyte-free water, which, being a poor conductor, increases resistance. These findings corroborate other work (Anderson, Simpson *et al.* 2001) suggesting that the ability of bioelectrical impedance analysis to detect changes in body water depends on whether the change is in pure water, or water and electrolytes. This greatly limits the role of bioelectrical impedance analysis in the clinical situation as a pure water (or electrolyte-poor water) excess registers as a decrease in TBW because of the increase in impedance $\left(TBW \propto \frac{height^2}{impedance} \right)$, and may explain, to some extent, why previous studies have not been able to accurately document fluid shifts using bioelectrical impedance analysis (Cha, Hill *et al.* 1995; Koulmann, Jimenez *et al.* 2000; Than, Woodrow *et al.* 2000; Zillikens, van den Berg *et al.* 1992). In addition, calculated changes in TBW after saline infusion were more accurate

using single frequency bioelectrical impedance analysis than dual frequency bioelectrical impedance analysis, corroborating previous studies that single frequency bioelectrical impedance analysis correlates more closely with dilutional techniques for TBW estimation than dual frequency (Simpson, Lobo *et al.* 2001) and multifrequency bioelectrical impedance analysis (Plank, Monk *et al.* 1995).

11. The effect of volume loading with 1 litre intravenous infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on the renin angiotensin aldosterone system and volume controlling hormones: A randomised, double blind, crossover study

Before our extremely remote ancestors could come ashore to enjoy their Eocene Eden or their Palaeozoic Palm Beach, it was necessary for them to establish an enclosed aqueous medium which would carry on the role of sea water.

John L. Gamble

11.1 Introduction

Although the endocrine and physiological responses to changes in water balance or to sodium deficit appear to be highly efficient, those to sodium excess seem less so. In a recent study we showed that normal subjects retained more than 60% of a 60 min 2 L 0.9% saline infusion after 6 h whereas a similar 5% dextrose load was entirely excreted by 2 h (Chapter 10) (Lobo, Stanga *et al.* 2001). Several lines of evidence suggest that suppression of the renin angiotensin aldosterone system (RAAS) is one important mechanism for both the immediate and long term regulation of sodium excretion following sodium loading (Brown, Davis *et al.* 1963). Previous studies have demonstrated that the suppression of specific components of the RAAS cascade, particularly renin and thereby angiotensin II (Ang II) (Singer, Markandu *et al.* 1994), aldosterone (Singer, Shirley *et al.* 1991) and together with atrial natriuretic peptide (Sagnella, Shore *et al.* 1985) have also been demonstrated to play an important role in sodium handling following saline infusion. However, to date the response of the RAAS and related volume controlling hormones when stimulated by an intravenous infusion of 0.9% (w/v) saline compared with an infusion of 5% dextrose has not been fully explored.

The present study was undertaken with two main objectives: firstly to compare the responses to such loading on the RAAS and volume controlling hormones in normovolaemic subjects, and secondly to develop a safe 1 L infusion test to measure salt and water tolerance in patients.

11.2 Methods

11.2.1 Study design and setting

Randomised, double blind crossover volunteer study set in a university teaching hospital.

11.2.2 Subjects

Five healthy young adult male volunteers with a body weight of 65-80 kg and a BMI of 20-25 kg/m^2 were recruited after obtaining written informed consent. Those with chronic medical conditions or acute illness in the six-week period preceding the study, on regular medication or with a history of substance abuse, were excluded.

11.2.3 Baseline assessment, blood and urine sampling

Subjects reported for the study at 0900 h after a fast from midnight and having abstained from alcohol, nicotine, tea and coffee from 1800 h. After voiding of the bladder, height was recorded, weight measured, and body mass index calculated. Subjects were not allowed to eat or drink for the duration of the study and remained supine most of the time. They stood up to void urine and be weighed, but blood samples were taken after lying supine for at least 20 min.

Two venous cannulae (19 G Venflon, Ohmeda, Helsingborg, Sweden) were inserted into the antecubital fossa of each arm, where they remained for the duration of the study. The cannula in the left arm was used solely for blood sampling and that in the right arm for infusion. Subjects rested for 20 min following cannula insertion. After this period, basal pulse rate and blood pressure

were determined from the right arm using an automatic sphygmomanometer (Dinamap, Critikon Inc., Tampa, USA). Measurements were made in duplicate and the mean recorded. An initial 30 mL blood sample was drawn from the indwelling venous cannula for analysis of full blood count, serum electrolytes (sodium, potassium, chloride and bicarbonate), urea, creatinine, albumin, osmolality, blood glucose, plasma active renin (PAR), plasma inactive renin (PIR), plasma angiotensinogen, aldosterone, arginine vasopressin (AVP), atrial natriuretic peptide (ANP) and insulin. The urine collected was analysed for osmolality and concentrations of urea, sodium, potassium and glucose. The sodium:creatinine ratio was also calculated to provide an indication of sodium balance prior to the study.

11.2.4 Infusion and sampling protocol

One litre of 0.9% saline (154 mmol/L sodium, 154 mmol/L chloride; Baxter Healthcare Ltd., Thetford, Norfolk, UK) or 5% dextrose (Baxter Healthcare Ltd., Thetford, Norfolk, UK) was infused over 60 min in random order on separate days, with subjects in the supine position. An IVAC infusion pump (IVAC Corporation, San Diego, CA, USA) was used to deliver the infusions at a constant rate (16.6 mL/min). A nurse who was not involved in the study masked all labels on the infusion bags with opaque tape and also performed the randomisation. The infusion started at time 0.

Body weight and blood samples for haematological, biochemical and hormonal tests were repeated at hourly intervals for 4 h. Subjects voided their bladders as the need arose and, in all cases, at the end of 4 h. The time of each

micturition was noted and urine volume measured. Urine samples were analysed for osmolality and concentrations of urea, sodium, potassium and glucose.

The experiment was repeated with a 1 L infusion of 5% dextrose in those who received 0.9% saline initially and vice versa 7-10 days later. The randomisation code was broken at the end of the study.

11.2.5 Hormonal analysis

Four mL of blood were collected for each hormonal assay (5 mL for ANP). Samples for plasma renins, angiotensinogen, AVP and insulin were collected in EDTA containing vacutainers (Becton Dickinson Vacutainer Systems Europe, France), samples for aldosterone in heparin coated vacutainers (Becton Dickinson) and samples for ANP in polypropylene tubes containing 250 μL EDTA:aprotinin (Trasylol) inhibitor mixture (Voto, Hetmanski *et al.* 1990). All blood samples for hormonal assays were centrifuged at 2000 rpm for 10 min at 4°C. The plasma was decanted and stored at -20° C until assay. All samples from each subject were analysed in the same assay. No samples were stored for longer than 3 months. All hormones reported are stable under these conditions for at least 12 months.

PAR and angiotensinogen were measured by radioimmunoassay (RIA) using the method described by Tetlow and Broughton Pipkin (Tetlow and Broughton Pipkin 1983). The inter-assay CV for these two hormones was 13% and 9%, respectively. Plasma for analysis of total renin concentration (TRC) was acid-activated using the method described by Lumbers (Lumbers 1971), and

samples measured using the method as for PAR. PIR was calculated by subtracting the PAR values from the TRC. The inter-assay CV was 6%.

Plasma aldosterone was measured by RIA using a 100-tube Coat-A-Count® Aldosterone assay kit (Diagnostics Products Corporation Ltd., Caernarfon, UK). The manufacturer's inter-assay and intra-assay CV was stated as 8.4% and 3.3%, respectively. All samples were measured in a single assay, with an intra-assay CV of 9.2%.

Plasma AVP samples were analysed using RIA according to the methods described by Rooke and Bayliss (Rooke and Baylis 1982). The CVs for this assay procedure were: intra-assay control 8.2%, aqueous inter-assay control 5.5%, 2 pmol/L extracted inter-assay control 14.1%, and 5 pmol/L extracted inter-assay control 8.0%.

Plasma ANP was measured using a Shionoria ANP *in vitro* test kit (CIS Bio International, Filiale de Schering S.A., France). The manufacturers inter-assay CV, assessed using 3 samples with different concentrations, was stated as 5.7% for 19.9 pg/mL, 6.0% for 95.5 pg/mL and 5.8% for 563.1 pg/mL. The intra-assay CV, assessed in the same way, was stated as 6.3% for 18.9 pg/mL, 4.1% for 92.0 pg/mL and 3.6% for 579.3 pg/mL. The samples were all measured in a single assay with an intra-assay CV of less than 10%.

Plasma insulin samples were analysed using an Immulite 2000 immunometric "sandwich" assay kit on a DPC Immulite 2000 analyser (Diagnostic Products Corporation, Los Angeles, USA). The intra-assay CV at the time of assay using an independent manufacturer's (Bio-Rad, Hemel Hempstead,

UK) quality control material was 11.8% for 8.10 μIU/mL, 13.3% for 27.6 μIU/mL and 12.7% for 74.7 μIU/mL.

11.2.6 Statistical analysis

Differences between group medians were tested for demographical, biochemical and haematological statistical significance using the Wilcoxon signed ranks test, and tests of between-subjects effects (saline *vs*. dextrose) were performed using the general linear model repeated measures procedure.

Summary data are presented as absolute or percentage change from baseline. This latter approach was used when baseline values differed. In such cases, statistical tests were performed on this transform data.

11.3 Results

The 5 male subjects had a median (IQR) age of 19.4 (19.3-31.8) years and height of 1.78 (1.73-1.85) m. Baseline parameters before the start of each infusion are summarised in Table 11.1. The sodium:creatinine ratios were comparable prior to study on both days (P=0.500; Table 11.1). Two subjects received 0.9% saline as the first infusion and three received 5% dextrose initially. All subjects remained haemodynamically stable throughout the study. All subjects completed the study and none experienced any side effects.

Changes in weight were equivalent to the volume of fluid infused and urine excreted (Fig. 11.1 and Table 11.2). Subjects gained 1 kg in weight at the end of each infusion. After the saline infusion, weight had returned to baseline at

the end of 4 h, but subjects had lost an additional 0.5 kg at the same time point after dextrose.

Table 11.1: Baseline parameters

	Before saline infusion	Before dextrose infusion
Weight (kg)	72.7 (67.7-78.4)	72.7 (68.1-78.3)
BMI (kg/m^2)	22.8 (22.4-23.3)	22.8 (22.5-23.3)
Pulse rate (beats/min)	61 (52-68)	57 (51-66)
Systolic blood pressure (mmHg)	126 (114-128)	127 (115-129)
Diastolic blood pressure (mmHg)	64 (56-80)	59 (56-79)
Haematocrit (%)	41.4 (41.0-43.9)	42.7 (40.2-44.0)
Serum albumin (g/L)	36.0 (34.0-38.5)	36.0 (34.0-37.5)
Serum osmolality (mOsm/kg)	295 (291-298)	290 (289-296)
Plasma active renin (ng/ml/hr)	3.4 (1.9-4.1)	2.3 (1.8-4.5)
Plasma inactive renin (ng/ml/hr)	13.7 (12.7-20.0)	13.4 (12.1-17.8)
Angiotensinogen (mg/ml)	1.07 (0.97-1.29)	0.93 (0.65-0.96)
Aldosterone (pg/ml)	49 (49-122)	66 (54-90)
Arginine vasopressin (pMol/l)	0.8 (0.5-1.6)	0.9 (0.5-2.7)
Atrial natriuretic peptide (pg/ml)	11.8 (11.6-16.8)	11.2 (10.3-16.1)
Insulin (μIU/ml)	5.3 (4.5-9.7)	7.6 (4.3-14.7)
Sodium:Creatinine ratio	9.1 (4.4-13.0)	11.7 (3.1-13.8)

n=5, all values are median (IQR). Differences between parameters not significant (Wilcoxon signed ranks test).

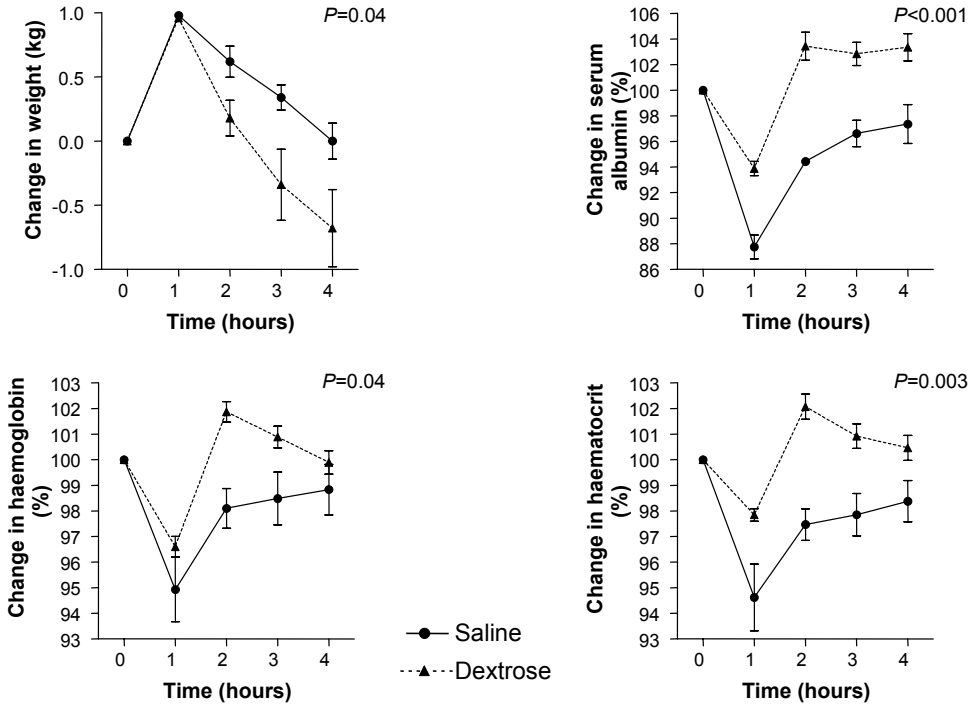


Fig. 11.1: *Changes in body weight, and percentage changes in serum albumin concentration, haemoglobin concentration and haematocrit after infusion of 1 litre of 0.9% saline and 5% dextrose over 1h. All values are Mean (SE). P values are for tests of between-subjects effects (saline vs. dextrose) obtained using the general linear model repeated measures procedure.*

Table 11.2: Urinary changes

	Saline	Dextrose	*P* value*
Total post-infusion urine volume over 4 h (mL)	730 (405-983)	1665 (745-1768)	0.04
Total post-infusion urinary sodium over 4 h (mmol)	93 (79-109)	44 (31-62)	0.04
Total post-infusion urinary potassium over 4 h (mmol)	30 (28-37)	24 (13-48)	0.69 (NS)
Osmolality of pre-infusion urine (mOsm/kg)	747 (651-1066)	840 (834-1028)	0.35 (NS)
Osmolality of pooled post-infusion urine (mOsm/kg)	486 (345-740)	194 (139-290)	0.04
Total post-infusion urinary urea over 4 h (mmol)	88 (73-102)	78 (67-98)	0.50 (NS)

*n=5, all values are median (IQR). *Wilcoxon signed ranks test.*

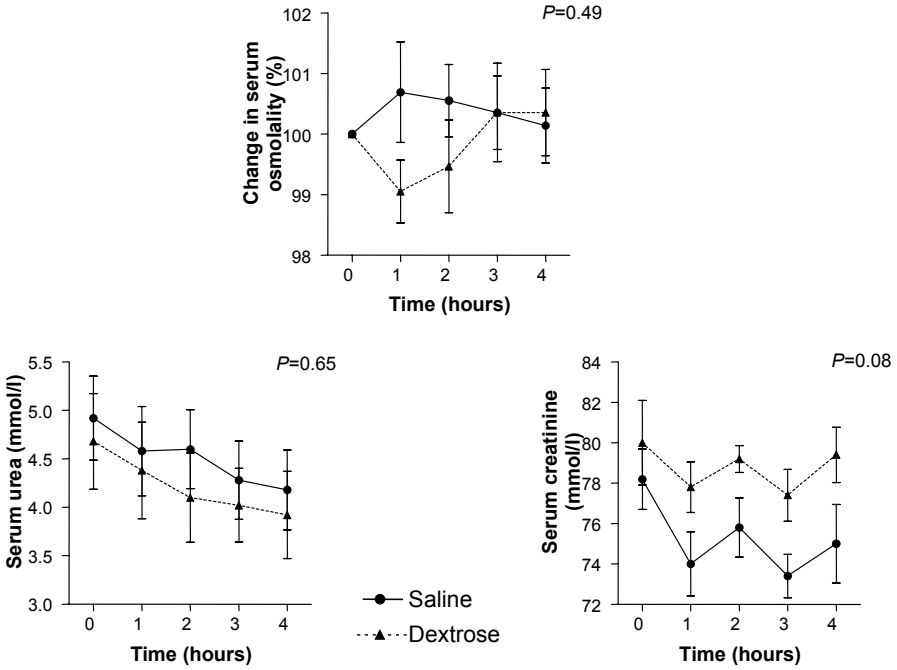


Fig. 11.2: *Percentage change serum osmolality, and changes in serum concentrations of urea and creatinine after infusion of 1 litre of 0.9% saline and 5% dextrose over 1h. All values are Mean (SE). P values are for tests of between-subjects effects (saline vs. dextrose) obtained using repeated measures testing.*

Serum albumin concentration fell significantly (≅12% after saline and 6% after dextrose) at 1 h after both infusions (Fig. 11.1). The decrease over the period of observation was more pronounced and prolonged after saline (P<0.001). Changes in haematocrit and haemoglobin were similar, but of a smaller magnitude (≅5% after saline and 3% after dextrose) (Fig. 11.1). Despite the changes in serum biochemistry (see below), mean corpuscular volume in each individual subject did not change by more than ±1 fL from baseline during the course of each experiment. Sequential changes in serum osmolality, urea, creatinine, sodium, potassium, chloride, bicarbonate, and blood glucose are shown in Figs. 11.2 and 11.3. Of particular note is the difference in evoked change in serum chloride concentration, which was maximal at 1 h after infusion (P<0.001). Urinary responses are summarised in Table 11.2. Three subjects had glycosuria (2+, 2.8-

5.5 mmol/L) in the first sample voided after infusion of dextrose. Glycosuria was not detected in pre-infusion or subsequent samples, or after saline infusions.

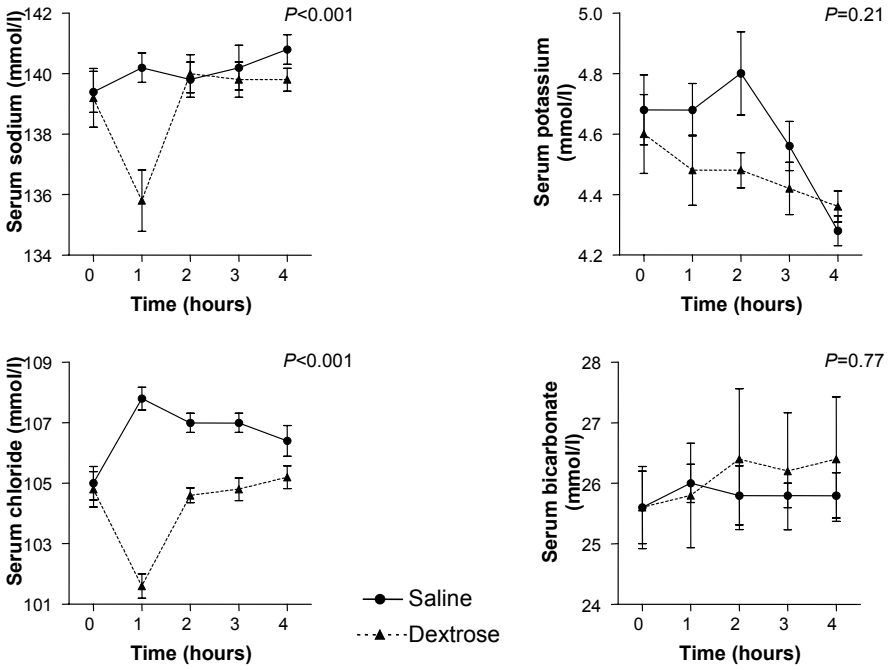


Fig. 11.3: *Changes serum concentrations of sodium, potassium, chloride and bicarbonate after infusion of 1 litre of 0.9% saline and 5% dextrose over 1h. All values are Mean (SE). P values are for tests of between-subjects effects (saline vs. dextrose) obtained using repeated measures testing.*

Plasma hormone responses are summarised in Figs. 11.4 and 11.5. There was a pronounced difference in the response of PAR depending upon whether volume expansion was generated by saline or dextrose infusion. Following both fluid administrations the PAR initially decreased dramatically. After saline, the decrease was more pronounced compared with the dextrose, and continued to decline until the end of the study period with no sign of returning to baseline (*P*=0.003). After dextrose, the initial fall in PAR began to return towards baseline over the remainder of the study.

The PIR response did not differ between the saline and dextrose administrations. Following saline, PIR fell and remained below baseline until the

end of the study, whereas after dextrose PIR concentrations fluctuated around basal levels.

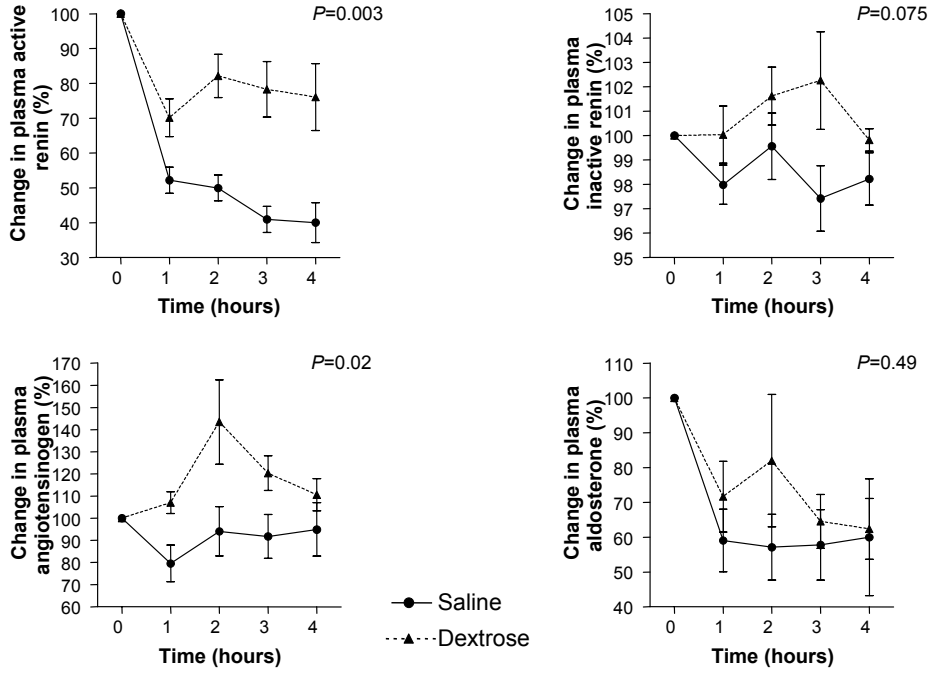


Fig. 11.4: *Hormones of the RAAS. Sequential percentage changes in plasma active renin concentration (PAR), plasma inactive renin concentration (PIR), plasma angiotensinogen and plasma aldosterone after 1 litre intravenous infusions of 0.9% saline and 5% dextrose. All values are Mean (SE). P values are for tests of between-subjects effects (saline vs. dextrose) obtained using repeated measures testing.*

The plasma angiotensinogen response also differed depending on the fluid infused (P=0.02). Following dextrose a delayed increase above basal concentrations was observed, compared with a small decline after saline, both returning toward baseline by the conclusion of the study. A pronounced fall in aldosterone concentration which was maintained until the end of the study was observed following both saline and dextrose.

Following both saline and dextrose an initial steep decline in plasma AVP concentrations was observed with no sign of return to baseline by the end of the

observation period in the saline group. In comparison, the dextrose response was more transient, with an initial steep decrease which was not maintained (*P*=0.41).

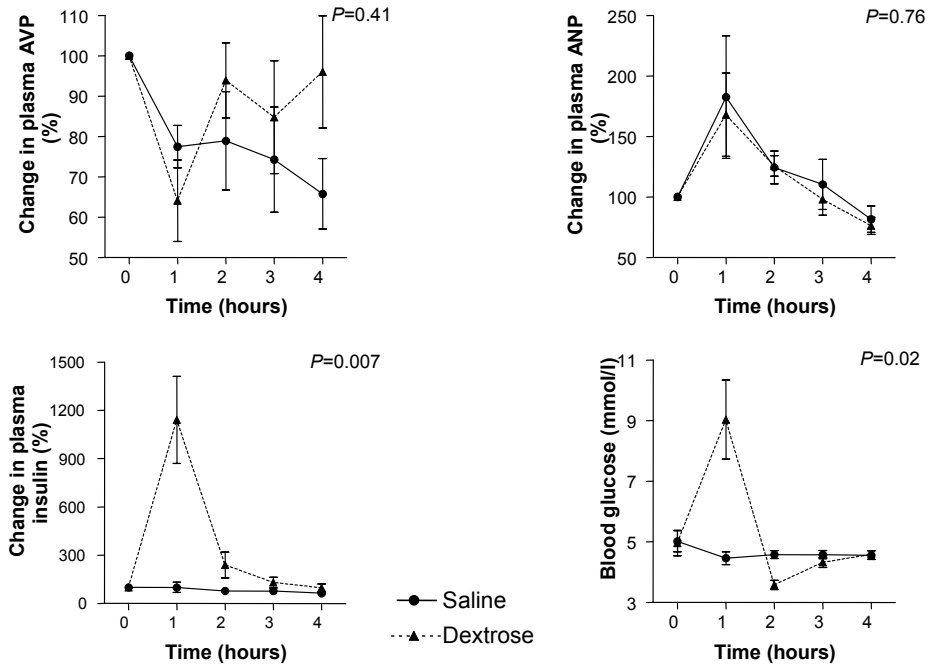


Fig. 11.5: *Sequential percentage changes in plasma arginine vasopressin (AVP), atrial natriuretic peptide (ANP), insulin and blood glucose concentration after 1 litre intravenous infusions of 0.9% saline and 5% dextrose. All values are Mean (SE). P values are for tests of between-subjects effects (saline vs. dextrose) obtained using repeated measures testing.*

The response of ANP to both infusions was remarkably similar. There was a marked increase after 1 h followed by a decline beyond basal concentrations by the conclusion of the study. Thus, no significant effect between treatments was observed (*P*=0.76).

As expected, dextrose administration was associated with a substantial increase in plasma insulin concentrations which returned to baseline within 4 h. This was associated with a similar transient peak in blood glucose concentrations. The saline infusion had no effect on either parameter.

11.4 Discussion

This study has confirmed our previous work (Chapter 10) (Lobo, Stanga *et al.* 2001) and that of others (Heller, Crocco *et al.* 1996) that the excretion of an intravenously infused bolus of dextrose is much more rapid than that of saline. In this study, at the end of 4 h, 93 mmol of the 154 mmol of the sodium and 730 mL of the 1 L of water in the saline infusion had been excreted in the urine although weight had returned to baseline, suggesting some insensible loss over the period of the experiment. In contrast, after a 1 L 5% dextrose load, subjects excreted approximately 1.6 L of water and were in a negative water balance of approximately 600 mL. Previously, when we infused a 2 L load, almost 2/3^{rds} of the infused saline was retained at 6 h while almost all the dextrose had been excreted at the end of 2 h (Chapter 10) (Lobo, Stanga *et al.* 2001). Singer et al. (Singer, Shore *et al.* 1987) also reported a slow excretion of saline after a 2 L intravenous load, only 29% having been excreted after 195 min. These findings suggest, as one might expect, that the manner in which the body handles fluid loads is dependent on both the nature and volume of the infusion.

The changes in haematocrit and haemoglobin after saline infusions were very similar to those demonstrated by Grathwohl *et al*. (Grathwohl, Bruns *et al.* 1996) who infused 30 mL/kg of 0.9% saline in normal volunteers over 30 min. The greater proportional fall at 1 h in serum albumin concentration (≅12% after saline and 6% after dextrose) compared with that in haemoglobin and haematocrit (≅5% after saline and 3% after dextrose) was qualitatively similar but of smaller magnitude than that seen after a 2 L infusion (Chapter 10) (Lobo, Stanga *et al.* 2001). We (Chapter 10) (Lobo, Stanga *et al.* 2001) found a 20% fall in serum

albumin after saline and 16% after dextrose, corresponding with falls in haematocrit of 7.5% and 6.5%, respectively. This may partly reflect the differential distribution of albumin and red blood cells within the intravascular space. Plasma volume expansion is equal to blood volume expansion in absolute terms (mL), but the relative expansion and dilution (%) is greater in the smaller plasma and albumin space. A decrease in haematocrit by 5.4% is the result of expansion of the blood volume by 5.7% $\left(\frac{100\times100}{100-5.4}-100\right)$. With a pre-infusion haematocrit of 42% (and plasma volume of 58%), this expansion in total blood volume would result in a 9.8% increase in plasma volume $\left(\frac{(58+5.7)\times100}{58}-100\right)$. Nonetheless, the 12.2% decrease in serum albumin concentration after saline infusion cannot be explained by dilution alone and suggests a change in albumin distribution as well and a hypothesis for this has been previously proposed (Aukland and Nicolaysen 1981; Lobo, Stanga *et al.* 2001; Parving, Rossing *et al.* 1974; Perl 1975; Taylor, Parker *et al.* 1981).

Even with a modest volume of infusion, all subjects developed hyperchloraemia after saline infusions, and serum chloride concentrations remained elevated even 4 h after the infusion (Fig. 11.3). This is consistent with published data (Ho, Karmakar *et al.* 2001; Lobo, Stanga *et al.* 2001; Williams, Hildebrand *et al.* 1999) and reflects the fact that the Na:Cl ratio in 0.9% saline is 1:1 while that in plasma is approximately 1.38:1 (Veech 1986). Little is known regarding the impact of serum chloride concentration on the RAAS. Studies in rodents have demonstrated that chloride depletion is a potent stimulus for the release of renin (Abboud, Luke *et al.* 1979; Kotchen, Luke *et al.* 1983; Welch, Ott

et al. 1985). Chronic chloride depletion has been shown to produce a significant increase in plasma renin activity and upregulation of angiotensin receptors in the adrenal gland, renal glomeruli and medulla (Ray, Castren *et al.* 1990) and anterior pituitary gland (Ray, Ruley *et al.* 1991). Hyperchloraemia has also been shown to induce renal vasoconstriction and a fall in glomerular filtration rate in anaesthetised dogs (Wilcox 1983). Similarly in man, elevated chloride concentrations have also been shown to suppress renin activity (Julian, Galla *et al.* 1982; Kotchen, Luke *et al.* 1983). However, we are not aware of published studies specifically investigating hypochloraemia as a stimulus to the RAAS in man.

Bicarbonate concentrations remained normal and neither in this study, nor following a 2 L infusion, were we able to demonstrate an acidosis (Chapter 10) (Lobo, Stanga *et al.* 2001). This is in contrast with an earlier study in which subjects received much greater volumes of 0.9% saline (50 mL/kg over 1 h) (Williams, Hildebrand *et al.* 1999).

Circulating renin is present in two forms, active (PAR) and inactive (PIR) (Leckie, McConnell *et al.* 1977). To date, stimuli for activation, although still relatively controversial, are thought to include a variety of proteases, such as cathepsins B, H, and D (Luetscher, Bialek *et al.* 1982; Morris 1978), kallikrein and plasmin (Inagami, Okamoto *et al.* 1982) and exposure to low pH (Leckie and McGhee 1980; Lumbers 1971). In view of this uncertainty, any stimulation of the RAAS which alters the ratio of active to inactive renin may contribute to our understanding in this field. At least three physiological stimuli for its secretion have been described, for example, intravascular hypovolaemia (Lamprecht, Miller

et al. 1979), hyponatraemia (Espiner, Christlieb *et al.* 1971; Skott and Briggs 1987), and possibly hypochloraemia (Lorenz, Weihprecht *et al.* 1991).

It is demonstrated that the initial volume expansion induced by both solutions was rapidly detected during the infusion, resulting in a decrease of PAR at 1 h. The volume effect may be attributed to the baroreflex response first described by Tobian *et al*. (Tobian, Tomboulian *et al.* 1959), whereby the rate of renin release is varied in response to changes in stretch detected by receptors present in the juxaglomerular apparatus. Thus, increased stretch causes inhibition of further renin secretion, as observed. Subsequently, PAR returned towards baseline after dextrose but remained suppressed following saline, which was incompletely excreted.

Following dextrose, serum sodium and chloride concentrations fell and acute hypervolaemia resolved rapidly, so that the return of renin towards baseline is explained. In contrast, saline was probably associated with a persistent extracellular fluid volume expansion as well as a higher chloride concentration, although sodium levels were only higher at the 1 h sample.

Interestingly, volume expansion after infusion of the two solutions appeared to have differential effects upon the concentration of inactive renin (Fig. 11.4). This may be associated with the dextrose-induced sodium loss and subsequent increased active renin release compared with the saline-induced sodium gain and subsequent inhibition of active renin.

The normal angiotensinogen concentration is less than the Km, and can therefore be used as a determination of angiotensin I (Ang I) production *in vivo* (Skinner, Dunn *et al.* 1975). Thus, angiotensinogen could play an important role

in circulatory homeostasis by exercising control over both Ang I and Ang II production. The administration of saline was associated with a decrease in plasma angiotensinogen concentrations. Therefore, a decline in the percentage of active renin would suggest that angiotensinogen levels would remain stable in these subjects. However, this is contrary to the response observed, and the physiological explanation for this decline remains unclear. Furthermore, the observed increase in angiotensinogen concentrations following dextrose administration was accompanied by an increase in PAR. Thus, the generation rate of Ang I and Ang II will also have increased. This coincided with the acute rise in the blood glucose and insulin levels (Fig. 11.5). An association between angiotensinogen release and hyperglycaemia has recently been reported in healthy young adult humans (Schorr, Blaschke *et al.* 1998).

For both infusates, the initial decline in renin concentrations coincided with a fall in aldosterone (Fig. 11.4). It is well recognised that renin, via Ang II, has the ability to regulate aldosterone secretion (Rayyis and Horton 1971; Scholer, Birkhauser *et al.* 1973). Nevertheless, the subsequent renin response differed between the two solutions, yet aldosterone remained suppressed for the duration of the study for both fluids, even though sodium balance was negative in the dextrose group at 4 h. We are unable to explain the phenomenon in either group.

As expected, the plasma levels of ANP increased 1 h after the start of both infusions in response to the presumed increase in right atrial filling (Watenpaugh, Yancy *et al.* 1992; Wingender, Neurser *et al.* 1988). Thereafter, the ANP concentrations declined almost in unison following saline administration compared with dextrose (Fig. 11.5). The results of the current study are in

agreement with previous work, in which immediately following saline infusion an increase in ANP levels has been noted which nevertheless had returned to basal at a time when urinary sodium excretion was still high (Sagnella, Shore *et al.* 1985; Singer, Shore *et al.* 1987). In the present study also, ANP levels returned to baseline by the conclusion of the study period. This suggests that the role of ANP in sodium excretion may only be to protect against intravascular hypervolaemia and that it is not responsive to excess sodium loading *per se*.

The increase in ANP observed was accompanied initially by a decrease in renin and aldosterone. It has been suggested previously that suppression of the RAAS during and after saline infusion may be in part mediated by the increase in ANP secretion (Singer, Shirley *et al.* 1991). However, following saline, PAR and aldosterone levels remained suppressed, whereas ANP levels decreased to baseline. Singer *et al*. (Singer, Shore *et al.* 1987) have suggested that ANP may play a role in determining the immediate increase in sodium excretion, but that other mechanisms, such as suppression of the RAAS may be of equal or greater importance in the longer term. The results of the present study appear to support this hypothesis.

A close physiological relationship between AVP and renin, central to the control of plasma volume, has been well documented. Intravenous infusion of AVP has been demonstrated to suppress plasma active renin in man (Hesse and Nielsen 1977; Khokhar, Slater *et al.* 1976). Furthermore, in man, it has been suggested that physiological amounts of AVP suppress the rate of plasma renin secretion indirectly by increasing plasma volume at the expense of the extracellular fluid (Khokhar, Slater *et al.* 1976).

An initial fall in AVP concentrations immediately following infusion of both solutions was observed, however this decline was more marked following dextrose (Fig. 11.5). The inhibition of AVP secretion can be attributed to the observed changes in osmolality. Following saline administration, AVP concentrations continued to decline, due to a decrease in osmolality, despite the increase in serum sodium concentrations. This response may suggest an additional effect of volume loading and/or Ang II suppression. Conversely, following dextrose the increase in the AVP concentration toward baseline corresponded with both the rise in serum sodium and the accompanying increase in osmolality. The plasma AVP concentrations returned to basal levels after two hours, possibly as a response to the continuing high urinary output.

For both solutions, the nature of the AVP and renin response showed similar patterns of decrease. Usberti *et al*. (Usberti, Federico *et al.* 1985) have shown during Ang II infusions a concomitant increase in plasma AVP concentrations in normal volunteers, thus supporting the findings of the present study.

In conclusion, this preliminary study has demonstrated that the role the RAAS plays in electrolyte and water homeostasis differs in response to saline and dextrose administration. This in turn has an impact on other hormonal factors controlling natriuresis and diuresis, which interrelate with one another. It also shows that whereas the mechanism for excreting excess water via changes in AVP secretion is highly efficient in normal individuals, that for excreting excess sodium is relatively ineffective, with ANP being responsive to acute intravascular hypervolaemia rather than to excess sodium. The passive effect of inactivation of

the RAAS appears to be more important in this respect. These findings have implications for the management of patients whose response to illness confers a further tendency to sodium and water retention when this is given in excess of requirements.

The results of this study are also in the PhD thesis of Deborah J. Myhill, submitted to the University of Nottingham.

12. (Ab)normal saline and physiological Hartmann's solution: A randomised double blind crossover study

Normal 0.9% salt solution is neither normal nor physiological.

Khalil G. Wakim

12.1 Introduction

Although Hartmann's solution (Ringer's lactate) is the recommended fluid for the resuscitation of patients with haemorrhagic shock (American College of Surgeons Committee on Trauma 1997), 0.9% sodium chloride (saline) continues to be one of the most frequently used crystalloids in the perioperative period, for both replacement and maintenance purposes (Lobo, Dube *et al.* 2001). The properties of the latter are not entirely physiological (Wakim 1970) and studies on both normal volunteers (Lobo, Stanga *et al.* 2001; Williams, Hildebrand *et al.* 1999) and patients (Ho, Karmakar *et al.* 2001; Scheingraber, Rehm *et al.* 1999; Veech 1986; Wilkes, Woolf *et al.* 2001) have shown that infusions of large amounts of 0.9% saline are associated with a hyperchloraemic acidosis which may have a deleterious effect. We recently studied the effects of a 2 L infusion of 0.9% saline and 5% dextrose over an hour in healthy volunteers and found that while almost 2/3^{rds} of the infused saline was retained at 6 h, most of the dextrose had been excreted an hour after completion of the infusion (Chapter 10) (Lobo, Stanga *et al.* 2001). When Hahn and Svensen studied the effects of an infusion of 40 mL/min of Ringer's acetate solution over a period of 40 min (Hahn and Svensen 1997), and of 25 mL/kg over 30 min (Svensen and Hahn 1997), they found that the kinetics of Ringer's solution were between those we observed with dextrose and saline (Lobo, Stanga *et al.* 2001). These findings are also consistent with those of Williams *et al*. (Williams, Hildebrand *et al.* 1999) who showed that, when volunteers were infused with 50 mL/kg of Hartmann's solution or 0.9% saline over 1 h, they passed urine significantly earlier after Hartmann's than after saline.

The present study was conducted to compare the responses of normal subjects to 2 L infusions of 0.9% saline and compound sodium lactate Hartmann's solution (sodium chloride 0.6%, sodium lactate 0.25%, potassium chloride 0.04%, calcium chloride 0.027%) over 1 h. In particular, the extent and time course of the effects of the two infusions on haematocrit, serum albumin, and serum biochemistry, and the resultant urinary responses were measured.

12.2 Methods

This double blind, crossover study was conducted on 10 healthy young adult male volunteers after obtaining informed consent, using a model previously described by us (Chapter 10) (Lobo, Stanga *et al.* 2001). Only those subjects with a body weight of 65-80 kg and a BMI of 20-25 kg/m^2 were included. Those with chronic medical conditions or acute illness in the six-week period preceding the study, on regular medication or with a history of substance abuse, were excluded.

Subjects reported for the study at 0900 hours after a fast from midnight. After voiding of the bladder, height was recorded, weight measured, and body mass index calculated.

Two venous cannulae were inserted; one in each forearm and blood was sampled for full blood count, haematocrit, serum electrolytes (sodium, potassium, chloride and bicarbonate), albumin and osmolality. Strong ion difference was calculated by subtracting the serum chloride concentration from the sum of the serum concentrations of sodium and potassium (Stewart 1983). The urine collected was analysed for osmolality and concentrations of sodium and potassium.

Two litres of 0.9% saline BP (Baxter Health Care, Thetford, UK) or compound sodium lactate BP Hartmann's solution (Baxter Health Care) (Table 1.5) were then infused over 60 min in random order on separate days, with subjects supine. A nurse who was not involved in the study masked all labels on the infusion bags with opaque tape and also performed the randomisation. Randomisation was performed using sequentially numbered paired sealed opaque envelopes. The infusion started at time 0. Pulse rate and blood pressure were recorded at 15 min intervals for 2 h and then at 30 min intervals for a further 4 h. Subjects were not allowed to eat or drink for the duration of the study and remained supine for most of the time. They stood up to void urine and be weighed, but blood samples were taken after lying supine for at least 15 minutes.

Body weight and the above blood tests were repeated at hourly intervals for 6 h. Subjects voided their bladders as the need arose and, in all cases, at the end of 6 h. The time of each micturition was noted and urine volume measured. Post infusion urine samples were pooled and then analysed for osmolality and concentrations of sodium and potassium.

The experiment was repeated with a 2 L infusion of Hartmann's solution in those who received 0.9% saline initially and vice versa 7-10 days later. All investigators, subjects and laboratory staff were blinded. The randomisation code was broken at the end of the study.

Data were presented as mean (SE) or median (IQR). Data were tested for statistical significance using the Wilcoxon signed ranks test and tests of between-subjects effects (saline *vs*. Hartmann's solution) were performed using the general linear model repeated measures procedure.

12.3 Results

Ten male volunteers were recruited for the study. One of the volunteers became unwell (unrelated to the study) a day before the second leg of his study and had to be withdrawn. The remaining 9 volunteers had a median (IQR) age of 21.0 (20.0-21.5) years and height of 1.81 (1.75-1.85) m. Baseline measurements prior to the infusion of each of the solutions are summarised in Table 12.1. Four volunteers received 0.9% saline as the first infusion and five received Hartmann's solution initially. All volunteers remained haemodynamically stable throughout the study.

Table 12.1: Baseline parameters prior to infusions

	Before saline	Before Hartmann's
Weight (kg)	76.3 (67.6-79.1)	76.2 (67.6-79.0)
BMI (kg/m^2)	23.4 (20.5-23.9)	23.3 (20.5-23.8)
Haemoglobin (g/dl)	15.2 (14.5-16.0)	15.3 (14.4-15.7)
Serum albumin (g/L)	42 (40-44)	42 (40-43)
Serum osmolality (mOsm/kg)	294 (292-297)	296 (293-298)
Serum urea (mmol/L)	5.0 (3.7-5.5)	4.6 (4.0-6.0)

n=9, all values Median (IQR). Differences not significant for all parameters (Wilcoxon signed ranks test).

Serum albumin concentration fell significantly at 1 h after both infusions (Fig. 12.1). The decrease was more pronounced and prolonged after saline (P=0.003). Changes in haematocrit and haemoglobin were similar, but of a smaller magnitude (Fig. 12.1). Sequential changes in serum sodium, potassium, chloride, bicarbonate, strong ion difference ($[Na^+] + [K^+] - [Cl^-]$) and osmolality are shown in Fig. 12.2. Urinary responses are summarised in Table 12.2.

Although there were no significant differences in postinfusion urinary osmolality and potassium excretion, subjects excreted 1.7 times more sodium after Hartmann's solution than after saline (Table 12.2). The difference in sodium excretion was even more pronounced when expressed as a percentage of the sodium infused.

Changes in weight were equivalent to the volume of fluid infused and urine excreted (Fig. 12.1 and Table 12.2). Although all volunteers gained 2 kg at the end of each infusion, weight returned to baseline more slowly after saline than after Hartmann's solution because of the different rate of excretion of these two solutions. One subject developed transient facial oedema after saline infusion. No other side effects or complications were observed.

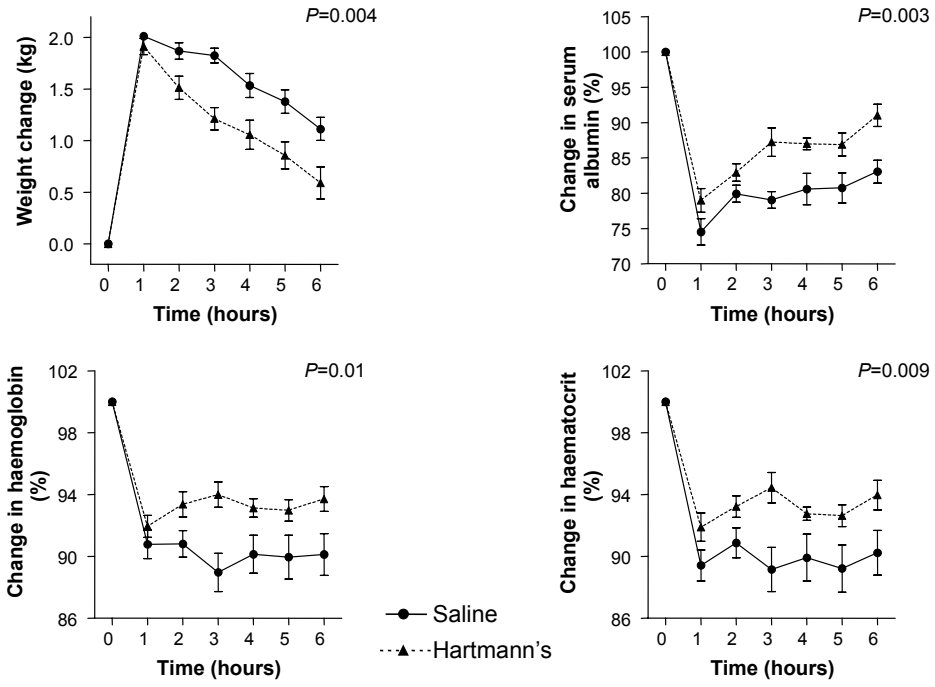


Fig. 12.1: *Changes in body weight, and percentage changes in serum albumin concentration, haemoglobin concentration and haematocrit after infusion of 2 litres of 0.9% saline and Hartmann's solution over 1 hour. All values are Mean (SE). P values are for tests of between-subjects effects (saline vs. Hartmann's solution) obtained using repeated measures testing.*

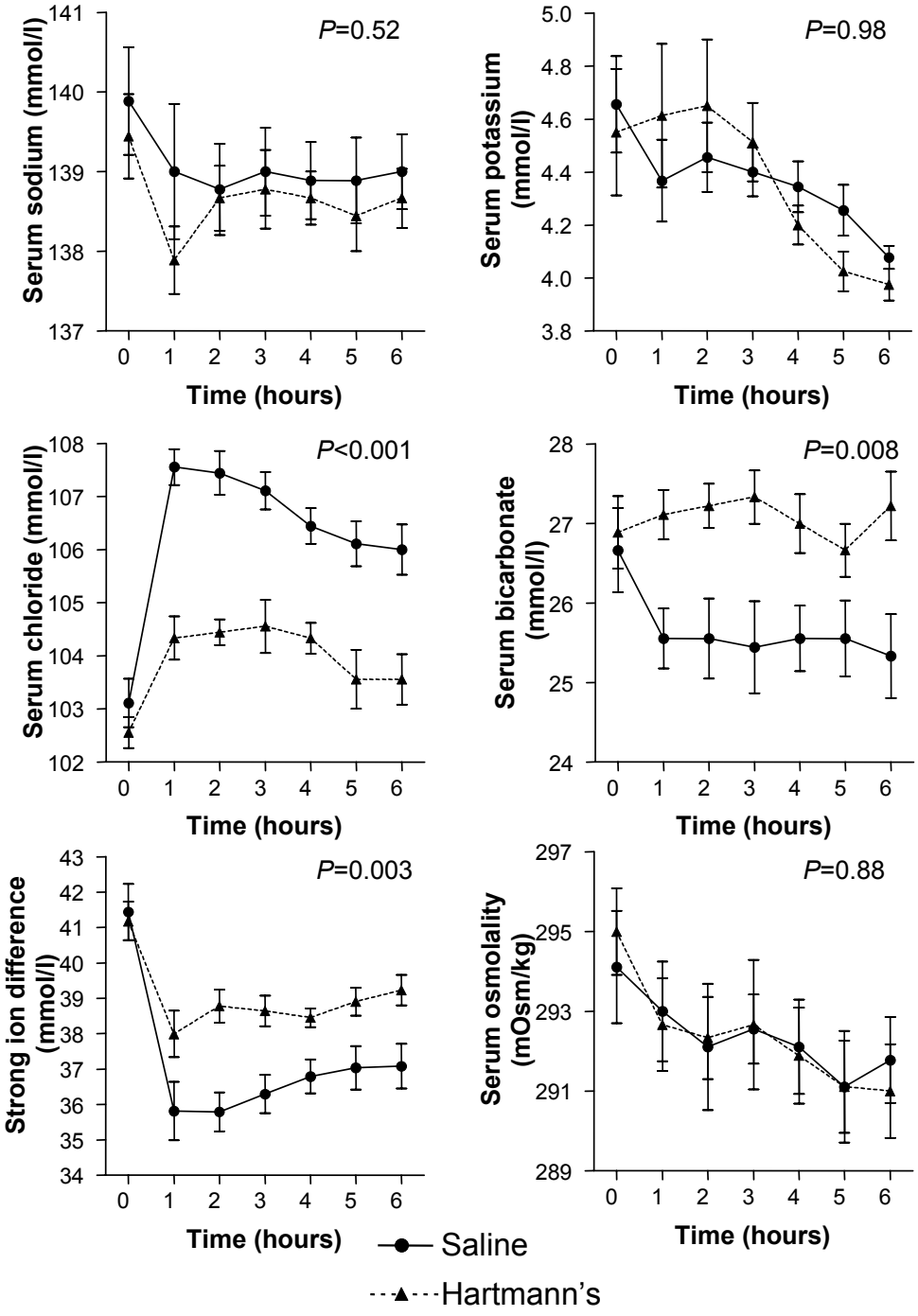


Fig. 12.2: *Changes serum concentrations of sodium, potassium, chloride, bicarbonate, strong ion difference ($[Na^+] + [K^+] – [Cl^-]$) and osmolality after infusion of 2 litres of 0.9% saline and Hartmann's solution over 1 hour. All values are Mean (SE). P values are for tests of between-subjects effects (saline vs. Hartmann's solution) obtained using repeated measures testing.*

Table 12.2: Urinary changes

	Saline	Hartmann's solution	*P* value*
Time to first micturition (min)	185 (135-280)	70 (65-165)	0.008
Number of micturitions over 6 h	2 (1-3)	3 (2-4)	0.02
Total post-infusion urine volume over 6 h (mL)	450 (355-910)	1000 (610-1500)	0.049
Total post-infusion urinary Na^+ over 6 h (mmol)	73 (54-110)	122 (79-175)	0.049
Na excretion as a percentage of Na^+ infused	23.5 (20.7-35.9)	46.9 (30.4-67.2)	0.02
Total post-infusion urinary K^+ over 6 h (mmol)	36 (26-49)	33 (31-49)	0.48
Osmolality of pre-infusion urine (mOsm/kg)	896 (831-972)	841 (771-1015)	0.86
Osmolality of pooled post-infusion urine (mOsm/kg)	670 (450-808)	432 (332-609)	0.48

*n=9, all values Median (IQR). *Wilcoxon signed ranks test used.*

12.4 Discussion

This detailed comparison of the effects of 2 L infusions of two "isotonic" crystalloid solutions over 1 h in healthy volunteers has shown that while 0.9% saline has greater and more prolonged blood and plasma volume expanding effects than Hartmann's solution, as reflected by the greater dilution of the haematocrit and serum albumin, and the sluggish urinary response, these effects are at the expense of the production of a significant and sustained hyperchloraemia. At 6 h, body weight measurements suggested that 56% of the infused saline was retained, in contrast to only 30% of the Hartmann's solution. The consistency of the results is implied by the fact that the changes seen after the saline infusion were almost identical with those observed by us previously (Chapter 10) (Lobo, Stanga *et al.* 2001).

The kinetics of Hartmann's solution were similar to those of Ringer's acetate shown by Hahn's group (Hahn and Svensen 1997; Svensen and Hahn 1997), but excretion of an identical volume of 5% dextrose (Lobo, Stanga *et al.* 2001) was more rapid than that of Hartmann's solution. Subjects emptied their bladders earlier and more frequently after Hartmann's solution than after saline infusions, similar to previously published results (Williams, Hildebrand *et al.* 1999).

The persistent hyperchloraemia after saline infusions is consistent with published data (Ho, Karmakar *et al.* 2001; Lobo, Stanga *et al.* 2001; Scheingraber, Rehm *et al.* 1999; Veech 1986; Wilkes, Woolf *et al.* 2001; Williams, Hildebrand *et al.* 1999) and reflects the lower $[Na^+]$:$[Cl^-]$ ratio in saline (1:1) than in Hartmann's solution (1.18:1) or in plasma (1.38:1) (Veech 1986). Bicarbonate concentrations remained in the normal range after both infusions, but there was a significant difference between the two, with an increase being noted after Hartmann's solution and a decrease after saline. Scheingraber *et al*. (Scheingraber, Rehm *et al.* 1999) studied the effects of randomly allocated infusions of almost 70 mL/kg (i. e. up to 5 L) over 2 h of 0.9% saline or Hartmann's solution in patients undergeroing elective gynaecological surgery and found that during the first 2 h of saline infusion, there was a significant decrease in pH (7.41 to 7.28), serum bicarbonate concentration (23.5 to 18.4 mmol/L) and anion gap (16.2 to 11.2 mmol/L), and an increase in serum chloride concentration from 104 to 115 mmol/L. Bicarbonate and chloride concentrations, and pH did not alter significantly after Hartmann's solution, but the anion gap decreased from 15.2 to 12.1 mmol/L over the same time interval. The decrease in anion gap after the two

infusions was also associated with a fall in the serum protein concentration (Scheingraber, Rehm *et al.* 1999). As the negatively charged albumin molecule accounts for about 75% of the anion gap (Oh and Carroll 1977), acute dilutional hypoalbuminaemia can effectively reduce the upper limit of the normal range for the anion gap (Prough and Bidani 1999), as evidenced by a reduction in anion gap by 2.5 mmol/L for every 10 g/L fall in serum albumin concentration in critically ill patients (Figge, Jabor *et al.* 1998). Stewart (Stewart 1983) has described a mathematical approach to acid base balance in which the strong ion difference ($[Na^+] + [K^+] - [Cl^-]$) in the body is the major determinant of the H^+ ion concentration. A decrease in the strong ion difference is associated with a metabolic acidosis and an increase with a metabolic alkalosis. Change in the chloride concentration is the major anionic contributor to the change in H^+ homeostasis. Hyperchloraemia, as a result of saline infusions, therefore, decreases the strong ion difference and results in a metabolic acidosis (Dorje, Adhikary *et al.* 1997; Miller, Waters *et al.* 1996; Prough and Bidani 1999; Scheingraber, Rehm *et al.* 1999). Although the volume of fluid replacement in Scheingraber's study (Scheingraber, Rehm *et al.* 1999) may be considered excessive, the study provided conclusive evidence that hyperchloraemic acidosis is an accompaniment of saline infusions, confirming the earlier observations of McFarlane and Lee who demonstrated a less severe acidosis after the infusion of 3 L over 200 min (McFarlane and Lee 1994).

The greater diuresis of water after Hartmann's solution compared with 0.9% saline may be partly explained by its lower osmolality and the reduced antidiuretic hormone secretion that this may have engendered. Although there was

no significant difference between the serum osmolality and sodium concentration between the two infusions, there appeared to be a slightly greater fall in both parameters 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. It is tempting to speculate that other factors such as the effect of the chloride ion on glomerular filtration rate may also have contributed. The greater excretion of sodium after Hartmann's solution despite the fact that it contains less sodium that 0.9% saline is more difficult to understand unless an effect of the chloride ion is also involved. Veech (Veech 1986) emphasised that when large amounts of saline are infused, the kidney is slow to excrete the excess chloride load. He also suggested that as the permeability of the chloride ion across cell membranes is voltage dependent, the intracellular chloride content is a direct function of the membrane potential. Wilcox found, in animal studies, that sustained renal vasoconstriction was specifically related to hyperchloraemia, which was potentiated by previous salt depletion and related to the tubular reabsorption of chloride (Wilcox 1983). The tubular reabsorption of chloride appeared to be initiated by an intrarenal mechanism independent of the nervous system and was accompanied by a fall in glomerular filtration rate. Wilcox also established that although changes in renal blood flow and glomerular filtration rate were independent of changes in the fractional reabsorption of sodium, they correlated closely with changes in the fractional reabsorption of chloride, suggesting that renal vascular resistance was related to the delivery of chloride, but not sodium, to the loop of Henle (Wilcox 1983). Chloride-induced vasoconstriction appeared to be specific for the renal

vessels and the regulation of renal blood flow and glomerular filtration rate by chloride could override the effects of hyperosmolality on the renal circulation (Wilcox 1983). It has also been shown, in an experimental rat model of salt-sensitive hypertension, that while loading with sodium chloride produced hypertension, sodium bicarbonate did not (Kotchen, Luke *et al.* 1983). Further studies on young adult men have shown that plasma renin activity was suppressed 30 and 60 min after infusion of sodium chloride, but not after infusion of sodium bicarbonate, suggesting that both the renin and blood pressure responses to sodium chloride are dependent on chloride (Kotchen, Luke *et al.* 1983).

Isotonic sodium-containing crystalloids are distributed primarily in the extracellular space and textbook teaching classically suggests that such infusions expand the blood volume by 1/3rd the volume of crystalloid infused (Kaye and Grogono 2000; Kramer, Svensen *et al.* 2001). The weight of the volunteers studied was 76 kg, and assuming a blood volume equivalent to 6% of body weight (Kramer, Svensen *et al.* 2001), the initial blood volume of the volunteers was 4.56 L. The peak blood volume expansion (equivalent to the percentage fall in haematocrit) at 1 h was 10.6% after saline and 8.1% after Hartmann's solution. Therefore, in absolute terms, after a 2 L infusion blood volume was expanded by 483 mL with saline and 369 mL with Hartmann's solution, resulting in a volume expanding efficiency of 24.1% and 18.4% respectively, which, although much less than the often quoted efficiency of 33%, accords with previously published data (Kramer, Svensen *et al.* 2001; Lamke and Liljedahl 1976; Svensen and Hahn 1997). The greater percentage change in serum albumin concentration than in haemoglobin or haematocrit reflects their difference in volume distribution and

may also be due to a "drag" effect whereby albumin follows solutes into the interstitium by convection (Lobo, Stanga *et al.* 2001; Perl 1975). The greater fall in serum albumin concentration after saline than after Hartmann's solution may not only be caused by the greater fluid retention, but may also be a compensatory response to reduce the anion gap caused by the hyperchloraemia.

Saline has been the mainstay of intravenous fluid therapy ever since Thomas Latta reported that intravenous saline infusions saved cholera victims from almost certain death (Latta 1832). Alexis Hartmann, in 1934, suggested that his lactated Ringer's solution was superior to saline infusions in the treatment of infantile diarrhoea (Hartmann 1934) and subsequent publications have confirmed the superiority of Hartmann's solution for resuscitation (Healey, Davis *et al.* 1998; Ho, Karmakar *et al.* 2001; Scheingraber, Rehm *et al.* 1999; Wilkes, Woolf *et al.* 2001). This may be due to the protective effect of Hartmann's solution on blood chloride and pH changes, as critically ill patients are prone to develop an acidotic state. As Hartmann's solution is excreted more rapidly than saline, its use in the critically ill may result in improved excretion of accumulated metabolites. Although Scheingraber *et al*. (Scheingraber, Rehm *et al.* 1999) felt that the hyperchloraemic acidosis caused by large volumes of saline infusions was without major pathophysiological implications in their study, 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, Woolf *et al.* 2001), and both respiratory and metabolic acidosis have been associated with impaired gastric motility in pigs (Tournadre, Allaouchiche *et al.* 2000). Salt and water overload has also been shown to delay recovery of gastrointestinal function

in patients undergoing colonic surgery (Lobo, Bostock *et al.* 2002b). Moreover acidosis impairs cardiac contractility and may decrease the responsiveness to inotropes. Large volumes (50 mL/kg over 1 h) of saline infusion in healthy volunteers have also 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 (Williams, Hildebrand *et al.* 1999).

The attempt to find a truly physiological crystalloid preparation for both scientific and clinical work has been going on for over three quarters of a century and the results have inevitably been a compromise. In conditions of peripheral circulatory failure or liver disease, there may be increased endogenous lactate production or decreased capacity to metabolise infused lactate (Veech 1986). On the other hand, the unphysiological proportion of chloride in 0.9% saline causes other problems as outlined. Clinicians should be aware of the shortcomings of both solutions and take particular care to tailor the dose of each to the pathophysiological condition being treated.

The results of this study are also in the BMedSci dissertation of Fiona Reid, submitted to the University of Nottingham.

13. The effect of an oral glucose load on sodium and water excretion after rapid intravenous infusion of 0.9% (w/v) saline

I don't care where the water goes if it doesn't get into the wine.

G. K. Chesterton

13.1 Introduction

Earlier studies on human subjects and animals subjected to starvation or the stress of illness and surgery have suggested that glucose enhances salt and water retention (Bloom 1962; Franch, Guirao *et al.* 1992; Gamble 1946-1947; Gil, Franch *et al.* 1997; Macfie, Smith *et al.* 1981; Veverbrants and Arky 1969). This may depend on the nutritional state and initial salt and water balance of the subjects studied. Although this phenomenon has not been studied specifically in normally nourished healthy volunteers without prolonged fasting, previous work from our group has shown that in such individuals, while an excess water load (in the form of 5% dextrose) is excreted rapidly, an excess sodium chloride load is excreted very slowly, and causes persistent dilution of haematocrit and serum albumin (Chapter 10) (Lobo, Stanga *et al.* 2001).

This study was undertaken to determine the effects on healthy volunteers of a 50 g oral glucose load on urinary excretion of sodium and water and changes in serum biochemistry after an intravenous bolus of 2 L 0.9% (w/v) sodium chloride. Our hypothesis was that although glucose may affect the response to a sodium load under conditions of nutritional depletion, prolonged starvation, injury and hypovolaemia, it may have little effect in healthy normal subjects who fast for less than 12 h.

13.2 Methods

This crossover study was conducted on 6 healthy young adult male volunteers after obtaining informed consent. Only those subjects with a body weight of 65-80 kg and a BMI of 20-25 kg/m^2 were included. Volunteers with

chronic illness or acute illness in the six-week period preceding the study, those on regular medication and those with a history of substance abuse were excluded.

Subjects reported for the study at 0900 h after a fast from midnight. After voiding of the bladder, height was recorded, weight measured, and body mass index calculated. Two venous cannulae were inserted; one in each forearm and blood was sampled for full blood count, haematocrit, serum electrolytes (sodium, potassium, chloride and bicarbonate), albumin, and osmolality, and blood glucose. The urine collected was analysed for osmolality and concentrations of sodium, potassium and glucose.

Two litres of 0.9% saline (154mmol/L sodium, 154mmol/L chloride; Baxter Healthcare Ltd., Thetford, Norfolk, UK) were then infused over 60 min with subjects in the supine position. Start of the infusion was recorded as time 0. Pulse rate and blood pressure were recorded at 15 min intervals for 2 h and then at 30 min intervals for a further 4 h. Subjects were not allowed to eat or drink for the duration of the study and remained supine for most of the time. They stood up to void urine and be weighed, but blood samples were taken after lying supine for at least 15 minutes.

Body weight and the aforementioned blood tests were repeated at hourly intervals for 6 h. Subjects voided their bladders as the need arose. The time of each micturition was noted and urine volume measured. Postinfusion urine samples were pooled and analysed for osmolality and concentrations of sodium and potassium. The glucose content of each urine sample was assessed using dipsticks.

The experiment was repeated a week later, with subjects drinking 100 mL of 50% (w/v) dextrose solution at the start of the 2 L infusion of 0.9% (w/v) saline.

Data were tested for statistical significance using Student's t-paired test and the Wilcoxon signed ranks test. Tests of between-subjects effects (saline *vs*. glucose + saline) were performed using the general linear model repeated measures procedure.

13.3 Results

Table 13.1: Baseline blood tests prior to infusions

	Saline	Glucose + saline	*P* value*
Haemoglobin (g/dL)	15.2 (0.3)	15.2 (0.4)	0.87
Haematocrit (%)	45.6 (0.6)	45.5 (0.7)	0.90
Serum albumin (g/L)	43.8 (1.2)	42.2 (1.4)	0.08
Serum sodium (mmol/L)	139.7 (0.7)	140.0 (0.7)	0.69
Serum potassium (mmol/L)	4.9 (0.1)	4.7 (0.2)	0.19
Serum chloride (mmol/L)	103.3 (0.8)	103.7 (0.6)	0.36
Serum bicarbonate (mmol/L)	27.0 (0.8)	26.2 (0.2)	0.36
Blood glucose (mmol/L)	4.3 (0.1)	4.7 (0.2)	0.27
Serum osmolality (mOsm/kg)	289.8 (1.1)	292.8 (1.9)	0.33

*n=6, all values Mean (SE), *Student's t-paired test used to calculate statistical significance*

The six male volunteers had a mean (SE) age of 20.9 (0.4) years, height of 1.79 (0.02) m, initial weight of 73.0 (1.5) kg and BMI of 22.7 (0.2) kg/m^2. Three volunteers received 0.9% saline as the first infusion and three received oral glucose with the saline infusion initially. Baseline haematological and serum

biochemistry tests prior to the two infusions were not significantly different (Table 13.1). All volunteers remained haemodynamically stable throughout the study.

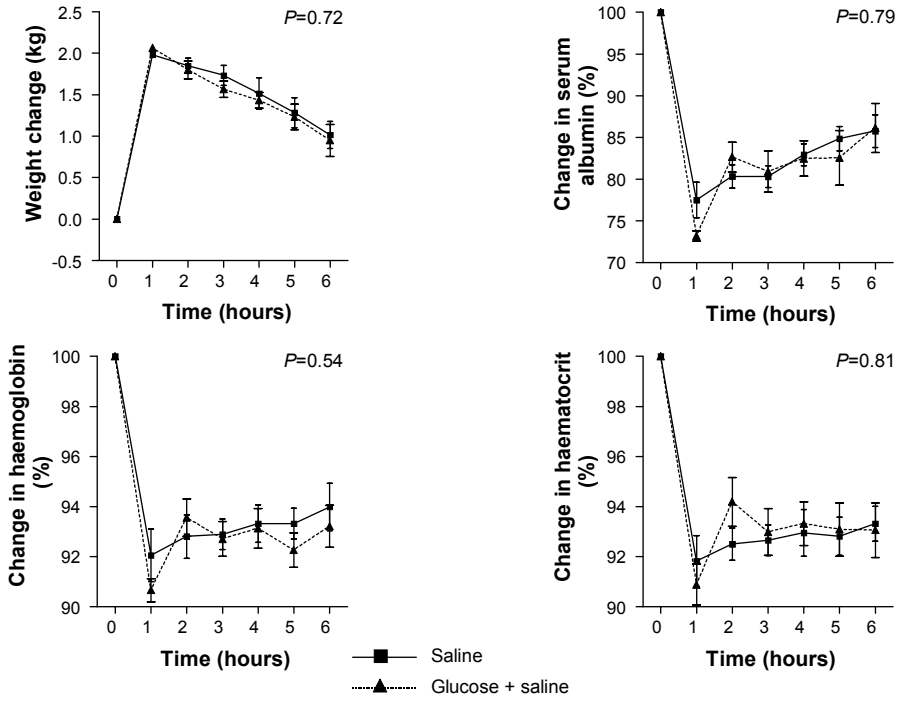


Fig. 13.1: *Changes in body weight, and percentage changes in serum albumin concentration, haemoglobin concentration and haematocrit after infusion of 2 litres of 0.9% saline alone and 0.9% saline with a 100 mL oral load of 50% glucose over 1 hour. All values are Mean (SE). P values are for tests of between-subjects effects (saline vs. glucose + saline) obtained using the general linear model repeated measures procedure.*

Subjects gained 2 kg in weight after each infusion and at the end of 6 h, weight remained about 1 kg above baseline (Fig. 13.1). The changes in body weight corresponded with the volume of urine excreted (Table 13.2) and there was no significant difference between the two infusions. Serum albumin concentration, haemoglobin and haematocrit fell to a similar extent after both infusions and did not return to baseline even after 6 h (Fig. 13.1). Sequential changes in serum sodium, potassium, chloride, bicarbonate, blood glucose and serum osmolality, were not significantly different when the effects of the two infusions were

analysed (Fig. 13.2). Urinary responses are summarised in Table 13.2. Glycosuria was not detected in any of the voided samples. No side effects were observed during the course of the study.

Table 13.2: Urinary changes

	Saline	Glucose + saline	*P* value*
Time to first micturition (min)	250 (150-298)	150 (109-178)	0.05
Number of micturitions over 6 h	1 (1-2.3)	2 (1.8-3)	0.10
Total post-infusion urine volume over 6 h (mL)	538 (350-995)	898 (365-1111)	0.17
Water balance over 6 h (mL)	1463 (1005-1650)	1202 (999-1735)	0.75
Total post-infusion urinary sodium over 6 h (mmol)	76 (69-111)	74 (92-174)	0.25
Total post-infusion urinary potassium over 6 h (mmol)	31 (29-40)	30 (20-36)	0.12
Osmolality of pre-infusion urine (mOsm/kg)	845 (333-985)	884 (630-954)	0.75
Osmolality of pooled post-infusion urine (mOsm/kg)	437 (332-664)	462 (378-828)	0.75

*n=6, all values Median (IQR), *Wilcoxon signed ranks test used to calculate statistical significance*

13.4 Discussion

This study has shown that, in the absence of significant physical stress or prolonged prior starvation, an oral glucose load of 50 g has no effect on the dilutional or redistributional effects of a rapid 2 L infusion of 0.9% saline in healthy volunteers; nor does it alter urinary excretion of sodium and water. These findings are in contrast to earlier studies in which subjects were preconditioned by either prolonged starvation or the stress of illness and surgery (Bloom 1962;

Franch, Guirao *et al.* 1992; Gamble 1946-1947; Gil, Franch *et al.* 1997; Macfie, Smith *et al.* 1981; Veverbrants and Arky 1969).

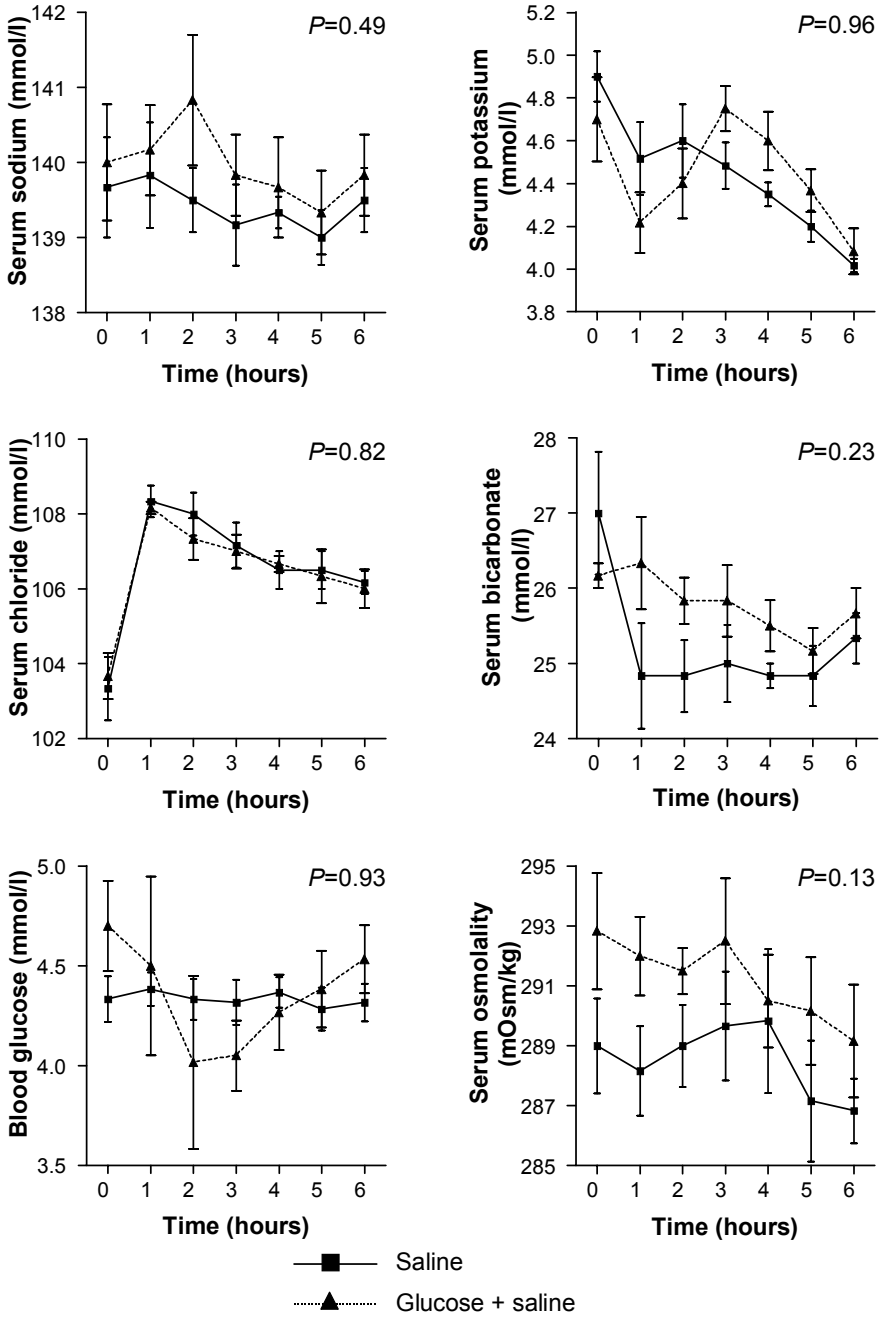


Fig. 13.2: *Changes in serum concentrations of sodium, potassium, chloride and bicarbonate, blood glucose, and serum osmolality after infusion of 2 litres of 0.9% saline alone and 0.9% saline with a 100 mL oral load of 50% glucose over 1 hour. All values are Mean (SE). P values are for tests of between-subjects effects (saline vs. glucose + saline) obtained using repeated measures testing.*

The effects of oral glucose on urinary excretion of sodium and water were first studied by Gamble in the 1940s (Gamble 1946-1947). In studies designed to help survival of mariners in life rafts, he studied the effect of giving only 1200 ml of water per day and the effect of 50 and 100 g oral glucose on water and sodium balance. By this means he induced a saving or positive balance of 175 ml water and 25 mmol sodium per day in subjects who were not only nutritionally depleted but also in negative salt and water balance. The urinary sodium excretion in a subject over a 6 day fast was about 350 mmol, which corresponded with a loss of 2.5 L of extracellular fluid. This loss of sodium was reduced by a little over 50% by an oral intake of glucose and it was found that maximal sparing was achieved by providing 50 g glucose per day. Gamble thought this finding unexpected and had no explanation for it, although he was able to demonstrate that it was not due to the antiketogenic effect of glucose. He concluded that this phenomenon had a role in the maintenance of the extracellular fluid volume.

Macfie *et al*. (Macfie, Smith *et al.* 1981) studied two groups of patients with gastroenterological disease requiring intravenous nutrition with one group receiving hypertonic glucose alone as an energy source and the other receiving 60% of non-protein energy as fat and 40% as hypertonic glucose. The authors were able to demonstrate significant weight gains in both groups over a two-week period. However, over the same time period, patients receiving hypertonic glucose alone gained 0.9 L more total body water than those in the other group. This effect on salt and water balance of replacing glucose with fat in parenteral nutrition preparations has also been demonstrated by Sitges-Serra's group in both rabbit (Franch, Guirao *et al.* 1992) and human studies (Gil, Franch *et al.* 1997). In all

these studies, the subjects, whether animal or human, were nutritionally depleted or injured, and it is possible that a certain amount of "preconditioning" is necessary for glucose to affect sodium and water retention. The authors suggest that the amount of glucose is primarily responsible for the changes in salt and water balance.

On the other hand, it has been shown, in diabetic patients, that acute hyperinsulinaemia can induce a reduced fractional sodium excretion, despite a relative resistance to the glucose lowering effects of insulin (Gans, Bilo *et al.* 1992). Hence, it is possible that the effects seen in the earlier studies (Franch, Guirao *et al.* 1992; Gil, Franch *et al.* 1997; Macfie, Smith *et al.* 1981) were a result of the hyperinsulinaemia induced by the high glucose loads, a state which may not occur in normal subjects who are not preconditioned. This hypothesis is further supported by another study (Finta, Rocchini *et al.* 1992) which demonstrated a significant insulin-mediated sodium retention in obese subjects when compared with non-obese ones. In a study of the effects of insulin on sodium handling in normal subjects, Norgaard *et al*. (Norgaard, Jensen *et al.* 1991) were able to demonstrate that, during a period of hyperinsulinaemia (hyperinsulinaemic euglycaemic clamp), urinary sodium was significantly reduced when compared with basal levels. However, when hyperinsulinaemia was combined with an infusion of 1 L 0.9% (w/v) saline over an hour, urinary sodium excretion remained low for the first hour during saline infusion, subsequent to which sodium excretion increased to 194% of basal excretion, due to an increased GFR of 10%, which is probably a compensatory response to the Na retention induced by the action of insulin on the distal tubule. This contrasts

with the suggestion that the effects of glucose on sodium metabolism are prolonged and the hypothesis that this may be influenced by delayed catecholamine activity (Garcia-Domingo, Llado *et al.* 1994; Veverbrants and Arky 1969) or the synthesis of as yet unknown mediators (Garcia-Domingo, Llado *et al.* 1994).

In conclusion, therefore, the previously observed effect of glucose, enhancing salt and water retention may be conditioned by prior starvation, nutritional or fluid depletion, or the response to injury. This effect may be mediated via insulin in view of the similar response seen following the initiation of insulin therapy in type I diabetes (Norgaard, Jensen *et al.* 1991). Bloom (Bloom 1962) in 1962 drew comparison between the diabetic patient where carbohydrate metabolism is limited by the deficit in carbohydrate utilization and the fasting patient where carbohydrate is unavailable. In both instances sodium excretion was decreased when carbohydrate utilisation was increased and was therefore dependant not on the level of serum glucose but on what was available for metabolism.

Glucose seems to have no effect on sodium and water excretion in normal subjects in whom positive salt and water balance is induced by rapid saline infusions. Clinically our findings suggest that under normal conditions, glucose may not contribute to the sodium retention normally seen under these circumstances although in the presence of nutritional depletion and/or sodium deficiency, it may do so, as shown by other works. The response may depend therefore upon the underlying condition.

Conclusions

Each of us finds lucidity only in those ideas which are in the same state of confusion as his own.

Marcel Proust
Within a Budding Grove,1918

The intake of water and electrolytes is inseparable from feeding by natural or artificial means and the physiological response to it is affected by injury, starvation and weight loss. Intravenous fluids are also the most common hospital prescription, yet the subject of fluid balance shares with that of nutrition a low level of knowledge and standard of practice among junior doctors due largely to a lack of training. Training and education programmes need to be modified to improve the situation. The normal requirement for sodium is 1 to 1.2 mmol/kg/day, yet patients often receive more than 5 L of water and 700 mmol of sodium/day for maintenance therapy. Salt and water overload may sometimes be an inevitable consequence of resuscitation, yet it may take up to three weeks to excrete this excess. It is important therefore to avoid unnecessary overload by prescribing excessive maintenance fluids after the need for resuscitation has passed. Our audit of patients referred for nutritional support showed that many had oedema and dilutional hypoalbuminaemia. The average weight excess, due to fluid overload, of those who had been through critical care was 10 L. Nutritional support with restricted volume and sodium content, combined with diuretics, and in some cases concentrated salt-poor albumin, cleared the oedema over 7-10 days with a rise in serum albumin of 1 g/L for every kg loss in body weight as dilution was reversed (Chapter 3). These changes were accompanied by clinical improvement and recovery of gastrointestinal function. Our measurements of transcapillary escape rate of albumin (TER_{alb}) in patients undergoing uncomplicated major surgery have documented a three-fold increase on day 1, followed by a return to normal by day 10 (Chapter 4). Whether complications prolong the period of increased TER_{alb} has not yet been established.

It is a common misconception that moderate salt and water excess is harmless, despite evidence showing increased postoperative complication rates resulting from it. Following the observations of Mecray in 1937, of delayed gastric emptying associated with hypoalbuminaemia and saline excess, we randomised 20 patients, undergoing colonic surgery for cancer, to receive standard postoperative fluids (more than 3 L of water and 154 mmol sodium/day) or restricted fluids (less than 2 L water and 77 mmol sodium/day) (Chapter 6). The restricted group had zero fluid balance but the standard group gained 3 kg positive saline balance. Solid and liquid phase gastric emptying times (measured by dual isotope radionuclide scintigraphy) (Chapter 5) were virtually normal in the restricted group but significantly longer in the standard group (median 72.5 vs 175 min, P=0.028, and 73.5 vs 110 min, P=0.017 respectively). In the standard group, passage of flatus was 1 day later (median 4 vs 3 days, P=0.001), passage of stool 2.5 days later (median 6.5 vs 4 days, P=0.01), and postoperative hospital stay 3 days longer (median 9.0 vs 6.0 days, P=0.001). We concluded that a small positive salt and water balance sufficient to cause 3 kg postoperative weight gain delays return of gastrointestinal function and prolongs hospital stay in patients undergoing elective colonic resection. This has clear implications for postoperative management.

Our concerns over fluid balance management led us to survey practice and knowledge among 200 junior doctors in the Trent Region (Chapter 7). Pre-registration House Officers were responsible for prescribing in 89% of instances. Only 56% of respondents said that fluid balance charts were checked daily. Although respondents expressed confidence in their prescribing ability, less than

half were aware of the sodium content of 0.9% saline or a patient's daily sodium requirement. Twenty-five percent prescribed 2 or more litres of saline a day for maintenance. Our survey of consultant surgeons (Chapter 8) found that junior staff were given written guidelines in only 22% of instances. Only 16% felt that their juniors were adequately trained, 15% said that there was little training on the firm, 35% thought fluid balance charts inaccurate, and only 30% thought that postoperative patients were receiving appropriate fluid prescription.

The literature is surprisingly sparse concerning the response of normal subjects to crystalloid infusion. Studies were therefore conducted in normal subjects to measure physiological responses to crystalloid solutions in common use. Ten male volunteers received 2 L 0.9% saline and 5% dextrose on separate occasions in random order over 1 h (Chapter 10). Serum albumin concentration fell in all subjects (20% after saline, 16% after dextrose), mainly due to dilution. While dextrose was rapidly excreted, two-thirds of the saline was retained after six hours, with continuing dilution of albumin and haematocrit. These observations illustrate the slowness with which salt and water is excreted, even in normal subjects, while water excess alone is rapidly and efficiently excreted.

The study was repeated with 1 L infusions to define hormonal responses (Chapter 11). Qualitatively similar changes were found. Plasma renin and total renin concentrations and angiotensinogen fell to a greater extent after saline than after dextrose ($P<0.04$). There was no significant difference between the response of plasma aldosterone, atrial natriuretic peptide and arginine vasopressin. In particular, natriuretic peptide rose during both infusions, but fell to normal within an hour, despite the positive sodium balance from the saline. This suggests that,

whereas fluctuations in water balance are dealt with efficiently through osmoreceptors and vasopressin, and saline deficiency is sensed by volume receptors and the renin angiotensin aldosterone system, the mechanism for dealing with sodium excess is passive and inefficient. ANP seems to be more sensitive to acute volume expansion than to sodium loading.

In a further study, we compared 2 L infusions of 0.9% saline and Hartmann's solution (Ringer lactate) (Chapter 12). Dilution of haematocrit and serum albumin was greater and more sustained after saline than after Hartmann's. Although two-thirds of the infused saline had been retained at six hours, 75% of the Hartmann's solution had been excreted. Subjects voided more urine (median 1000 vs 450 mL) of higher sodium content (median 122 vs 73 mmol) after Hartmann's than after saline (P=0.49). This was despite the lower sodium content of Hartmann's solution. Saline caused hyperchloraemia and reduced bicarbonate, sustained for more than six hours, but chloride levels were normal after Hartmann's (P=0.001). The chloride ion may therefore play a more important role in these mechanisms than generally recognised. It has been reported for example, that hyperchloraemia may reduce glomerular filtration rate.

Fluid and electrolyte balance is an intrinsic part of diet and nutritional support. Excretion of salt and water is impaired by both starvation and the response to injury. Salt and water excess not only delays return of gastric emptying and intestinal function, postponing oral intake but increases postoperative complications. In nutritional support therefore it is just as important to consider salt and water needs as those for energy and protein.

Further studies

Although this thesis has helped answer some of the unresolved issues regarding the management of fluid and electrolyte balance, it has also raised a number of new questions and highlighted some problems. It is hoped that the work started would be carried on in the following areas.

1. Further studies are needed to study the natural history of changes in TER_{alb} in patients who have had postoperative complications and sepsis as it would be useful to determine when TER_{alb} returns to normal in this group.
2. Data from this thesis have been adopted by the Stockholm group led by Professor Olle Ljungqvist to develop the enhanced recovery after surgery (ERAS) protocol. It would also be useful to conduct further studies in critically ill patients relating salt and water balance to recovery of gastrointestinal function.
3. We plan to test the hypothesis that treatment of congestive cardiac failure results in improvement of gastrointestinal function and enhanced absorption of orally administered drugs.
4. Our surveys have shown that training in the area of fluid and electrolyte prescribing is deficient. We hope to institute new training programmes and then reaudit the responses of junior doctors and complete the audit loop.
5. Based on our study on the hormonal responses to fluid infusions, we hope to develop a saline tolerance test to help characterise patients, who through genetic or acquired mechanisms, are predisposed to retain salt, with consequences for changes in blood pressure and/or idiopathic oedema.

6. Eventually, we hope to develop a large animal model to study the effects of salt and water overload on intra-abdominal pressure, mesenteric blood flow, wound healing, coagulation and immunological function.

List of abbreviations

Ang I	angiotensin I
Ang II	angiotensin II
ANOVA	analysis of variance
ANP	atrial natriuretic peptide
AVP	arginine vasopressin (antidiuretic hormone)
BIA	bioelectrical impedance analysis
BMI	body mass index
BNP	brain natriuretic peptide
BP	British Pharmacopoeia
CI	confidence interval
CNU	Clinical Nutrition Unit
CRP	c-reactive protein
CV	coefficient of variance
CVP	central venous pressure
DFBIA	dual frequency bioelectrical impedance analysis
DTPA	diethylenetriamine pentaacetic acid
ECF	extracellular fluid
ECW	extracellular water
ICF	intracellular fluid
IQR	interquartile range
MRCS	Member of the Royal College of Surgeons
NCEPOD	National Confidential Enquiry into Perioperative Deaths
NS	not significant

OSCE	objective structured clinical examination
PAR	plasma active renin concentration
PIR	plasma inactive renin concentration
PRHO	Preregistration House Officer
RAS	renin-angiotensin system
RAAS	renin-angiotensin-aldosterone system
RIA	radioimmuno assay
SD	standard deviation
SE	standard error
SFBIA	single frequency bioelectrical impedance analysis
SHO	Senior House Officer
TBW	total body water
TER_{alb}	transcapillary escape rate of albumin
TRC	total renin concentration
w/v	weight/volume

References

A little learning is a dang'rous thing;
Drink deep, or taste not the Pierian spring:
There shallow draughts intoxicate the brain,
And drinking largely sobers us again.

Alexander Pope

(1998). Human albumin administration in critically ill patients: systematic review of randomised controlled trials. Cochrane Injuries Group Albumin Reviewers. *BMJ* **317**: 235-240.

(1999). Electronic responses. Hyponatraemia after orthopaedic surgery. *eBMJ* **318**: (www.bmj.com/cgi/content/full/318/7195/1363#responses).

(2000). General Protocol for Radioimmunoassay Kit. San Carlos, CA, Peninsula Laboratories Inc.

Abboud HE, Luke RG, Galla JH and Kotchen TA (1979). Stimulation of renin by acute selective chloride depletion in the rat. *Circ Res* **44**: 815-821.

Alleyne GA (1966). Cardiac function in severely malnourished Jamaican children. *Clin Sci* **30**: 553-562.

Allison SP (1996). Nutrition in Medicine: A Physician's View. Brussles, Institut Danone.

Allison SP and Lobo DN (2000). Debate: Albumin administration should not be avoided. *Crit Care* **4**: 147-150.

Alsous F, Khamiees M, DeGirolamo A, Amoateng-Adjepong Y and Manthous CA (2000). Negative fluid balance predicts survival in patients with septic shock : A retrospective pilot study. *Chest* **117**: 1749-1754.

American College of Surgeons Committee on Trauma (1997). Advanced Trauma Life Support for Doctors, Student Course Manual. Chicago, American College of Surgeons.

Anderson JA, Simpson JAD, Lobo DN, Macdonald IA, Neal KR, Allison SP*, et al.* (2001). The effect of oral fluid loading on body water volumes, as

measured by dual frequency bioelectrical impedance analysis. *Int J Surg Invest* **3**: 129-133.

Arieff AI (1999). Fatal postoperative pulmonary edema: pathogenesis and literature review. *Chest* **115**: 1371-1377.

Aukland K and Nicolaysen G (1981). Interstitial fluid volume: local regulatory mechanisms. *Physiol Rev* **61**: 556-643.

Baldo-Enzi G, Baiocchi MR, Vigna G, Andrian C, Mosconi C and Fellin R (1987). Analbuminaemia: a natural model of metabolic compensatory systems. *J Inherit Metab Dis* **10**: 317-329.

Ballmer PE, Ochsenbein AF and Schutz-Hofmann S (1994). Transcapillary escape rate of albumin positively correlates with plasma albumin concentration in acute but not in chronic inflammatory disease. *Metabolism* **43**: 697-705.

Ballmer-Weber BK, Dummer R, Kung E, Burg G and Ballmer PE (1995). Interleukin 2-induced increase of vascular permeability without decrease of the intravascular albumin pool. *Br J Cancer* **71**: 78-82.

Barden RP, Thompson WD, Ravdin IS and Frank IL (1938). The influence of the serum protein on the motility of the small intestine. *Surg Gynecol Obstet* **66**: 819-821.

Bastow MD, Rawlings J and Allison SP (1983). Benefits of supplementary tube feeding after fractured neck of femur: a randomised controlled trial. *BMJ (Clin Res Ed)* **287**: 1589-1592.

Bell DR and Mullins RJ (1982a). Effects of increased venous pressure on albumin- and IgG-excluded volumes in muscle. *Am J Physiol* **242**: H1044-1049.

Bell DR and Mullins RJ (1982b). Effects of increased venous pressure on albumin- and IgG-excluded volumes in skin. *Am J Physiol* **242**: H1038-1043.

Black DAK (1960). Essentials of Fluid Balance. Oxford, Blackwell.

Bland JM and Altman DG (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* **1**: 307-310.

Bloom WL (1962). Inhibition of salt excretion by carbohydrate. *Arch Int Med* **109**: 26-32.

Boldt J (2000). The good, the bad, and the ugly: should we completely banish human albumin from our intensive care units? *Anesth Analg* **91**: 887-895.

Brown JJ, Davis DL, Lever AF and Robertson JIS (1963). Influence of sodium loading and sodium depletion on plasma renin in man. *Lancet* **2**: 278-279.

Callum KG, Gray AJG, Hoile RW, Ingram GS, Martin IC, Sherry KM*, et al.* (1999). Extremes of Age: The 1999 Report of the National Confidential Enquiry into Perioperative Deaths. London, National Confidential Enquiry into Perioperative Deaths.

Campbell IT, Green CJ and Jackson MJ (1998). Muscle glycogen and electrolyte concentrations in multiple organ failure [abstract]. *Proc Nutr Soc* **57**: 111A.

Carrio I, Notivol R, Estorch M, Berna L and Vilardell F (1988). Gender-related differences in gastric emptying [letter]. *J Nucl Med* **29**: 573-575.

Cha K, Hill AG, Rounds JD and Wilmore DW (1995). Multifrequency bioelectrical impedance fails to quantify sequestration of abdominal fluid. *J Appl Physiol* **78**: 736-739.

Cheek DB (1953). Estimation of the bromide space with a modification of Conway's method. *J Appl Physiol* **5**: 639-645.

Cheek DB (1961). Extracellular volume: its structure and measurement and the nfluence of age and disease. *J Pediatr* **58**: 103-125.

Cheng AT, Plank LD and Hill GL (1998). Prolonged overexpansion of extracellular water in elderly patients with sepsis. *Arch Surg* **133**: 745-751.

Choi PTL, Yip G, Quinonez LG and Cook DJ (1999). Crystalloids vs. colloids in fluid resuscitation: A systematic review. *Crit Care Med* **27**: 200-210.

Christian PE, Datz FL, Sorenson JA and Taylor A (1983). Technical factors in gastric emptying studies [editorial]. *J Nucl Med* **24**: 264-268.

Christian PE, Moore JG, Sorenson JA, Coleman RE and Weich DM (1980). Effects of meal size and correction technique on gastric emptying time: studies with two tracers and opposed detectors. *J Nucl Med* **21**: 883-885.

Clark RG (1977). Part II: Water and sodium metabolism after trauma. Folia traumatologica Geigy: Metabolic Responses to Trauma. H. B. Stoner, R. G. Clark, K. N. Frayn and A. Fleck. Basle, CIBA-Geigy**:** 5-8.

Clark RG and Karatzas T (1988). Pre-operative nutritional status. *Br J Clin Pract* **42**: 2-7.

Coller FA, Bartlett RM, Bingham DLC, Maddock WG and Pedersen S (1938). The replacement of sodium chloride in surgical patients. *Ann Surg* **108**: 769-782.

Coller FA, Campbell KN, Vaughan HH, Iob LV and Moyer CA (1944). Postoperative salt intolerance. *Ann Surg* **119**: 533-541.

Coller FA, Dick VS and Maddock WG (1936). Maintenance of normal water exchange with intravenous fluids. *JAMA* **107**: 1522-1527.

Cuthbertson DP (1930). Effect of injury on metabolism. *Biochem J* **2**: 1244.

Cuthbertson DP (1932). Observations of the disturbance of metabolism produced by injury to the limbs. *Q J Med* **1**: 233-246.

Cuthbertson DP and Tompsett SL (1935). Note on the effect of injury on the level of the plasma proteins. *Br J Exp Pathol* **16**: 471-475.

Datz FL, Christian PE and Moore J (1987a). Gender-related differences in gastric emptying. *J Nucl Med* **28**: 1204-1207.

Datz FL, Christian PE and Moore JG (1987b). Differences in gastric emptying rates between menstruating and postmenopausal women [abstract]. *J Nucl Med* **28**: 604-605.

De Jong PCM, Wesdorp RIC, Volovics A, Roufflart M, Greep JM and Soeters PB (1985). The value of objective measurements to select patients who are malnourished. *Clin Nutr* **4**: 61-66.

Degen LP and Phillips SF (1996). Variability of gastrointestinal transit in healthy women and men. *Gut* **39**: 299-305.

Dick M, Dasta JF, Choban PS, R. S and Flancbaum L (1994). Serum aldosterone concentrations and urine output in oliguric intensive care patients receiving low dose dopamine. *Ann Pharmacother* **28**: 837-841.

Dorje P, Adhikary G, McLaren ID and Bogush S (1997). Dilutional acidosis or altered strong ion difference [letter]. *Anesthesiology* **87**: 1011-1012; discussion 1013-1014.

Doweiko JP and Nompleggi DJ (1991a). Interactions of albumin and medications. *JPEN J Parenter Enteral Nutr* **15**: 212-214.

Doweiko JP and Nompleggi DJ (1991b). The role of albumin in human physiology and pathophysiology, Part III: Albumin and disease states. *JPEN J Parenter Enteral Nutr* **15**: 476-483.

Drummer C, Gerzer R, Heer M, Molz B, Bie P, Schlossberger M*, et al.* (1992). Effects of an acute saline infusion on fluid and electrolyte metabolism in humans. *Am J Physiol* **262**: F744-754.

Durr ED, Hunt DR, Roughneen PT, Andrassy RJ and Rowlands BJ (1986). Hypoalbuminemia and gastrointestinal intolerance to enteral feeding in head injured patients [abstract]. *Gastroenterology* **90**: 1401.

Edelman IS and Leibman J (1959). Anatomy of body water and electrolytes. *Am J Med* **27**: 256-277.

Espiner EA, Christlieb AR, Amsterdam EA, Jagger PI, Dobrzinsky SJ, Lauler DP*, et al.* (1971). The pattern of plasma renin activity and aldosterone secretion in normal and hypertensive subjects before and after saline infusions. *Am J Cardiol* **27**: 585-594.

Evans GH (1911). The abuse of normal salt solution. *JAMA* **57**: 2126-2127.

Figge J, Jabor A, Kazda A and Fencl V (1998). Anion gap and hypoalbuminemia. *Crit Care Med* **26**: 1807-1810.

Finta KM, Rocchini AP, Moorehead C, Key J and Katch V (1992). Urine sodium excretion in response to an oral glucose tolerance test in obese and nonobese adolescents. *Pediatrics* **90**: 442-446.

Flear CT and Singh CM (1973). Hyponatraemia and sick cells. *Br J Anaesth* **45**: 976-994.

Flear CT and Singh CM (1982). The sick cell concept and hyponatremia in congestive heart failure and liver disease. *Lancet* **2**: 101-102.

Fleck A (1988). Plasma proteins as nutritional indicators in the perioperative period. *Br J Clin Pract* **42**: 20-24.

Fleck A, Raines G, Hawker F, Trotter J, Wallace PI, Ledingham IM*, et al.* (1985). Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. *Lancet* **1**: 781-784.

Franch G, Guirao X, Garcia-Domingo M, Gil MJ, Salas E and Sitges-Serra A (1992). The influence of calorie source on water and sodium balance during intravenous refeeding of malnourished rabbits. *Clin Nutr* **11**: 59-61.

Franch-Arcas G (2001). The meaning of hypoalbuminaemia in clinical practice. *Clin Nutr* **20**: 265-269.

Frawley JP, Howard JM, Artz CP and Anderson P (1955). Investigations of serum protein changes in combat casualties. *Arch Surg* **71**: 605-611.

Frier M and Perkins AC (1994). Radiopharmaceuticals and the gastrointestinal tract. *Eur J Nucl Med* **21**: 1234-1242.

Frost A, Wakefield CH, Sengupta F and Fearon KCH (2001). Relationship between fluid administrations and outcome in colorectal surgery [abstract]. *Proc Nutr Soc* **60**: 113A.

Gamble JL (1946-1947). Physiological information gained from studies on the life-raft ration. *Harvey Lectures* **42**: 247-273.

Gans RO, Bilo HJ, Nauta JJ, Heine RJ and Donker AJ (1992). Acute hyperinsulinemia induces sodium retention and a blood pressure decline in diabetes mellitus. *Hypertension* **20**: 199-209.

Garcia-Domingo M, Llado L, Guirao G, Franch G, Oliva A, Munoz A*, et al.* (1994). Influence of calorie source on the physiological response to parenteral nutrition in malnourished rabbits. *Clin Nutr* **13**: 9-16.

Gibbs J, Cull W, Henderson W, Daley J, Hur K and Khuri SF (1999). Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. *Arch Surg* **134**: 36-42.

Gil MJ, Franch G, Guirao X, Oliva A, Herms R, Salas E*, et al.* (1997). Response of severely malnourished patients to preoperative parenteral nutrition: a randomized clinical trial of water and sodium restriction. *Nutrition* **13**: 26-31.

Gosling P (1999). Fluid balance in the critically ill: the sodium and water audit. *Care of the Critically Ill* **15**: 11-16.

Grathwohl KW, Bruns BJ, LeBrun CJ, Ohno AK, Dillard TA and Cushner HM (1996). Does hemodilution exist? Effects of saline infusion on hematologic parameters in euvolemic subjects. *South Med J* **89**: 51-55.

Greenfield RH, Bessen HA and Henneman PL (1989). Effect of crystalloid infusion on hematocrit and intravascular volume in healthy, nonbleeding subjects. *Ann Emerg Med* **18**: 51-55.

Gryback P, Naslund E, Hellstrom PM, Jacobsson H and Backman L (1996). Gastric emptying of solids in humans: improved evaluation by Kaplan-

Meier plots, with special reference to obesity and gender. *Eur J Nucl Med* **23**: 1562-1567.

Guirao X, Franch G, Gil MJ, Garcia-Domingo MI, Girvent M and Sitges-Serra A (1994). Extracellular volume, nutritional status, and refeeding changes. *Nutrition* **10**: 558-561.

Guyton AC (1959). Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary oedema. *Circ Res* **7**: 649-657.

Hahn RG and Drobin D (1998). Urinary excretion as an input variable in volume kinetic analysis of Ringer's solution. *Br J Anaesth* **80**: 183-188.

Hahn RG and Svensen C (1997). Plasma dilution and the rate of infusion of Ringer's solution. *Br J Anaesth* **79**: 64-67.

Hannan WJ, Cowen SJ, Plester CE, Fearon KC and deBeau A (1995). Comparison of bio-impedance spectroscopy and multi-frequency bio-impedance analysis for the assessment of extracellular and total body water in surgical patients. *Clin Sci (Colch)* **89**: 651-658.

Hardy JG and Perkins AC (1985). Validity of the geometric mean correction in the quantification of whole bowel transit. *Nucl Med Commun* **6**: 217-224.

Hartmann AF (1934). Theory and practice of parenteral fluid administration. *JAMA* **103**: 1349-1354.

Healey MA, Davis RE, Liu FC, Loomis W and Hoyt DB (1998). Lactated Ringer's is superior to normal saline in a model of massive hemorrhage and resuscitation. *J Trauma* **45**: 894-898; discussion 898-899.

Heller MB, Crocco T, Prestosh JC and Patterson JW (1996). Effectiveness of different crystalloid i.v. solutions in establishing urine flow. *J Emerg Med* **14**: 1-3.

Hesse B and Nielsen I (1977). Suppression of plasma renin activity by intravenous infusion of antidiuretic hormone in man. *Clin Sci Mol Med* **52**: 357-360.

Heyland DK, Tougas G, King D and Cook DJ (1996). Impaired gastric emptying in mechanically ventilated, critically ill patients. *Intensive Care Med* **22**: 1339-1344.

Hill GL (1992a). Fluid and electrolyte therapy and disorders of acid base balance. Disorders of Nutrition and Metabolism in Clinical Surgery: Understanding and Management. G. L. Hill. Edinburgh, Churchill Livingstone**:** 45-63.

Hill GL (1992b). Jonathan E. Rhoads Lecture. Body composition research: implications for the practice of clinical nutrition. *JPEN J Parenter Enteral Nutr* **16**: 197-218.

Hinton P, Allison SP, Littlejohn S and Lloyd J (1973). Electrolyte changes after burn injury and effect of treatment. *Lancet* **2**: 218-221.

Ho AM, Karmakar MK, Contardi LH, Ng SS and Hewson JR (2001). Excessive use of normal saline in managing traumatized patients in shock: a preventable contributor to acidosis. *J Trauma* **51**: 173-177.

Hoch-Ligeti C, Irvine K and Sprinkle EP (1953). Investigation of serum protein patterns in patients undergoing operation. *Proc Soc Exp Biol Med* **84**: 707-710.

Horowitz M, Maddern GJ, Chatterton BE, Collins PJ, Petrucco OM, Seamark R, *et al.* (1985). The normal menstrual-cycle has no effect on gastric-emptying. *Br J Obstet Gynaecol* **92**: 743-746.

Hunter J (1794). A Treatise on the Blood, Inflammation and Gunshot Wounds, G. Nichol.

Inagami T, Okamoto H, Ohtsuki K, Shimamoto K, Chao J and Margolius HS (1982). Human-plasma inactive renin-purification and activation by proteases. *J Clin Endocrinol Metab* **55**: 619-627.

Ingenbleek Y and Carpentier YA (1985). A prognostic inflammatory and nutritional index scoring critically ill patients. *Int J Vitam Nutr Res* **55**: 91-101.

Julian BA, Galla JH, Guthrie GP, Jr. and Kotchen TA (1982). Renin and aldosterone responses to short-term NaCl or $NaHCO_3$ loading in man. *J Lab Clin Med* **100**: 261-268.

Kamp-Jensen M, Olesen KL, Bach V, Schutten HJ and Engquist A (1990). Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid-base and haemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers. *Br J Anaesth* **64**: 606-610.

Kaye AD and Grogono AW (2000). Fluid and electrolyte physiology. Anesthesia. R. D. Miller, R. F. Cucchiara, E. D. Miller, Jr.et al. Philadelphia, Churchill Livingstone. **1:** 1586-1612.

Keys A, Brozek J, Henschel A, Mickelsen O and Taylor HF (1950). The Biology of Human Starvation. Minneapolis, University of Minnesota Press.

Khokhar AM, Slater JD, Forsling ML and Payne NN (1976). Effect of vasopressin on plasma volume and renin release in man. *Clin Sci Mol Med* **50**: 415-424.

Kim J, Wang Z, Gallagher D, Kotler DP, Ma K and Heymsfield SB (1999). Extracellular water: sodium bromide dilution estimates compared with other markers in patients with acquired immunodeficiency syndrome. *JPEN J Parenter Enteral Nutr* **23**: 61-66.

Klahr S and Alleyne GA (1973). Effects of chronic protein-calorie malnutrition on the kidney. *Kidney Int* **3**: 129-141.

Kong MF, Perkins AC, King P, Blackshaw PE and Macdonald IA (1998). Reproducibility of gastric emptying of a pancake and milkshake meal in normal subjects. *Nucl Med Commun* **19**: 77-82.

Kotchen TA, Luke RG, Ott CE, Galla JH and Whitescarver S (1983). Effect of chloride on renin and blood pressure responses to sodium chloride. *Ann Intern Med* **98**: 817-822.

Koulmann N, Jimenez C, Regal D, Bolliet P, Launay JC, Savourey G*, et al.* (2000). Use of bioelectrical impedance analysis to estimate body fluid compartments after acute variations of the body hydration level. *Med Sci Sports Exerc* **32**: 857-864.

Kramer GC, Svensen CH and Prough DS (2001). To bolus or not to bolus - is that the question? [editorial] *Clin Sci (Lond)* **101**: 181-183.

Lamke LO and Liljedahl SO (1976). Plasma volume changes after infusion of various plasma expanders. *Resuscitation* **5**: 93-102.

Lamprecht F, Miller WL, Kawasaki T and Bartter FC (1979). Responses of plasma renin activity and dopamine-beta-hydroxylase to increased intravascular volume. *J Neural Transm* **46**: 35-45.

Lane N and Allen K (1999). Hyponatraemia after orthopaedic surgery [editorial]. *BMJ* **318**: 1363-1364.

Latta T (1832). Malignant cholera. Documents communicated by the Central Board of Health, London, relative to the treatment of cholera by copious injection of aqueous and saline fluids into the veins. *Lancet* **ii**: 274-277.

Le Quesne LP and Lewis AAG (1953). Postoperative water and sodium retention. *Lancet* **1**: 153-158.

Leckie BJ, McConnell A, Grant J, Morton JJ, Tree M and Brown JJ (1977). An inactive renin in human plasma. *Circ Res* **40 (Suppl 1)**: I46-51.

Leckie BJ and McGhee NK (1980). Reversible activation-inactivation of renin in human plasma. *Nature* **288**: 702-705.

Lobo DN, Bjarnason K, Field J, Rowlands BJ and Allison SP (1999). Changes in weight, fluid balance and serum albumin in patients referred for nutritional support. *Clin Nutr* **18**: 197-201.

Lobo DN, Bostock KA, Bush D, Macdonald IA, Perkins AC, Neal KR*, et al.* (2002a). Reproducibility and normal ranges for gastric emptying in normal volunteers using a test meal designed for postoperative patients. *Nucl Med Commun* **23**: 97-101.

Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ and Allison SP (2002b). Effect of salt and water balance on recovery of gastrointestinal

function after elective colonic resection: a randomised controlled trial. *Lancet* **359**: 1812-1818.

Lobo DN, Dube MG, Neal KR, Simpson J, Rowlands BJ and Allison SP (2001). Problems with solutions: drowning in the brine of an inadequate knowledge base. *Clin Nutr* **20**: 125-130.

Lobo DN, Stanga Z, Simpson JAD, Anderson JA, Rowlands BJ and Allison SP (2001). Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. *Clin Sci (Lond)* **101**: 173-179.

Lorenz JN, Weihprecht H, Schnermann J, Skott O and Briggs JP (1991). Renin release from isolated juxtaglomerular apparatus depends on macula densa chloride transport. *Am J Physiol* **260**: F486-493.

Lucas CE (2001). The water of life: a century of confusion. *J Am Coll Surg* **192**: 86-93.

Lucas CE, Weaver D, Higgins RF, Ledgerwood AM, Johnson SD and Bouwman DL (1978). Effects of albumin versus non-albumin resuscitation on plasma volume and renal excretory function. *J Trauma* **18**: 564-570.

Luetscher JA, Bialek JW and Grislis G (1982). Human kidney cathepsins B and H activate and lower the molecular weight of human inactive renin. *Clin Exp Hypertens A* **4**: 2149-2158.

Lumbers ER (1971). Activation of renin in human amniotic fluid by low pH. *Enzymologia* **40**: 329-336.

Macfie J, Smith RC and Hill GL (1981). Glucose or fat as a nonprotein energy source? A controlled clinical trial in gastroenterological patients requiring intravenous nutrition. *Gastroenterology* **80**: 103-107.

Mackie C, Hulks G and Cuschieri A (1986). Enterogastric reflux and gastric clearance of refluxate in normal subjects and in patients with and without bile vomiting following peptic ulcer surgery. *Ann Surg* **204**: 537-542.

Marik PE (1993). The treatment of hypoalbuminemia in the critically ill patient. *Heart Lung* **22**: 166-170.

Maughan RJ and Leiper JB (1996). Methods for the assessment of gastric emptying in humans: an overview. *Diabet Med* **13**: S6-10.

McFarlane C and Lee A (1994). A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. *Anaesthesia* **49**: 779-781.

Mecray PM, Barden RP and Ravdin IS (1937). Nutritional edema: its effect on the gastric emptying time before and after gastric operations. *Surgery* **1**: 53-64.

Miller LR, Waters JH and Provost C (1996). Mechanism of hyperchloremic metabolic acidosis [letter]. *Anesthesiology* **84**: 482-483.

Mitchell JP, Schuller D, Calandrino FS and Schuster DP (1992). Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterisation. *Am Rev Respir Dis* **145**: 990-998.

Moore FD (1959). Metabolic Care of the Surgical Patient. Philadelphia, W. B. Saunders.

Moore FD and Shires G (1967). Moderation. *Ann Surg* **166**: 300-301.

Moore PJ and Clarke RG (1982). Colloid osmotic pressure and serum albumin following surgery. *Br J Surg* **69**: 140-142.

Morris BJ (1978). Activation of human inactive ("pro-") renin by cathepsin D and pepsin. *J Clin Endocrinol Metab* **46**: 153-157.

Mullen JL, Buzby GP, Matthews DC, Smale BF and Rosato EF (1980). Reduction of operative morbidity and mortality by combined preoperative and postoperative nutritional support. *Ann Surg* **192**: 604-613.

Mullins RJ and Bell DR (1982). Changes in interstitial volume and masses of albumin and IgG in rabbit skin and skeletal muscle after saline volume loading. *Circ Res* **51**: 305-313.

Mullins RJ and Garrison RN (1989). Fractional change in blood volume following normal saline infusion in high-risk patients before noncardiac surgery. *Ann Surg* **209**: 651-659; discussion 659-661.

Norgaard K, Jensen T, Skott P, Thorsteinsson B, Bruun NE, Giese J*, et al.* (1991). Effects of insulin on renal haemodynamics and sodium handling in normal subjects. *Scand J Clin Lab Invest* **51**: 367-376.

Nyboer J (1972). Workable volume and flow concepts of bio-segments by electrical impedance plethysmography. *TIT J Life Sci* **2**: 1-13.

Oh MS and Carroll HJ (1977). The anion gap. *N Engl J Med* **297**: 814-817.

Parving HH, Rossing N, Nielsen SL and Lassen NA (1974). Increased transcapillary escape rate of albumin, IgG, and IgM after plasma volume expansion. *Am J Physiol* **227**: 245-250.

Patrono C and Peskar BA, Eds. (1987). Radioimmunoassay in Basic and Clinical Pharmacology. Heidelberg, Springer-Verlag.

Perl W (1975). Convection and permeation and albumin between plasma and interstitium. *Microvasc Res* **10**: 83-94.

Plank LD, Connolly AB and Hill GL (1998). Sequential changes in the metabolic response in severely septic patients during the first 23 days after the onset of peritonitis. *Ann Surg* **228**: 146-158.

Plank LD and Hill GL (2000). Similarity of changes in body composition in intensive care patients following severe sepsis or major blunt injury. *Ann N Y Acad Sci* **904**: 592-602.

Plank LD, Monk DN, Gupta R, Franch-Arcas G, Pang J and Hill GL (1995). Body composition studies in intensive care patients: comparison of methods of measuring total body water. *Asia Pacific J Clin Nutr* **4**: 125-129.

Plante GE, Chakir M, Lehoux S and Lortie M (1995). Disorders of body fluid balance: a new look into the mechanism of disease. *Can J Cardiol* **11**: 788-802.

Power FH, Pedersen S and Maddock WG (1942). Clinical experience with sodium chloride replacement. *Surgery* **12**: 438-444.

Pringle H, Maunsell RCB and Pringle S (1905). Clinical effects of ether anaesthesia on renal activity. *BMJ* **ii**: 542-543.

Prough DS and Bidani A (1999). Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline [editorial]. *Anesthesiology* **90**: 1247-1249.

Pulimood TB and Park GR (2000). Debate: Albumin administration should be avoided in the critically ill. *Crit Care* **4**: 151-155.

Ravdin IS (1938). Factors involved in the retardation of gastric emptying after gastric operations. *Pennsylvania Med J* **41**: 695-700.

Ray PE, Castren E, Ruley EJ and Saavedra JM (1990). Different effects of sodium or chloride depletion on angiotensin II receptors in rats. *Am J Physiol* **258**: R1008-1015.

Ray PE, Ruley EJ, Bernardini R and Saavedra JM (1991). Chronic sodium or chloride depletion upregulates angiotensin II receptors in the anterior pituitary lobe of young rats. *Neuroendocrinology* **53**: 556-561.

Rayyis SS and Horton R (1971). Effect of angiotensin II on adrenal and pituitary function in man. *J Clin Endocrinol Metab* **32**: 539-546.

Rhoads JE (1957). Fluid and electrolytes. Surgery Principles and Practice. J. G. Allen, H. H. Harkins, C. A. Moyer and J. E. Rhoads. London, Pitman Medical Publishing**:** 65-79.

Robinson JR and McCance RA (1952). Water metabolism. *Annu Rev Physiol* **14**: 115-142.

Rooke P and Baylis PH (1982). A new sensitive radioimmunoassay for plasma arginine vasopressin. *J Immunoassay* **3**: 115-131.

Rose BD and Post TW (2001). Clincal Physiology of Acid-base and Electrolyte Disorders. New York, McGraw-Hill.

Roth E, Lax LC and Maloney JV, Jr. (1969). Ringer's lactate solution and extracellular fluid volume in the surgical patient: a critical analysis. *Ann Surg* **169**: 149-164.

Rothschild MA, Oratz M and Schreiber SS (1972). Albumin synthesis. 1. *N Engl J Med* **286**: 748-757.

Russi E and Weigand K (1983). Analbuminemia. *Klin Wochenschr* **61**: 541-545.

Sagnella GA, Shore AC, Markandu ND and Macgregor GA (1985). Effects of changes in dietary-sodium intake and saline infusion on immunoreactive atrial natriuretic peptide in human-plasma. *Lancet* **2**: 1208-1211.

Salmon JB and Mythen MG (1993). Pharmacology and physiology of colloids. *Blood Rev* **7**: 114-120.

Scheingraber S, Rehm M, Sehmisch C and Finsterer U (1999). Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology* **90**: 1265-1270.

Schierhout G and Roberts I (1998). Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *BMJ* **316**: 961-964.

Schoeller DA and Jones PJH (1987). Measurement of total body water by isotope dilution: a unified approach for calculations. London, Institute of Physical Sciences in Medicine.

Scholer D, Birkhauser M, Peytremann A, Riondel AM, Vallotton MB and Muller AF (1973). Response of plasma aldosterone to angiotensin II, ACTH and potassium in man. *Acta Endocrinol (Copenh)* **72**: 293-307.

Schorr U, Blaschke K, Turan S, Distler A and Sharma AM (1998). Relationship between angiotensinogen, leptin and blood pressure levels in young normotensive men. *J Hypertens* **16**: 1475-1480.

Shires GT, Brown FT, Canizaro PC and Somerville N (1960). Distributional changes in extracellular fluid during acute hemorrhagic shock. *Surg Forum* **11**: 115-117.

Shires GT, Williams J and Brown F (1961). Acute changes in extracelular fluids associated with major surgical procedures. *Ann Surg* **154**: 803-810.

Shires GTI, Barber A and Shires GT (1999). Fluid and electrolyte management of the surgical patient. Principles of Surgery. S. I. Schwartz, G. T. Shires, F. C. Spenceret al. New York, McGraw-Hill**:** 53-75.

Shizgal HM (1981). The effect of malnutrition on body composition. *Surg Gynecol Obstet* **152**: 22-26.

Shoemaker WC, Bryan-Brown CW, Quigley L, Stahr L, Elwyn DH and Kark AE (1973). Body fluid shifts in depletion and poststress states and their correction with adequate nutrition. *Surg Gynecol Obstet* **136**: 371-374.

Simpson JAD, Anderson JA, Lobo DN, MacDonald IA, Rowlands BJ, Allison SP*, et al.* (2000). Consistent differences in total body water as determined by two different bioelectrical impedance analysis devices. *Proc Nutr Soc* **59**: 166A.

Simpson JAD, Lobo DN, Anderson JA, Macdonald IA, Perkins AC, Neal KR*, et al.* (2001). Body water compartment measurements: a comparison of bioelectrical impedance analysis with tritium and sodium bromide dilution techniques. *Clin Nutr* **20**: 339-343.

Singer DR, Markandu ND, Morton JJ, Miller MA, Sagnella GA and MacGregor GA (1994). Angiotensin II suppression is a major factor permitting excretion of an acute sodium load in humans. *Am J Physiol* **266**: F89-93.

Singer DR, Shirley DG, Markandu ND, Miller MA, Buckley MG, Sugden AL*, et al.* (1991). How important are suppression of aldosterone and stimulation

of atrial natriuretic peptide secretion in the natriuretic response to an acute sodium load in man? *Clin Sci (Lond)* **80**: 293-299.

Singer DRJ, Shore AC, Markandu ND, Buckley MG, Sagnella GA and Macgregor GA (1987). Dissociation between plasma atrial-natriuretic-peptide levels and urinary sodium-excretion after intravenous saline infusion in normal man. *Clin Sci (Lond)* **73**: 285-289.

Sitges-Serra A (1999). The Sixth John M. Kinney-Baxter Healthcare Award for Parenteral Nutrition. Water and sodium restriction during preoperative TPN in severely malnourished patients: the history [see comments]. *Nutrition* **15**: 431-436.

Sitges-Serra A and Franch-Arcas G (1998). Fluid and sodium problems in perioperative feeding: what further studies need to be done? *Curr Opin Clin Nutr Metab Care* **1**: 9-14.

Skinner SL, Dunn JR, Mazzetti J, Campbell DJ and Fidge NH (1975). Purification, properties and kinetics of sheep and human renin substrates. *Aust J Exp Biol Med Sci* **53**: 77-88.

Skott O and Briggs JP (1987). Direct demonstration of macula densa-mediated renin secretion. *Science* **237**: 1618-1620.

Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L*, et al.* (1999). Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* **341**: 403-409.

Starker PM, Lasala PA, Askanazi J, Gump FE, Forse RA and Kinney JM (1983). The response to TPN. A form of nutritional assessment. *Ann Surg* **198**: 720-724.

Starling EH (1896). On the absorption of fluids from connective tissue spaces. *J Physiol* **19**: 312-326.

Stewart PA (1983). Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* **61**: 1444-1461.

Stone HH and Fulenwider JT (1977). Renal decapsulation in the prevention of post ischemia oliguria. *Ann Surg* **186**: 343-355.

Stoneham MD and Hill EL (1997). Variability in post-operative fluid and electrolyte prescription. *Br J Clin Pract* **51**: 82-84.

Svensen C and Hahn RG (1997). Volume kinetics of Ringer solution, dextran 70, and hypertonic saline in male volunteers [see comments]. *Anesthesiology* **87**: 204-212.

Taylor AE, Parker JC, Granger DN, Mortillaro NA and Rutili G (1981). Assessment of capillary permeability using lymphatic protein flux: estimation of the osmotic reflection coefficient. The Microcirculation. R. Effros. New York, Academic Press**:** 19-32.

Tetlow HJ and Broughton Pipkin F (1983). Studies on the effect of mode of delivery on the renin-angiotensin system in mother and fetus at term. *Br J Obstet Gynaecol* **90**: 220-226.

Than N, Woodrow G, Oldroyd B, Gonzalez C, Turney JH and Brownjohn AM (2000). Effect of peritoneal fluid on whole body and segmental multiple

frequency bioelectrical impedance in patients on peritoneal dialysis. *Eur J Clin Nutr* **54**: 450-451.

Thompson WT (1968). Salt and water. *Va Med Mon (1918)* **95**: 587-590.

Tindall SF and Clark RG (1981). The influence of high and low sodium intakes on post-operative antidiuresis. *Br J Surg* **68**: 639-644.

Tobian L, Tomboulian A and Janecek J (1959). The effect of high perfusion pressures on the granulation of juxtaglomerular cells in an isolated kidney. *J Clin Invest* **38**: 605-610.

Tournadre JP, Allaouchiche B, Malbert CH and Chassard D (2000). Metabolic acidosis and respiratory acidosis impair gastro-pyloric motility in anesthetized pigs. *Anesth Analg* **90**: 74-79.

Trout HM (1913). Proctoclysis - an experimental study. *Surg Gynecol Obstet* **16**: 560-562.

Turner DAB (1996). Fluid, electrolyte and acid-base balance. Textbook of Anaesthesia. A. R. Aitkenhead and G. Smith. New York, Churchill Livingstone**:** 361-375.

Usberti M, Federico S, Di Minno G, Ungaro B, Ardillo G, Pecoraro C*, et al.* (1985). Effects of angiotensin II on plasma ADH, prostaglandin synthesis, and water excretion in normal humans. *Am J Physiol* **248**: F254-259.

Vaisman N, Pencharz PB, Koren G and Johnson JK (1987). Comparison of oral and intravenous administration of sodium bromide for extracellular water measurements. *Am J Clin Nutr* **46**: 1-4.

Vantrappen G (1994). Methods to study gastric emptying. *Dig Dis Sci* **39**: 91S-94S.

Vaughan BE and Boilin EA (1961). Rapid assay procdure for tritium labelled water body fluids. *J Lab Clin Med* **57**: 159-164.

Veech RL (1986). The toxic impact of parenteral solutions on the metabolism of cells: a hypothesis for physiological parenteral therapy. *Am J Clin Nutr* **44**: 519-551.

Veverbrants E and Arky RA (1969). Effects of fasting and refeeding. I. Studies on sodium, potassium and water excretion on a constant electrolyte and fluid intake. *J Clin Endocrinol Metab* **29**: 55-62.

Voto LS, Hetmanski DJ and Broughton Pipkin F (1990). Determinants of fetal and maternal atrial natriuretic peptide concentrations at delivery in man. *Br J Obstet Gynaecol* **97**: 1123-1129.

Wakim KG (1970). "Normal" 0.9 per cent salt solution is neither "normal" nor physiological. *JAMA* **214**: 1710.

Watenpaugh DE, Yancy CW, Buckey JC, Lane LD, Hargens AR and Blomqvist CG (1992). Role of atrial natriuretic peptide in systemic responses to acute isotonic volume expansion. *J Appl Physiol* **73**: 1218-1226.

Webb AR (1999). Crystalloid or colloid for resuscitation. Are we any the wiser? *Critical Care* **3**: R25-R28.

Welch WJ, Ott CE, Guthrie GP, Jr. and Kotchen TA (1985). Renin secretion and loop of Henle chloride reabsorption in the adrenalectomized rat. *Am J Physiol* **249**: F596-602.

Wilcox CS (1983). Regulation of renal blood flow by plasma chloride. *J Clin Invest* **71**: 726-735.

Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R*, et al.* (2001). The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg* **93**: 811-816.

Wilkinson AW, Billing BH, Nagy G and Stewart CP (1949). Excretion of chloride and sodium after surgical operations. *Lancet* **1**: 640-644.

Wilkinson AW, Billing BH, Nagy G and Stewart CP (1950). Excretion of potassium after partial gastrectomy. *Lancet* **2**: 135-137.

Williams EL, Hildebrand KL, McCormick SA and Bedel MJ (1999). The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. *Anesth Analg* **88**: 999-1003.

Wingender W, Neurser D, Weber H, Morich FJ, Horstmann R and Kuhlmann J (1988). Increase in plasma atrial natriuretic factor and right atrial area during endogenous and exogenous volume loading in healthy volunteers: effect on plasma renin activity, aldosterone and antidiuretic hormone. *J Hypertens Suppl* **6**: S314-316.

Winick M, Ed. (1979). Hunger Disease: Studies by the Jewish Physicians in the Warsaw Ghetto. New York, Wiley.

Woods MS and Kelley H (1993). Oncotic pressure, albumin and ileus: the effect of albumin replacement on postoperative ileus. *Am Surg* **59**: 758-763.

Zillikens MC, van den Berg JW, Wilson JH and Swart GR (1992). Whole-body and segmental bioelectrical-impedance analysis in patients with cirrhosis

of the liver: changes after treatment of ascites. *Am J Clin Nutr* **55**: 621-625.