THE STUDY OF WATER AND SODIUM HOMEOSTASIS IN THE SURGICAL PATIENT WITH PARTICULAR REFERENCE TO HYPONATRAEMIA AND SODIUM FLUX

by

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being a thesis submitted to the University of London for the Degree of Doctor of Philosophy

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ABSTRACT

The objective of this study was to delineate normal and abnormal serum sodium concentration in relation to surgical injury with particular reference to their role in decision-making.

In Part I of the thesis the relevant literature on sodium and water homeostasis in health and in disease is reviewed.

Part II of the thesis begins with a study of the distribution of a water overload in healthy volunteers; it was confirmed that the induced hyponatraemia was dilutional. Precise delineation of post-injury dilutional hyponatraemia was then achieved by establishing a confidence band using a conventional fluid regimen. Departures from this band have enabled osmolal gaps to be identified in seriously ill surgical patients. In these patients, in vitro studies of erythrocytes showed no change in sodium flux across the membrane. Though post-traumatic antidiuresis is one factor in causing a fall in serum sodium concentration, a study of urinary volume, concentration, and solute excretion in the post-operative period demonstrated that at least for the first eighteen hours, concentration is not that seen with maximum antidiuretic hormone (ADH) activity. It is suggested that factors other than ADH are operative.

In Part III of the thesis, a physiological model is described that distinguishes the water obligated to glycogen storage from that due to possible changes in body sodium. A hypothesis is proposed that interlinks water and sodium movements with that of glycogen storage. The rational use of glucose-

potassium-insulin therapy in hyponatraemia is then discussed.

Part IV of the thesis deals with parenteral water and sodium with respect to intestinal surgery in rabbit small bowel. Extracellular volume expansion was shown to exaggerate an anatomical third space and oedema so induced at the suture line is persistent and may be deleterious.

Finally, a general discussion about the significance of the results and recommendations for future work is given in Part V.

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ACKNOWLEDGEMENTS

The work for this thesis was made possible by a grant from the Locally Organised Research Scheme, Kensington and Chelsea and Westminster Area Health Authority in 1979, and the award of a Research Fellowship from the Wellcome Trust in 1980.

Professor H. A. F. Dudley first taught me the essentials of fluid and electrolyte balance in 1969 at Monash University, Australia. Ten years later, at St. Mary's Hospital Medical School, London, he provided the initial questions and directions for this thesis. Throughout the two years of this work, he gave constant encouragement, advice and constructive criticism, for which I am most grateful.

I also wish to thank my colleagues in the Surgical Unit Laboratory, in particular Mr. Andrew Johnson, Mr Andrew Radcliffe and Mr Raj Kapadia, for the long hours of useful discussion regarding many aspects of this work.

Finally, to the late Dr. M. M. Bluhm and Mr. S. A. J. Suddle of the Department of Clinical Physics, St. Mary's Hospital, London, for help with isotope dilution studies; and to Christine Terry and Joan Newman for typing this thesis.

P A R T I

BACKGROUND TO THE WORK

C H A P T E R 1

REVIEW OF THE LITERATURE

1.1 INTRODUCTION

The concentration of sodium in a serum sample may be lowered by an increase in the amount of fluid or a decrease in the amount of dissolved sodium. The diluent is, of course, water. Sodium and water balance and its control in man in health and disease has been the subject of many studies and reviews. However, disorders of water balance, in particular hyponatraemia, continue to cause difficulty in clinical practice.

In this section of the thesis, a historical review of the physiology of sodium and water metabolism is presented first (Section 1.2). Special emphasis is given to the development of hyponatraemia in relation to surgical injury (Section 1.3). This preliminary will lead up to the studies of Part II of this thesis.

In order to place in proper perspective the current status of water and electrolyte regimens, the development of the technique of intravenous therapy is reviewed (Section 1.4) and reference is made to parenteral feeding in the surgical patient in relation to starvation and injury (Section 1.5). This was a prerequisite to the study of metabolic substrate and water-electrolyte movements after injury in Part III, and the effects of water and sodium infusion on the water content of intestinal

anastomosis in Part IV of this thesis.

1.2 Historical

Though the literature relating extracellular fluid (ECF) volume to sodium (Na^+) and water metabolism has existed for little more that a century, an early insight into the intricacies between Na^+, the kidneys and the circulation can be found in ancient Chinese writings. The Chinese emperor, Huang Ti (2650 B.C.), believed to be the author of "Nei Ching Su Wen" - "The Yellow Emperor's Classic of Internal Medicine" - described the complex relationship between salt and kidney function and too much salt was said to affect the pulse through the mediation of the heart (Veith, 1973). The study of the pulse remains a central theme in Chinese medical practice to this day.

Modern medicine has its roots in Ancient Greek civilisation through the teachings and writings of Hippocrates (460-355, B.C.) and his immediate followers. From the school of Alexandria came, perhaps, an early hint that disturbance of fluid balance may be an important cause of disease. Erasistratus (circa 300, B.C.), recognised by some as the founder of physiology, regarded the nerves as hollow tubes filled with fluid and he did experiments which led him to reject the accepted view that disease was due to maladjusted humours. Instead, he attributed disease to plethora, or an excessive blood supply (Guthrie, 1958).

Writers in antiquity had often speculated about how fluid

taken orally passed from the gut to the bladder. Galen of Pergamos (130-200, A.D.) first demonstrated that urine was formed in the kidneys and reached the bladder by way of the ureters (Fulton and Wilson, 1966). Theories concerning kidney function were provided from the 13th Century when William of Salicet (1210-1277) propounded his ideas of urine formation and gave classical accounts of renal "dropsy".

The next epoch germane to this review is the Renaissance, which probably marks a peak in the history of medicine and of science. Although the subtle nature of water and electrolyte problems was not a direct concern of the physicians and surgeons of this era, much was achieved that paved the way for future understanding provided by more advanced technology. Foremost among the great medical contributions during this period of enlightenment was the work of Andreas Vesalius (1514-1564) published in "De Humani Corporis Fabrica". The description and delineation of the structures of the human body marked a great advance upon any previous work, and also provided one of the fundamental data on which Harvey based his discovery of the circulation of the blood (Singer, 1957).

Renaissance surgery was dominated by the great name of Ambroise Pare (1510-1590) who trusted his own observations rather than to books (Keynes, 1968). Furthermore, his career exemplified that war has ever been a great teacher of surgery, for he was one of the leading army surgeons of his time. It is of interest to

note that even at that period great rivalry existed between surgeons and physicians and it was the renowned Renaissance physician, Paracelsus (1493-1541) who first expoused a "chemical view of life". He stated that man was composed of three elements - sulphur, mercury and salt - and all disease the result of maladjustment of the three.

The 17th Century saw the development of new ideas and discoveries that took root and flourished. Great names around this period included those of Francis Bacon (1561-1626), René Descartes (1596-1650) and Galileo Galilei (1564-1642), all of whom had a profound influence upon medical science. In many ways the basis for a more scientific analysis of fluid and electrolyte metabolism was being laid. William Harvey (1578-1657) published "De Motu Cordis et Sanguinis" in 1628, although he had already reached the conclusion regarding the circular motion of blood in his Lumleian lectures during 1616 (Singer, 1957). Harvey's study of vascular physiology introduced a new conception of the functions of the human body just as Vesalius had given a new view of its structure. Together they had changed the centre of outlook in medical science and laid the foundation of modern practice.

Following on the work of Harvey, the quest for a new basis to explain all the phenomena of health and disease on a materialistic basis had begun. The 'iatro-physicists' sought to explain all the workings of the human body as physical or mechanical in nature; the 'iatro-chemists' regarded life as a

series of chemical processes, assuming that the body was a sort of test tube (Guthrie, 1958). Sanctorius Sanctorius (1561-1636) of Padua may be said to have begun the study of what we now call 'metabolism'. He created a weighing balance from which he estimated the weight of his own "invisible perspiration", upon which he laid great stress. Perspiration, Sanctorius tells us, must be distinguished from sweating. Franciscus Sylvius (1614-1672), a professor at Leyden, placed chemical physiology upon a sounder basis. He studied the nature of the juices of the body - saliva, pancreatic juice, bile, etc. - and recommended that a knowledge of acids and alkalis furnished an index of the appropriate treatment.

The next landmark in the history of Na^+ and water metabolism was provided by the Reverend Stephen Hales of Teddington, Middlesex (1677-1761). In 1733, he demonstrated the objective measurement of blood pressure for the first time and his series of experiments on the hydraulics of the vascular system must rank as the most significant and original work on the circulation after the discoveries of Harvey (Hales, 1733). Somewhat later, Na^+ as an element was discovered by electrolysis by Davy, in 1807 (St. John, 1928). Physiological chemistry and the special study of diseases of metabolism during this period were greatly assisted by the researches of Justus von Liebig (1803-1873) of Giessen, while Richard Bright's (1836) classical observations upon "certain kinds of dropsy with albuminous urine and with a diseased state of the kidneys" first revealed the role

of the kidney in disease since ancient writings, and threw light upon its normal functions. However, in the absence of techniques for measuring the serum Na^+, the precise role of Na^+ metabolism in disease was not yet forthcoming.

At this juncture of our historical review, the most significant milestone in the study of water and Na^+ metabolism has been reached. The work of Claude Bernard (1813-1878) contributed enormously to our knowledge relating ECF to Na^+ and water metabolism. In 1865 he published his thoughts upon the principle of the constancy of the 'milieu intérieur' or internal environment in "Introduction à l'étude de la médecine expérimentale' (Bernard, 1865). This principle was a corollary to Bernard's doctrine of determinism, namely, that vital phenomena were determined by physico-chemical conditions which, he pointed out, were those of the 'milieu intérieur', not those of the external world. Bernard was guided in the development of this concept by the recently enunciated cell theory of Schleiden and Schwann in 1839, which was being vigorously applied to pathology by Rudolf Virchow (1821-1902). In the light of the cell theory, Bernard saw the fundamental problems of physiology in the relation between the cells and their immediate surrounding environment (Holmes, 1974). Subsequently, the progress of physiology has revealed the far-reaching significance of Bernard's concept. As more - and more varied and elaborate - physiological mechanisms have been studied, each is seen to contribute, directly or

indirectly, to the maintenance of constant internal conditions (Fulton and Wilson, 1966). Lawrence Henderson wrote in 1913: "This theory of the constancy of the 'milieu intérieur' was an induction from relatively few facts, but the discoveries of the last fifty years and the introduction of physico-chemical methods into physiology have proved that it is well founded" (Henderson, 1913). It may also be noted that Claude Bernard has left his mark on many other branches of physiology, one of which was the discovery of glycogen, to which this thesis will refer again in Part III.

Paralleled with Bernard's work, the first serious consideration of water and electrolyte imbalance took place in the early 19th Century when an English physician, W. B. O'Shaughnessy (1831), described deficits of water, saline and alkali in the blood of cholera victims. O'Shaughnessy suggested intravenous replacement of those deficits with a saline solution while Thomas Latta (1832), a practitioner in Scotland, was the first to carry out this method of therapy.

The turn of the century witnessed many advances in chemistry and it was at this time that chemical methods for determining body fluid constituents began to be more widely employed. In 1904, Ambard and Beaujard were the first to relate salt retention to hypertension. During treatment with a low-salt diet, blood pressure was correlated with chloride balance (Swales, 1975); the chloride ion could readily be measured by chemical methods then,

while the Na^+ ion was still not susceptible to laboratory analysis. It was not until a quarter of a century later that chemical methods for measuring the serum Na^+ began to be widely employed (Varley, 1967).

In 1926, Archibald Macallum (1858-1934) gave historical and phylogenetic meaning to the constancy of the 'milieu intérieur'. He made many determinations of the ionic composition of body fluids for the first time. In "The Paleochemistry of the Body Fluids and Tissues" he demonstrated the startling resemblance between the ionic composition of blood sera and that of sea water - namely, the dominancy of Na^+ and chloride ions - and suggested that tissue cells could only live within a relatively narrow range of physico-chemical conditions - conditions which represented those of the ancient ocean in which the cells of ancestral organisms had taken their origin (Macallum, 1926). Although criticised, this idea has not lost its biological attractiveness and emphasises the concept of ionic constancy. In the same year, Walter Cannon (1871-1945) outlined for the first time his classic concept of "homeostasis" to delineate the process by which physiological reactions tend to restore the internal environment to a steady state which he was later to develop so successfully in "The Wisdom of the Body" (Fulton and Wilson, 1966).

As indicated previously, chemical methods for measuring the serum Na^+ concentration did not come into use until the 1920s. Initially, there was little interest in the role

of the Na^+ ion, which could only be monitored with extreme difficulty by a lengthy chemical technique (Swales, 1975). The Na^+ ion came into its own in the post-war years in the late 1940s with the development of the flame photometer (Hald, 1947). However, it should be pointed out that the fundamentals of electrolyte distribution and control had already been worked out before the advent of the flame photometer, and particularly noteworthy in this respect are the classical studies of James Gamble on the composition of body fluids (Gamble, 1942).

Flame photometry, for measuring serum Na^+ concentration, and measurement of exchangeable body Na^+ (Na_e) and total body water (TBW) by isotope dilution, are now firmly established laboratory techniques. The application of the flame photometer for measuring serum Na^+ concentration has made it possible to carry out the increased number of determinations rapidly with a great saving of time and with increased accuracy and precision, compared with chemical methods, which rapidly fell into disuse.

With the advent of automated biochemical services, hardly a patient can escape having his serum Na^+ concentration measured as part of a profile of "urea and electrolytes". However, like most advances in medical technology, the flame photometer has proved a mixed blessing. The interpretation of the serum Na^+ concentration for the individual patient still often remains confused and uncertain (Editorial; Lancet, 1978). In Part II (Chapter 3) of this thesis, some clear numerical directives

regarding the magnitude and significance of a fall in serum Na^+ concentration after injury will be developed, and the practical utility of this approach will be demonstrated in Chapter 4 of this thesis.

1.3 Physiology of Water and Na^+ Metabolism in the Post-operative Period.

The effects of injury on bodily functions have been recognised since ancient times. Ascribed to the presence of toxins or the consumption of tissue by starvation, wasting of the tissues and loss of body weight were regarded as being inevitable consequences of accidental or surgical injury, inflammation and fevers (Wilkinson, 1973).

Injury sets in train a complex neurohumoral series of adjustments which, if interpreted teleologically, can be seen as designed to conserve body water and electrolytes in a situation where ability to obtain these may be reduced. Thus, the events seen are identical to those which take place when intake of water and electrolytes is withdrawn, but in the case of injury they are driven by stimuli other than those involved in normal homeostasis.

Though man possesses this inherent capacity to survive the combination of injury and starvation, the biochemical basis of these metabolic disturbances in the post-traumatic period had not begun to be delineated until the early 20th Century.

1.31 Effects of injury on water balance.

It is axiomatic that water balance is achieved when the total fluid intake from ingestion and metabolic sources equals the total output in urine, faeces and insensible loss. During and after surgical injury there is a net positive balance for water. That surgical injury alters water balance and turnover was first remarked upon in 1905 by the Dublin surgeons, Pringle, Maunsell and Pringle (Pringle et al., 1905). They observed that during "full ether anaesthesia" there was a decrease in urine volume and concluded that "in cases of prolonged ether anaesthesia this inhibition of renal activity must exercise a most injurious effect on the general metabolism and condition of the patient". They also commented that this state of low urinary volume - volume down to 0.4 ml/min - seemed neither to be related to the fluid intake nor to the extent of vomiting! Many workers have subsequently documented this phenomenon of post-traumatic oliguria (Mengoli 1971) and it has since been realised that the role of the anaesthetic agent is only one of the stimuli to the sum of metabolic changes which occur after injury and that the magnitude of the response reflects the severity of the injury.

In 1925, Starling and Verney demonstrated that a circulating hormone existed which had a profound effect on the handling of water by the isolated kidney. The importance of this antidiuretic hormone (ADH), its identity, and a good deal of information concerning its mechanism of action were subsequently uncovered by

Verney in a series of animal experiments and were presented in his outstanding Croonian lectures (Verney, 1947). Verney suggested that the receptors for stimulation of ADH were within the distribution zone of the internal carotid artery and that this hormone was released in response to hyperosmolality, emotional stress, and exercise. It has since been demonstrated that an inhibition of water diuresis occurs in response to pain (Moran et al., 1964) and that haemorrhage is also a stimulus for ADH release (Share, 1967). Subsequent work has demonstrated that ADH is released from the supra-optic nuclei of the neurohypophysis and that the action of ADH on the kidney is to produce increased reabsorption of water in the collecting ducts, thereby limiting free water excretion (Bie, 1980).

The discovery of an antidiuretic hormone released in response to stress, pain, and blood loss offered an explanation for the oliguria and impairment of water excretion which follows anaesthesia and surgery. Moreover, it pointed out that altered renal function after surgery was not due to an anatomic change in the kidney but to an alteration of renal physiology. Moyer, in 1950, reviewing the possible causes of altered renal function after surgery, pointed out the dangers of giving too much water to a patient under the influence of ADH, while Zimmermann and Wangensteen in 1952, reported seventeen cases of water intoxication after extensive surgery and they reviewed the clinical setting in which it was most likely to occur. LeQuesne and Lewis (1953) in a study of the immediate post-operative

period in patients undergoing major abdominal surgery, identified a condition of "primary water retention" which became evident if fluids were administered in excess of renal excretory capacity in the first 36 post-operative hours. Close study of this phenomenon by Dudley et al. in 1954 has shown that the change in water metabolism produced by injury is almost identical with that resulting from the administration of pitressin, the posterior pituitary extract (Dudley et al., 1954). They also produced evidence that an antidiuresis occurs during and after surgery, by transfusing 5% dextrose in water to subjects and patients. Increased levels of antidiuretic activity have since been demonstrated in blood and urine during the post-injury period (Eisen and Lewis, 1954; Moran et al., 1964; Haas and Glick, 1978; Cochrane et al., 1981) and it is tempting to suggest a cause-and-effect relationship between the increased blood ADH concentration and the oliguria. Further discussions and work will be presented in Part II (Chapter 6) of this thesis that urinary concentration in the post-operative period is not that seen with maximum ADH activity and that other factors may be operative.

Apart from the profound antidiuresis that characterised water metabolism following injury, Moore and others have emphasised a second distinguishing characteristic of post-traumatic water balance that is related to the important concept of endogenous water formation (Moore, 1958, 1959; Gump et al., 1968). As injury is usually associated with a period of

starvation, a certain volume of water is produced daily from the oxidation of endogenous food components. The oxidation of 1 g of protein generates 0.41g of water, which is added to the available pool of body water. Oxidation of fat remains important in generating newly formed water, as a progressively larger proportion of the energy requirements during starvation is met by triglyceride. The oxidation of 1 kg of fat to carbon dioxide and water results in the formation of about 1000 ml of sodium-free water which is added to the body economy. In the acute phase of starvation, the oxidation of 1 g of glycogen produces 0.60 g water (Davidson et al., 1979).

In addition to "water of oxidation", intracellular water is liberated from many tissues as a result of consumption of glycogen and body protein stores. Glycogen is stored primarily in liver and muscle in a ratio of 3 g of water for each 1 g of glycogen (Drenick, 1980). With fasting, nearly 60 per cent of hepatic glycogen store is expended in the first two to three days (Hultman, 1967) releasing about 400 ml of water, whilst muscle glycogen content decreases to one-half normal within two days of starvation, releasing another 600-700 ml of glycogen-bound water to the body pool. The breakdown of protoplasmic protein releases bound intracellular water in a ratio of 3 g of water for each 1 g of protein (Drenick, 1980). Because of the antidiuresis in traumatised subjects, these contributions of endogenous water of oxidation and bound intracellular water to total body water may be

retained in the immediate post-injury period (Moore, 1959). In Part III of this thesis the dynamics of water that is obligated to glycogen storage will be developed and evidence is presented that suggests that mobilisation of glycogen obligated water in the post-traumatic state may be an important contributing factor to dilutional hyponatraemia as its excretion is opposed by antidiuresis.

1.32 Effects of injury on urinary Na^+ excretion

The observation by Pringle et al. (1905) that urinary volume is decreased following injury has already been remarked upon in Section 1.31. Further examination of their data reveals a decrease in post-operative solute output in addition to the oliguria - the volume obligatoire that is necessary to excrete the solute load at the highest attainable concentration.

Somewhat later, others have noted a decreased urinary output of Na^+ and that saline was not handled normally following surgery (Evans, 1911; Trout, 1913; Jones and Eaton, 1933) and it has since been well documented that major surgery is almost always accompanied by Na^+ conservation (Moyer, 1950; LeQuesne and Lewis, 1953; Cochrane, 1978), the duration and degree of such retention being related to the severity of the injury.

A series of complex and incompletely understood neurohumoral and haemodynamic factors govern the excretion of Na^+ following injury. Although several components of this interplay of factors

are recognised, the relative importance of each is controversial.

In the 1950s, evidence in support of the role of adrenal steroids in causing Na^+ conservation came to the fore. It has been demonstrated that there is a wave of increased adrenocortical hormones after injury, blood levels of which may double for 24 hours (Moore et al., 1955; Casey et al., 1957). The isolation of aldosterone by Simpson et al. (1952) gave new impetus to the study of the relationship between adrenal steroids and post-operative Na^+ conservation. Adrenocorticotrophic hormone (ACTH) is released by the anterior pituitary during major surgery and blood levels remain elevated during the immediate post-operative period (Cooper and Nelson, 1962). While ACTH is important in both long- and short-term control, it is unlikely to be a specific stimulant to aldosterone but rather a general stimulant of corticosteroid secretion (Fraser et al., 1979). Furthermore, Hume et al. (1962) by direct measurement of adrenal secretion have demonstrated that operative aldosterone secretion is not dependent upon ACTH release. Subsequently, the elucidation of the renin-angiotensin-aldosterone system has provided further understanding of the renal control of Na^+ excretion and that aldosterone secretion is predominantly influenced by angiotensin II (Laragh and Sealey, 1973).

The tenfold increase in the secretion of aldosterone concurrently with the observed reduction in the urinary Na^+:K^+ ratios has been taken to imply that aldosterone release accounts for the Na^+ retention (Casey et al., 1957). That there is an

aldosterone response to injury is not disputed (Engquist et al., 1978; Cochrane, 1978); however, that aldosterone is the prime cause of Na^+ retention following injury remains an area of some dispute.

It is known that adrenalectomised subjects maintained with basal cortisone supplements only still retain Na^+ after surgery (Mason, 1955; Robson et al., 1955; Dudley et al, 1957) and that infants whose aldosterone production is impaired tend to reabsorb nearly all the Na^+ filtered at the glomerulus (Aperia et al., 1972). The time course of aldosterone secretion and Na^+ retention suggests that aldosterone secretion alone cannot be responsible for Na^+retention. The high cumulative balance of Na^+, which is prolonged, must be caused by factors other than the seven-and-a-half-hour rise in plasma aldosterone in the post-operative period (Cochrane, 1978). It may be that aldosterone is responsible for Na^+ conservation after injury but that in its absence other mechanisms take over this role.

It has been suggested that Na^+ conservation following injury may represent a response to a need for extra Na^+ to fill a fluid volume deficit and that the elevated aldosterone levels may be due to the same cause as the renal retention of Na^+, that is, decreased effective ECF volume. Thus, aldosterone levels are not elevated to the same degree in patients undergoing surgery given a 'high' Na^+ intake compared to those given a 'low' Na^+ intake (Hayes et al., 1957; Shires and Jackson, 1962;

Engquist et al., 1978; Cochrane, 1978). In 1961, Shires and his colleagues showed that major surgery was associated with an apparent fall in the 'functional' ECF (Shires et al., 1961). As a consequence, both mineralocorticoid and ADH secretion would be increased and this could then account for the oliguria and Na^+ retention associated with injury. That ECF is sequestered during major surgery is conceptually attractive because the post-operative patient in some respects resembles the Na^+-depleted normal subject with elevated levels of aldosterone, renin and ADH (Swales, 1975). This concept has exercised a significant influence on replacement therapy in the past 15 years and this will be mentioned again in Section 1.4 of this thesis when intravenous water and electrolyte therapy is discussed. However, it should be pointed out that more rigorous measurement of the presumed ECF deficits has not revealed them to exist to anything like the degree already postulated (Roth et al., 1967, 1969) and that when inulin was used for measurement of ECF volume, Randall and Papper (1958) failed to demonstrate a deficit in patients undergoing major surgery. Discrepancies appeared concerning the validity of the $^{35}SO_4$ space in shock situations due to changes in the shape and equilibration time induced by the unsteady state. There is no doubt that fluid sequestration can occur and major surgery or extensive trauma produces large areas of damaged tissue into which ECF leaks; this anatomical aspect of 'third space fluid sequestration' will be presented in further work developed in Part IV (Chapter 9) of this thesis.

It is clear that neither mineralocorticoid secretion nor ECF sequestration can adequately account for the peri-operative Na^+ excretion. The hypothesis that changes in renal haemodynamics may be responsible for changes in Na^+ excretion following injury has recently been emphasised (Bevan et al., 1973; Bevan, 1979). Studies in salt-restricted and salt-loaded subjects demonstrated that Na^+ retention is associated with a decrease in cortical blood flow and an increase in juxtamedullary flow and that saline loading reverses the redistribution and produces a natriuresis (Hollenberg et al., 1970). In a recent review, however, data from a large number of studies employing the radiolabelled microsphere method of determining blood flow found no correlation between the changes in renal blood flow distribution and urinary Na^+ excretion, and it must be concluded, at present, that clear-cut evidence is lacking for re-distribution of blood flow being a major determinant of Na^+ excretion (Lameire et al., 1977).

The kidney has an abundant sympathetic nerve supply with noradrenaline as the principal neurotransmitter and it is known that noradrenergic nerves are vasoconstrictive and Na^+ retaining (Silverberg et al., 1978). Though it has been proposed that sympathetic stimulation by surgery may be an important factor in Na^+ conservation, paralysis of the renal sympathetic nerves by continuous epidural blockade does not consistently prevent post-operative Na^+ retention (Bevan, 1971; Gow and Cochrane, 1979).

Furthermore, the interaction between noradrenergic nerves and the recently discovered dopaminergic nerves in the kidney - which may cause vasodilation, diuresis and Na^+ loss - remains undefined in the post-injury period (Gunn et al., 1981).

Apart from angiotensin II from renin release, various investigators have sought to define a role for other vasoactive hormones in the control of Na^+ excretion. Renal cortical extracts contain kallikrein, a kininogenase that releases the vasodilator bradykinin from an alpha-globulin plasma substrate. Urinary kininogenase activity is reduced during and immediately after major surgery and returns to normal or elevated levels by the second or third post-operative day, a time that marks the termination of post-operative Na^+ retention (Ofstad and Nustad, 1969). Prostaglandins, mainly E_2, F_2 and D_2, have been isolated from the renal medulla and they have been demonstrated to have natriuretic activity (Dunn and Hood, 1977), although reports of the effect of surgery on prostaglandin release and renal Na^+ balance are lacking.

From the foregoing discussion, it is clear that a wide range of physical and biochemical factors influence tubular absorption of Na^+. The greatest uncertainty in the analysis of these factors exists in deciding which factors control Na^+ excretion in normal circumstances, as distinct from those which can be shown to change Na^+ excretion experimentally. In this regard, mention may be made of the well-known cross-circulation experiments of De Wardener et al. (1961) that have led to a continuing search for

a 'third factor' or 'natriuretic hormone' in the regulation of tubular Na^+ re-absorption. Evidence for the existence and isolation of 'natriuretic hormone' is suggestive but by no means conclusive, although there are several pointers that it may originate in the brain (De Wardener and Hugh, 1978). Finally, the existence of volume receptors controlling Na^+ excretion has also been postulated (Smith, 1957), and moreover it has been suggested that juxtaventricular Na^+-sensitive receptors play an important role in the control of body fluid homeostasis, the receptor system being predominantly determined by the composition of the cerebrospinal fluid (Anderson, 1977).

1.33 Disturbances of the extracellular compartment in relation to Na^+ and water metabolism following injury.

It is now just over 100 years since Claude Bernard (1865) first drew attention to the importance of a stable and constant composition of the ECF compartment. Though the maintenance of normal body function is dependent upon the interplay of many systems - neurological, cardio-respiratory and renal, to name but three - central to all is the fluid and electrolyte medium in which all cells are bathed and which constitutes the body's transport system. The control of the volume of this system within relatively narrow limits constitutes the 'fixity of the internal environment' ('milieu intérieur') which Bernard rightly regarded

as the essential 'condition of a free (that is, independent) life'. Homeostasis is the term applied to systems regulation as a whole in the body, and has particular relevance to body fluids.

1.331 Normal body composition.

Anatomical and other studies show that, broadly speaking, two sub-volumes of body water can be defined - intracellular fluid (ICF) and extracellular fluid (ECF) - separated by the cell membrane, which is freely permeable to water (Fig. 1.1). In addition to these compartments, a certain amount of water is always present in body cavities - gastrointestinal tract, cerebrospinal fluid, aqueous humor; such water has been processed through cells to reach these sites and is thus appropriately known as the transcellular fluid (TCF). The ECF is sub-divided into two segments, the plasma and the interstitial fluid, with an approximate volume ratio of 1:3. The volumes of these several compartments may be estimated with the use of agents that distribute themselves uniformly throughout a particular compartment (Edelman et al., 1952; Edelman and Leibman, 1959). In this fashion, one can estimate the total volume of body water (TBW), the ECF, and the plasma volume. The volume of ICF cannot be estimated directly, but can be calculated as the difference between TBW and the volume of ECF.

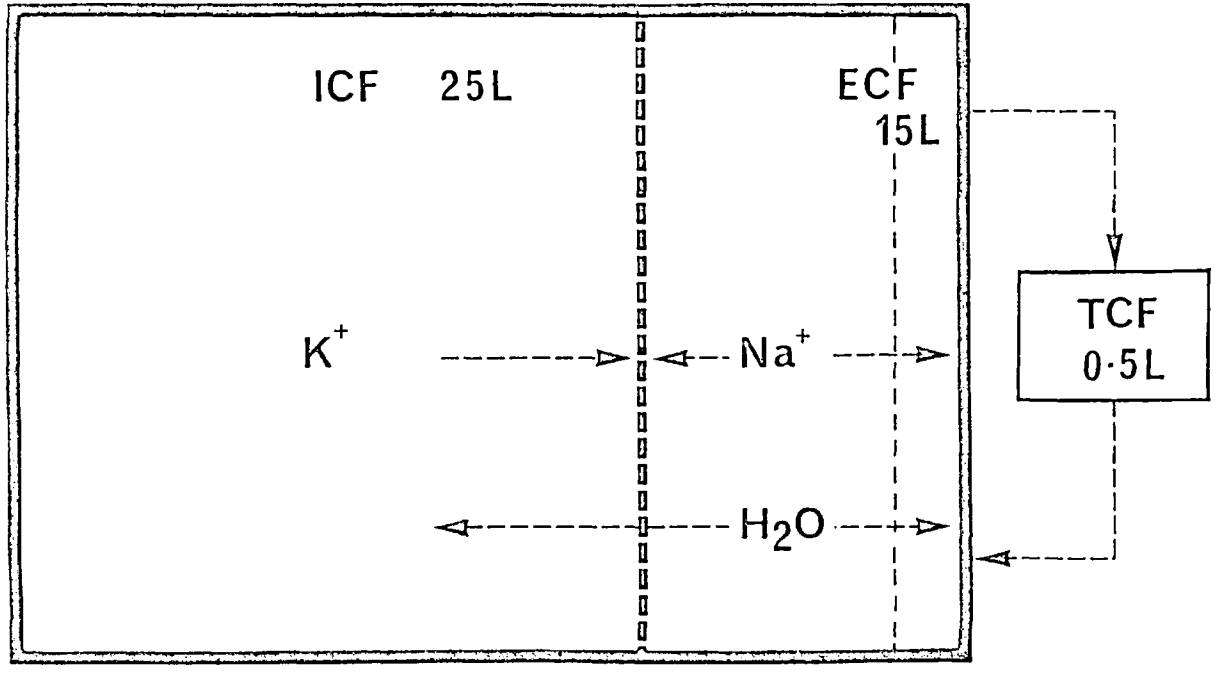


Figure 1.1

Normal Body Fluid Compartments

(Adapted from H A F Dudley: An Aid to Clinical Surgery, Churchill Livingstone, 1979)

With some exceptions, namely, secretory glands and the distal nephrons, osmotic equilibrium is maintained across the cell membrane. Electroneutrality between anions and cations is present in the ECF and the ICF but there may be an electrochemical gradient across membranes.

Na^+ is the principal cation in the ECF, and chloride (Cl^-) and bicarbonate (HCO_3^-) are the major anions. In the ICF, potassium (K^+) is the main cation and phosphate and ionised protein are the most abundant anions.

Because the ECF is about 15 litres in a healthy adult and the normal Na^+ concentration 140 mmol/l, 2000-2100 mmol of Na^+ are found in the ECF. In the ICF, Na^+ is only 10 mmol/l (Gamble, 1942) but because there are 25 litres of intracellular water, there are a further 250 mmol of Na^+ in the cell. Finally, there is some Na^+ in bone (circa 450 mmol) which is less freely exchangeable. Thus the body contains about 40 mmol of Na^+/kg body weight, or 2800 mmol in a 70 kg adult (Moore et al., 1963). Na^+ intake by the salt-eating western population ordinarily ranges between 100 and 250 mmol/day (Beevers et al., 1980) and a similar amount is excreted, chiefly in the urine. The body can adapt to a wide range of intakes by adjusting kidney excretion (Strauss et al., 1958). Of all the substances handled by the kidney, Na^+ is one that is most zealously preserved. Thus, in normal circumstances, if intake falls to zero renal output will not exceed 5 mmol/day (see Part III,

Chapter 7). Conversely, if intake is increased, output rises to equate with this. Up to 300 mmol/day can be ingested and excreted in normal people without short term ill effects, but at that level of intake, ECF volume is larger by about 10 per cent.

Total body potassium (K_e) is about 47 mmol/kg weight in the adult male (or 3200 mmol in a 70 kg man) and, because of a smaller muscle mass, about 40 mmol/kg in the adult female (Moore et al., 1963). Ninety-eight per cent of body K^+ is located in the cells, where its concentration is 150 mmol/l. The total amount of K^+ in ECF is only 60 mmol and the concentration is about 4-5 mmol/l. Serum, or ECF-K^+ concentration, which is commonly measured in clinical practice, does not have a necessary or direct relationship to total body potassium. Daily K^+ intake ordinarily amounts to about 100 mmol and output is identical. Some K^+ is excreted in faeces (5 mmol/day) but the greatest amount is excreted in the urine (95 mmol/day). Whenever cells are injured, K^+ is released into the ECF. In cell death, K^+ and nitrogen are released in a ratio of 3 mmol/g (Moore et al., 1963).

The composition of the body can be studied by the use of isotopes and by calculation of what is referred to as the total exchangeable quantity of a given ion, such as that of Na^+ (Na_e) or K^+ (K_e). Some of the most extensive data have been collected by Moore and his associates (1963) and in Part II, Chapter 3, of this thesis, these measurements of isotope

dilution will be presented in relation to the studies on post-operative hyponatraemia. Measurement of the electrolyte composition of the body in clinical medicine is, of necessity, confined to determinations of ion concentrations in ECF and, more specifically, to plasma or serum analyses. The concentration of the filterable ions in the interstitial compartment of ECF can be calculated from the values in serum with a correction for serum water (SW) and the Donnan ratio, which describes the relative concentrations in serum and its ultra-filtrates (Mudge and Welt, 1975). This ratio is 0.95 for cations and 1.05 for anions. Thus:

$$Na_{IF} = \frac{Na_S}{SW} \times 0.95$$

where the subscripts IF and S refer to interstitial fluid and serum, respectively. Normal laboratory determinations report the concentration/litre of serum. In the vast majority of circumstances, this matters very little since the water content of serum (92%) is reasonably constant within the population and normally varies only to a negligible extent. Since the composition of the interstitial fluid is only slightly but predictably different from that of plasma, for many purposes the plasma and interstitial fluids may be considered together as ECF, and the serum electrolyte concentrations may be used as an estimate of those for the entire compartment.

1.332 Body fluid tonicity.

It has already been stated that the cell membrane maintains certain ionic gradients while being freely permeable to water between ECF and ICF; that is, it behaves as a semi-permeable membrane. When a solution is separated from a quantity of a pure solvent by a membrane which is permeable to the solvent and not to the solute, then the solvent tends to be drawn through the membrane into the solution so as to dilute it. Movement of solvent can be prevented by applying a certain hydrostatic pressure to the solution. This pressure is called the osmotic pressure.

The osmolality of a solution is the osmotic pressure per unit of solvent. The total osmolality of all body fluids under normal conditions is believed to be the same. One of the major functions of the kidney is to maintain the constant osmolality of all body fluids (Peters, 1944). Thus, the total particle concentration of ICF and ECF is the same, although large concentration differences exist across cell membranes for individual ions. In most tissues, no gradient exists for water. With few exceptions, including the renal medulla, the body does not tolerate osmotic gradients.

The osmolality of ECF is almost entirely the result of its electrolyte content and is normally 285-295 mOsm/kg, giving an osmotic pressure of about 7.6 atmospheres (Moore et al., 1963). Presumably, the osmolality of ICF is identical. In plasma,

electrolyte accounts for 98% of the osmolality, and the most abundant ion, Na^+, is responsible for 50% of the osmotic pressure. In fact, in normal circumstances, plasma or serum osmolality (in mOsm/kg) coincidentally amounts to a number that is twice the serum Na^+ concentration (in mmol/l). Similarly, the K^+ ion is the most important determination of cell osmolality. Osmolality may be determined with an osmometer, which measures one of the colligative properties of a solution (Bevan, 1978). Knowledge of the osmotic concentration indicates whether a solution is hypo-, iso-, or hypertonic. Serum and urine osmometry will be presented in the work in Part II of this thesis in relation to surgical injury.

Colloid osmotic pressure is that small fraction of total plasma osmolality produced by colloids such as the plasma proteins. It accounts for only 1% of total plasma osmolality or 2-3 mOsm/kg. Because capillaries are permeable to water and crystalloids, but are impermeable to colloids, the colloid osmotic pressure is an important influence on the movement of water and electrolytes across the capillary wall.

1.333 Cellular mechanisms of electrolyte control - the Na^+ pump.

Much of the metabolic energy consumed by cells is used to establish high intracellular concentrations of K^+ and low concentrations of Na^+, the reverse of the relative

concentrations of these ions in the ECF (Sweadner and Goldin, 1980). The extrusion of Na^+ requires its movement against a gradient of concentration (higher outside than inside) and electrical potential (inside about 70 mV more negative than outside); work is therefore needed to overcome this electrochemical gradient. An important component of this transmembrane pumping of Na^+ and K^+ was isolated by Skou (1957) when he discovered adenosine triphosphatase (ATPase) activity, which was activated by the addition of Na^+ and K^+ to the assay medium. There is now overwhelming evidence that this Na-K-activated ATPase is a component of the cellular pump (Glynn, 1968).

These ionic transport mechanisms are responsible for the regulation of cell volume (Pollock and Arieff, 1980); because the cells contain proteins that exert a colloidal osmotic pressure, the cell volume would expand and the cell ultimately disrupt, were it not for the mechanism of active transport that maintains the total quantity and quality of the ions fairly constant. In addition, these mechanisms of transport serve to establish and maintain the electrical potential gradients across the cell membrane that are essential for the generation and propagation of action potentials in excitable cells.

The possibility of the decline in Na^+ concentration gradient and in flux across cell membrane has been proposed as an explanation for post-traumatic hyponatraemia (Flear, 1970;

Flear and Singh, 1973). In Part II, Chapter 5, of this thesis, direct measurement of Na^+ flux in erythrocytes and intracellular Na^+ will be presented to test this hypothesis in relation to surgical injury.

1.334 Extracellular hypotonicity following surgical injury.

As already described in sections 1.31 and 1.32, the characteristic, unmodified response to surgery by the kidney is a reduction in the excretion of Na^+ and water, the magnitude and duration of which are proportional to the severity of the operation. It has also long been recognised that for some days after surgical operations the serum Na^+ concentration tends to be low, even without loss to the body of the Na^+ ion (Coller et al., 1938; Ariel et al., 1943; Moore and Ball, 1952; Wynn and Rob, 1954; Zimmermann et al., 1956). So common is this biochemical finding, that it has become accepted as part of the normal metabolic response to trauma. The serum Na^+ concentration is usually lowest on the first and second days after operation; the effect persists for several days, and sometimes even longer. Serum hypotonicity, or hyponatraemia as it is sometimes called, is usually greatest and most prolonged with extensive operations (Wilson et al., 1954; Goodyer and Glenn, 1955). Coincidental with these serum changes, total body Na^+ is usually increasing (unless there is extra-renal loss of Na^+) because of the low renal excretion of this ion. This

apparent metabolic anomaly of a falling serum Na^+ concentration with total excess of Na^+ in the body has been termed by Moore and Ball (1952) the 'sodium paradox'. Usually, the serum hypotonicity which follows trauma is of moderate extent and symptomless, but severe hypotonicity may follow and produce serious symptoms (Wynn and Rob, 1954).

During the 1950s, the cause of this serum or ECF hypotonicity after trauma, when Na^+ is being retained, was extensively investigated, but with conflicting results. It was suggested that water may be retained in osmotic excess of electrolytes, thus diluting the body fluids (Deming and Gerbode, 1953; Wynn and Rob, 1954). According to Zimmermann et al. (1956), water retention alone is inadequate to account for the apparent disappearance of Na^+. Others have suggested that serum hypotonicity after operation is caused, partly at least, by the movement of Na^+ into a site where it becomes 'osmotically inactive' -in cells, in connective tissue, in bone, or within the gut (Dudley et al., 1954; Wilson et al., 1954). Allied to this theory is the possibility inferred by Elkinton et al. (1947) that in some unexplained way, the osmotic activity of the cell-solutes is lowered without water passing into or solutes passing out of the cells - 'the osmotic inactivation of cell base'. A further theory was advanced that serum hypotonicity following trauma is due to the movement of cell-water in excess of cell-solutes to the

ECF, the osmolality of this fluid therefore falling, while that of the cell rises (DeCosse et al., 1956). Unequal osmolality inside and outside cells was also implied by Graber et al. (1956), who claimed that steroids administered in severe hypotonicity after operation caused the movement of hypotonic fluid into the cells. More recently, Flear (1970) has adduced evidence that the primary disturbance following trauma is at the cell membrane with imbalances in exchanges of water and electrolytes leading to net gains of Na^+ and CI^- and water and loss of K^+ together with the escape of non-diffusible solutes from cells.

According to the classical views, usually attributed to Gamble et al. (1923), there is osmotic equality between the cells and the ECF, and a change in the osmolality on either side of the cell membrane is followed by a redistribution of water, or solutes, or both, until equilibrium is re-established. Except in circumstances when there are excessive amounts of glucose in the serum, the effective osmolality of the body fluids (upon which the distribution of water across cell membrane depends) is measured, as a close approximation, by the total electrolyte concentration of the body fluids (Leaf et al., 1954). The external balance of the osmotically active electrolyte, mainly the salts of Na^+ and K^+, measures the change in the total amount of such solutes in the body. Osmotic gradients can therefore be depicted with reasonable accuracy by using the total cation concentration of the ECF to measure the effective osmolality of

this fluid, and the external cation (Na^+ plus K^+) balance to measure changes in the osmotically active solute content of the body.

Independent clinical investigations (Wynn and Houghton, 1957; Wynn, 1957; Edelman et al., 1958) have been carried out which strongly support the idea that the osmotic pressure of the cellular fluid and ECF are equal and, with the possible exception of "osmoreceptors" which are sensitive to changes in their own volume (Verney, 1947; Jewell and Verney 1957), cells behave passively like perfect osmometers, adapting their volume to the osmolality of their surroundings (Pollock and Arieff, 1980). This behaviour is unaffected by disease and, in particular, surgical injury does not cause body fluids to be distributed in any unusual way as had been suggested by many previous investigators (Wynn and Houghton, 1957). These findings strongly suggest that water retention is the major cause of serum or ECF hypotonicity following surgical injury, that is, dilutional hypotonicity. In Part II of this thesis, evidence is presented for dilutional changes after surgical operations and demonstrates that these changes are much more prolonged than was at first thought.

1.4 Development of the Technique of Intravenous Water and Electrolyte Therapy.

The administration of fluids intravenously is one of the commonest therapeutic techniques used in medicine today - more than ten million such administrations are made every year in Britain (Wildsmith, 1980). Although one of the cornerstones of modern surgical practice, the proper management of parenteral water and electrolytes after injury remains a controversial problem, despite the contributions of numerous studies during the past 50 years. The question of which regimen of therapy is best is obscured by the remarkable tolerance of the body to extremes of fluid and electrolyte replacement and by the difficulty in assessing the true state of the intracellular and extracellular compartments.

In order to put the present position into better perspective, a brief review of the history of fluid and electrolyte therapy in surgical patients will be discussed.

As indicated in Section 1.2 of this historical review, W. B. O'Shaughnessy (1831) in a letter to 'The Lancet' first gave serious consideration to water and electrolyte imbalance when he described deficits of water, saline and alkali in the blood of cholera victims. O'Shaughnessy suggested intravenous replacement of those deficits with a saline solution, but Thomas Latta (1832), a practitioner in Scotland, was the first to carry out this method of therapy "having inserted a tube into the basilic vein,

cautiously". Latta, together with two of his fellow practitioners in Leith - Drs. Craigie and Lewins - reported fifteen patients treated in this fashion, with five survivals (Lewins, 1832).

For the treatment of haemorrhage, the first recorded use of saline solutions appeared in 'The Lancet' in 1891 and was described by a prominent British surgeon of the day, W. Arbuthnot Lane. Lane had written a eulogy for his recently deceased friend, Dr. Woolridge, who shortly before his death had performed haemorrhage experiments in a dog (Lane, 1891). In the final paragraph of that report, Lane describes the first recorded use of electrolyte solution for the treatment of haemorrhagic shock in man.

The introduction of a radical new treatment to counter a cause of death which had not previously been appreciated was greeted with suspicion, and intravenous fluid therapy did not gain acceptance at that time and was put aside for another 100 years. During that period many futile efforts were directed towards identifying a toxic substance that could explain the 'shock syndrome' following injury and haemorrhage (Moss, 1972).

The origin of intravenous therapy in the post-operative period is difficult to pin-point, but by the early 1900s proctoclysis was occasionally used to support patients who were unable to take fluids by mouth (Gibbon, 1907), although its importance had not yet been fully realised. The details of

proctoclysis, including the design of nozzles to fit in the anal canal, the height of the enema can, and the volume and nature of the enema fluid were discussed in detail by J. B. Murphy in 1908. Hypodermoclysis had also been described by this time and there were sporadic reports of intravenous fluid therapy. However, the theory behind fluid support after surgery was very rudimentary and the benefits ascribed to a dilutional effect on circulatory toxins (Murphy, 1908).

The next milestone in the introduction of intravenous fluid therapy and its routine use as a clinical tool was that of the work of Rudolph Matas, who pointed out clearly the shortcomings of proctoclysis and hypodermoclysis as the prevalent methods of fluid administration (Matas, 1924). He then described in detail his technique of the continuous administration of fluid through a glass cannula into the basilic vein and administered 4-5 litres of fluid per 24 hours, preferring a 5% glucose solution. He advised the prophylactic use of "the intravenous drip in the very feeble, ill-nourished patients whose ability to survive an operation is doubtful". In these cases the "intravenous drip is started with the operation and is continued guttatim (drop by drop), during and after the operation, as long as doubt exists as to the efficiency of the circulation". A year before Matas presented his paper to the American Surgical Association, Penfield and Teplitsky (1923) had advised the intermittent infusions of 800-1500 ml/h of normal saline or 5% glucose in water during a two- to four-hour period

and stressed the importance of measuring the venous pressure as an objective parameter of fluid replacement.

During the next two decades the intravenous drip was slowly accepted into medical practice, and currently a variety of commercially-available solutions have been designed to repair the average deficits that one might anticipate in most clinical situations.

1.41 The concept of fluid deficit.

Although the similarities between such conditions as intestinal obstruction, peritonitis and pancreatitis had been noted at the turn of the century, according to the thinking of the time they were believed to be linked by a common circulating toxin (Whipple, 1916). That fluids were needed to replace existing and developing deficits in ICF and ECF volumes was not realised, and the beneficial effects of intravenous fluids were ascribed to "diluting or washing out of blood toxins".

The origins of rational fluid therapy in surgical patients began with the work of Hartwell and Houget in 1912, which related death in intestinal obstruction to severe fluid deficits. They studied the cause of death in dogs with intestinal obstruction without strangulation and realised that the fluid loss was in terms of litres, not millilitres, and they were able to prolong life for several weeks by the subcutaneous administration of large

quantities of physiological saline solution. MacCallum et al. (1920) confirmed the concept that fluid deficits can occur and can be responsible for morbidity and mortality. Using dogs with surgically-produced pyloric obstruction as a model, they demonstrated a fall in serum Cl^- and a rise in carbon dioxide combining power in these animals, and reported increased survivals after the administration of sodium chloride. As mentioned previously, during that period the Cl^- ion was measured with relative ease compared to the Na^+ ion. Gamble and Ross (1924), in their studies of pyloric obstruction, measured Na^+ and Cl^- in the ionic form and stressed the importance of Na^+ in repairing the fluid deficit. In subsequent articles, Gamble (1929) attacked the toxaemia theory as it had been applied to mortality from infants with diarrhoea. He presented the electrolyte content of gastric, biliary and intestinal juices, and pointed out that their loss in diarrhoea must be replaced with physiological saline solution. Fluid deficit, not intestinal toxins, was the killer in this condition also. Commenting on the role of saline in maintaining the volume of the ECF, Gamble wrote: "For the maintenance of extracellular fluid only three materials are directly required: water, sodium and chloride ion ..... these considerations also enable us to understand the remarkable efficiency of an extremely simple therapeutic agent, physiologic salt solution, for repair of defects in the volume and structure of extracellular fluid". Further emphasis on the importance of

volume replacement (and the final demise of the toxaemia theory) was placed by Alfred Blalock in 1943 in an article entitled "The Present Status of the Shock Problem" in which Blalock stated: "Since the major single cause of shock seems to be a decrease in the volume of the circulatory blood, treatment is based on checking such loss and replacing body fluids by the best means at hand".

1.42 Water versus saline.

With the realisation that certain surgical conditions were accompanied by fluid deficits and that replacement of these deficits enhanced patient survival, the importance of fluid therapy in the post-operative period became fully appreciated. However, there was controversy as to the nature of the fluid which should be given in the post-operative period. Trout (1913) in an extensive clinical investigation of this problem involving over 2000 post-operative patients believed that salt solution aggravated "post-operative nephritis". Rudolph Matas (1924) believed that physiologic saline solution was suitable for "emergencies and temporary purposes", but preferred 5% glucose solution in these circumstances, and especially when long-term administration was necessary. This reliance on dextrose and water in the post-operative period was strengthened by Coller and Maddock (1932) when they presented a careful balance study in 18 patients during surgery and in the first four post-operative

hours. These investigators noted that the insensible loss of water during this brief period could amount to one litre, and during a 24-hour period, as much as two litres could be lost by this route. Since this mechanism of fluid loss involved very little salt loss they recommended replacement with dextrose and water. As noted earlier in Section 1.2 of the historical review, this concept of insensible loss of water had already been emphasised by Sanctorius as early as 1614, which he referred to as "perspiratio insensibilis". Rowntree (1922) had reviewed the water balance of the body and mentioned studies performed in the late 1800s and early 1900s which accurately documented the volume of water lost daily by insensible means. Coller and Maddock (1935), however, were the first to emphasise the importance of these losses in the post-operative period and advise replacement on a measured scientific basis. They went on to outline a programme for fluid therapy which leaned heavily on water rather than on salt administration.

In 1936, Coller, Dick and Maddock reported the results of a clinical trial in which three small groups of post-operative patients were treated with normal saline solution, Ringer's lactate solution, or 5% dextrose in water. They found that the patients receiving salt solutions retained fluid and the glucose and water group did not, and re-stated their reluctance to use saline solution in the post-operative period. Later on, however, they advised replacement of gastrointestinal losses, millilitre

for millilitre, with normal saline solution and formulated a "clinical rule" for replacing salt based on the serum level of Cl^- but realised subsequently that the Cl^- level is not important in maintaining the ECF volume and does not maintain a fixed relationship to the Na^+ concentration (Coller et al., 1944). Coller's subsequent policy of fluid and electrolyte therapy in the post-operative period emphasised salt restriction and became the standard practice for the next two decades.

1.43 What is the most appropriate regimen of fluid and electrolyte therapy?

As noted in Section 1.3 of this thesis, the early 1950s was a period of inquiry into the physiology of Na^+ and water metabolism in the post-operative phase. Reviewing the possible causes of altered renal function after surgery, Moyer (1950) discussed blood loss, water deprivation, Na^+ deficit, hypotension, and the anaesthetic agent itself. He dismissed these as the primary mechanism of oliguria which characterised the post-operative patient and considered a functional Na^+ loss resulting from sequestration of Na^+ in the operative site, but discarded this mechanism as he had observed that "the provision of large amounts of Na^+ with and without an excess of water does not change the picture appreciably". He did, however, conclude that fluid was being lost to the circulation without being lost to the body by internal redistribution, and emphasised the part played

by pain in the production of post-operative oliguria.

The prevailing emphasis on salt restriction after surgery was thought by some to be excessive, and the recommendations during this period reflect an awareness of the dangers of giving too much glucose in water to a patient under the influence of ADH (Zimmermann and Wangensteen, 1952; Drucker et al., 1953).

Measurements of the ECF volume had been made by several investigators in the 1930s and 1940s, but in the late 1950s the ECF volume came more clearly into focus in the body's handling of Na^+ and water. Strauss and Smith (1957) independently reviewed the literature relating ECF volume to Na^+ and water metabolism (Strauss, 1957; Smith, 1957). Their work and that of many other investigators (Bartter et al., 1956) suggested that isotonic contraction or expansion of the ECF volume affected the release of ADH and aldosterone resulting in profound changes in urinary excretion of water and Na^+.

Measurements with thiocyanate as a marker had initially suggested that the total ECF volume expanded after surgery (Lyon et al., 1949) but Randall and Papper (1958) emphasised the importance of the shrinkage of the "effective" ECF volume. Strong support for the latter conclusions was provided by Shires and his colleagues (1961). Using radioisotopes to measure red cell mass, plasma volume and "functional" ECF volume, they demonstrated reductions in the "functional" ECF as great as 28 per cent during uncomplicated major surgery. This work and subsequent studies by

Shires suggested that if appropriate amounts of electrolyte and water were provided during surgery, the "functional" ECF volume, that is, the physiologically active extracellular space as measured by $^{35}SO_4$, could be maintained and post-operative oliguria avoided (Shires, 1967). It has since been shown, however, that in these circumstances isotope dilution techniques are misleading, since the time taken for markers to equilibrate is prolonged in the post-operative period. When time is allowed for markers to equilibrate fully, their volume of distribution is normal or greater than normal (Roth et al.,1969), though the reason for this delayed equilibration remains to be explained.

Since the work of Shires et al., the severe restriction of fluid and salt in the post-operative period characteristic of the 1950s has been virtually abandoned. The extent of this reversal has been illustrated by a random sample of 50 patients selected by the impartial judgement of the digital computer from all those who had cholecystectomies at the University of California (Los Angeles Hospital) between 1963 and 1967 (Roth et al., 1969). During these years there was an average twofold increase in the volume of intra-operative infusions, and a fivefold increase in the amount of Na^+ given, so that some patients received what would formerly have been regarded as a week's supply of Na^+ during an operation of two or three hours.

Fluid and electrolyte regimens were worked out suggesting certain volumes should be given by the clock, or matched to

specific amounts of blood loss and replacement. Massive infusions of electrolyte and water do increase urine flow and Na^+ excretion over the operative period, and may thus protect the kidney against the evils of low-flow states and circulating nephrotoxins (if these, in fact, ever exist). However, balance studies show that this is only achieved at the cost of fluid overload which persists for several days (Irvin et al., 1972; Cochrane, 1978; Tindall and Clark, 1981). Approximately one-third of this extra fluid is excreted in the urine. More rigorous measurement of the presumed deficits in ECF volume has not revealed them to exist to anything like the degree postulated by Shires (Roth et al., 1969), nor has there been any objective evidence that massive infusion of ECF-type liquids does any good (Editorial: Lancet, 1969; Pluth et al., 1967). Furthermore, water balance will build up as attempts are made to maintain urine output constant in the face of the changes in circulating antidiuretic hormone that accompany injury and blood loss (Moran and Zimmermann, 1967) and especially in the elderly, frail, and those with cardio-pulmonary diseases, pulmonary oedema can be precipitated with some ease. It may well be that a steady drip into the urine bag does more to reassure the surgical team than to preserve the patient's renal function.

In 1967, Moore and Shires, in an editorial, cautioned 'moderation' in the replacement of fluid and electrolytes

(Editorial: Ann. Surg., 1967) and currently it seems that the exaggerated amounts of fluid and electrolyte given in the early years post-Shires have now tapered, but to a level still well above that of the post-Coller days. In Part II, Chapter 3, of this thesis, work will be presented in support of the further recession of the high tide of salt water following surgery, while in Part IV, Chapter 9, the effects of water and Na^+ infusion on the water content of intestinal anastomoses will be demonstrated.

1.5 Development of Parenteral Feeding Therapy.

Intravenous feeding therapy has a long history, reflecting that of many branches of medicine. After Harvey discovered the circulation of the blood in 1628, it became logical to believe that food reached many of the body tissues through the blood vessels. The first recorded account of parenteral feeding is the short experiment of Sir Christopher Wren in 1656 in which he injected liquors into the veins of animals (Wren, 1656). Dr. Richard Lower, in 1665, successfully transfused a dog with blood from another living dog, and Lower and King, in 1667, transfused arterial blood of a young sheep into a human arm vein (Cuthbertson, 1979).

Probably the first intravenous administration of fat was that of William Courten (1710-12), who reported the effect on the dog of an infusion of olive oil, but with discouraging results. During this period, sporadic experiments at intravenous feeding continued when knowledge of chemistry, microbiology, blood groups and immunology were only fragmentary. Subsequently the work of Pasteur (1822-1895) who gave us knowledge of microbiology, that of Lister (1827-1912) who demonstrated so convincingly the value of antiseptics in the conduct of surgery, and the myriad contributions that marked the rapid development of biochemistry, all contributed to the development of intravenous nutrition as we

now know it (Rhoads, 1975).

Friedrich (1904) was probably the first investigator who purposefully carried out complete parenteral feeding therapy when he administered peptone solution, fat, glucose and salt simultaneously via the intravenous route. In 1913, Henriques and Andersen of Denmark demonstrated that nitrogen equilibrium could be maintained in animals with intravenous amino acids, the product of an enzymic hydrolysis, as the sole intake of nitrogen. Robert Elman (1937-38) was able to bring adult dogs fed with sucrose into nitrogen equilibrium when injected with a 'complete mixture of amino acids combined with glucose'. The observations of Cuthbertson (1932) in his studies of long bone fractures have identified a state of post-traumatic tissue catabolism. It became evident that the metabolic response to injury involved the breakdown of tissue and the urinary excretion of intracellular constituents, particularly nitrogen, K^+, phosphorus and sulphur. A negative nitrogen balance became the major feature of what Cuthbertson calls the 'flow' or catabolic phase, as opposed to the 'ebb' or shock phase of injury.

The early attention to the increased urinary excretion of nitrogen and K^+ following injury established the basis for metabolic balance studies of injured patients, which were widely utilised during the 1940s and 1950s (Wilkinson et al., 1950(a); 1950(b); Moore and Ball, 1952). Moore and other co-workers

extended the use of metabolic balance studies by the application of isotope dilution techniques to the study of body composition in surgical patients (Moore et al., 1963) and it became increasingly evident that the flow phase after injury is associated with the loss of body protein and other intracellular constituents at a time when the ECF volume of the body is maintained, or even expanded.

In addition to demonstrating an increase in nitrogen excretion, Cuthbertson's observations (1932) also revealed a 30 per cent rise in basal oxygen consumption following trauma. Since then, there has been a growing interest in the details of the changes in energy metabolism which are associated with the metabolic response to injury (Kinney et al., 1970; Wilmore et al., 1974). Furthermore, with renewed interest in the metabolic needs of the critically ill and 'catabolic' patient, total parenteral feeding began to be more widely employed (Schuberth and Wretlind, 1961; Dudrick et al., 1968).

The first demonstration that growth and development could be achieved by supplying basic nutrients exclusively by the intravenous route came in 1967 (Dudrick et al., 1967). In a preliminary study, six beagle puppies had been fed entirely intravenously for 72 to 225 days and compared with their orally fed litter mates, all the intravenously fed puppies outstripped their controls in weight gain, and matched them in skeletal growth, development and activity. The following year Dudrick et

al. (1968) reported further on the production both of a positive nitrogen balance and gain in weight in patients fed exclusively by vein.

After many technical and biochemical setbacks and adjustments, it is now possible to provide complete intravenous nutrition comprising amino acids, carbohydrate, fat, electrolytes and water, trace elements and vitamins; indeed, in extreme situations this form of total parenteral nutrition has become a form of life support in some patients (Ellis et al., 1976; Grant, 1980). Of late, however, the use of parenteral nutrition has come under increasing clinical and financial scrutiny (Goodgame, 1980). The question of whether energy should be provided via the parenteral route and, more importantly, what is the outcome of such energy provision, remains debatable. Merely to insert substrate into the patient's vein is no guarantee of its utilisation. In Part III of this thesis, the issue of substrate provision and storage in relation to starvation and injury will be further considered.

1.51 Body composition and nutritional flux following starvation and injury

During the early 1900s a considerable amount of information was gained about the overall metabolic changes induced by starvation. One of the key advances was made about 1915, when Dubois began his classic studies of metabolic rates in healthy

volunteers and patients, and not long thereafter Benedict began his equally classic studies on the biochemical, physiological and psychological response of men subsisting voluntarily on a moderately reduced diet which led to a weight loss of about 10 per cent over many months. Benedict also studied the effects of total nutrient deprivation (other than water) for 31 days in a volunteer man and provided data of the amounts of carbohydrate, protein and fat metabolised during the first week (Levenson et al., 1975).

As mentioned previously, in the early 1960s there was a renewed interest in the metabolic effects of injury and illness in which reduction of food intake plays an important role (Kinney et al., 1970), while the effects of starvation per se were further investigated by Cahill and co-workers (Cahill, 1970).

The early studies established the relative rates of weight loss during prolonged deprivation of all nutrients other than water, and demonstrated that only 10 to 15 per cent of the calories expended was the result of protein metabolism, while 85 to 90 per cent was supplied by non-protein material, namely fat. During starvation, adaptations take place to maintain satisfactory levels of blood glucose while satisfying the substrate requirements of organs, such as the brain, and minimising the loss of whole body protein (Kinney, 1981).

The normal response to starvation may be considered in three successive phases (Felig, 1979): the post-absorptive phase (after

an overnight fast), short-term starvation (lasting three to 10 days), and prolonged starvation (lasting two weeks or more).

The post-absorptive phase is characterised by liver glycogen breakdown which provides maintenance of blood glucose, while the brain and certain glycolytic tissues are utilising glucose at approximately 200 g per day. Stores of liver glycogen are limited, and are exhausted within a period of 12 hours of starvation (Davidson et al., 1979). The majority of the fuel requirements of other tissues are being met by the mobilisation of free fatty acids from adipose tissue. Gluconeogenesis is possible from pyruvate, lactate (Cori cycle), alanine, most other amino acids and glycerol (Fig. 1.2). In the post-absorptive state, approximately one-third of the lactate and alanine delivered to the liver is removed by the hepatic cells. As starvation is prolonged, gluconeogenesis declines because of decreased substrate availability. As liver glycogen becomes exhausted the ability to increase gluconeogenesis becomes critical to fulfil the obligatory tissue needs for glucose .

During short-term starvation, there is an accelerated gluconeogenesis and ketogenesis as a consequence of lowered levels of insulin and the altered insulin:glucagon ratio. There is an increase in the hepatic extraction of alanine; the fall in insulin stimulates lipolysis and the delivery of free fatty acids to the liver (Fig. 1.2). This is associated with increased fatty acid oxidation and ketogenesis (Kinney, 1981). Resting energy

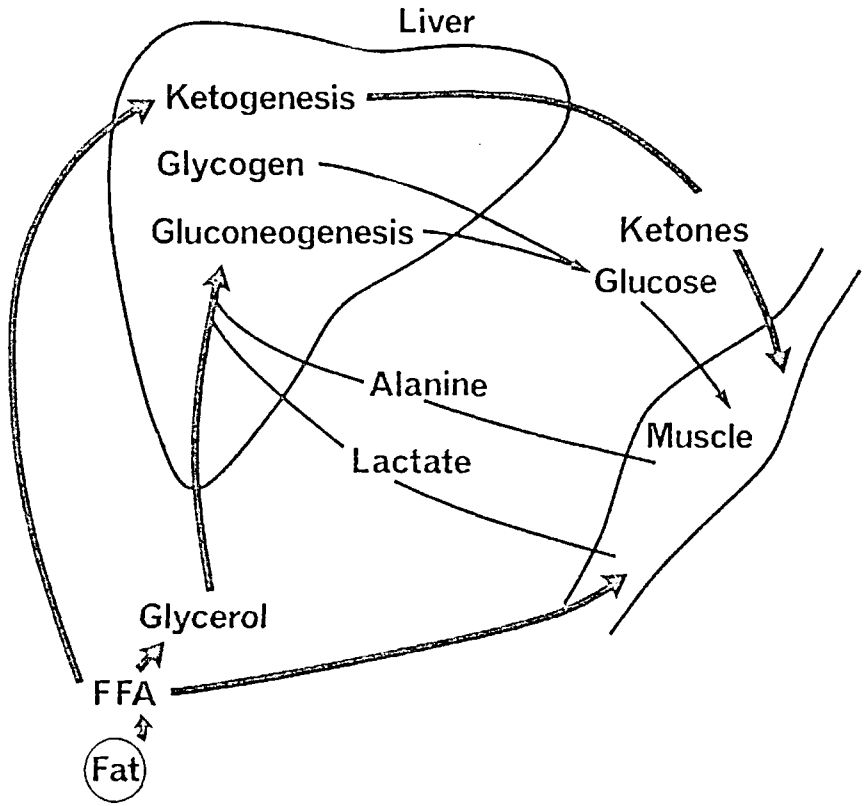


Figure 1.2

Composite diagram of the Glucose-Alanine and Cori cycle

expenditure and urinary nitrogen excretion tend to decrease in parallel after the first two to three days of starvation.

With prolonged starvation, increased lipolysis and the consequent high concentrations of acetyl CoA lead to the increased production of ketone bodies (Cahill, 1970). Owen et al. (1967) found that on prolonged fasting ketone bodies, specifically beta-hydroxybutyrate and acetoacetate, displaced glucose oxidation in the brain, thereby sparing gluconeogenesis and, in consequence, sparing body protein. Muscle can also oxidise ketones instead of the branched-chain amino acids, which again spares protein. Resting energy expenditure and nitrogen excretion reach extremely low levels after approximately four weeks of fasting. The decrease in energy expenditure during prolonged starvation, together with the increased production and utilisation of ketones, results in the benefits of maintaining an adequate blood glucose while conserving body protein. Basal metabolic rate has been observed to decline by 20 per cent in three weeks of total starvation (Benedict, 1915) and over 40 per cent in six months of partial starvation (Keys et al., 1950).

When fatty acid utilisation is maximum during starvation, the non-protein respiratory exchange ratio (RER) theoretically should be 0.70, indicating that fat is the only non-protein fuel. Owen et al. (1980) have found that during prolonged starvation the RER may reach values below 0.70; their explanation is that some

10 per cent of the ketone bodies produced by hepatic ketogenesis is unaccompanied by CO_2 production because of ketonuria (Reichard et al., 1974).

The overall changes in body composition during starvation may be viewed thus: an initial and gradual but transient increase in nitrogen excretion, apparently associated with the exhaustion of residual glucose stores as gluconeogenesis from protein "tunes up" to its starvation maximum. Next is a phase of mild "protein conservation" with a gradual decline in nitrogen loss while body-fat oxidation reaches a maximum. Following on is a phase of "ketoadaptation" with nitrogen loss rates reduced and the obligate glucose-burning tissues, such as brain, fully adapted to oxidation of ketone derivatives of both fat and protein.

Before reaching this late ketoadapted change, net loss of body cell mass also depends on the presence or absence of so-called stress-injury catabolism factors - such as fever, sepsis, infection, or continued trauma - which accelerate nitrogen loss (Moore and Brennan, 1975). Kinney et al. (1970) compared the rates of weight loss following injury with those found by Benedict (1915) during starvation; major injury, associated with approximately 50 per cent of the required calorie intake, gives the same rate of weight loss as Benedict found during total starvation without injury.

Using principles of indirect calorimetry, studies by Kinney (1981) have revealed that uncomplicated post-operative

convalescence has a resting energy expenditure which is usually between ± 10 per cent of the pre-operative values, while major third degree thermal injuries cause sustained increase in energy expenditure which is commonly between 40 and 100 per cent above normal.

1.511 Effects of starvation on water and electrolyte metabolism.

In his classic study, Benedict (1915) observed that during starvation weight loss exceeded that due to caloric deprivation. Gamble et al. (1923) demonstrated a loss of urinary Na^+ and K^+ during fasting and since then it has been well documented that acute starvation results primarily in water and electrolyte loss. Winkler et al. (1944) in a study of human volunteers during water deprivation and starvation found that the initial loss of fluids and electrolytes occurred predominantly from the ECF compartment. The effects of a 10-day period of starvation with water intake ad libitum were evaluated by Consolazio and co-workers (1967). They demonstrated a total body weight loss of about seven kilograms, or 10 per cent of the total body weight. A negative water balance was noted, with a cumulative negative balance of 2.6 litres by Day 3. There was a large mineral loss concomitant with the large body water loss, the Na^+ excretion averaging 30 mmol/day and the K^+ excretion averaging 20 mmol/day. Serum electrolyte levels of Na^+ and K^+ were significantly reduced during the starvation period, while plasma osmolalities remained

fairly constant.

More recent data on the effects of starvation regarding water and electrolyte metabolism have been obtained from obese volunteers. Veverbrants and Arky's (1969) studies demonstrated a mean daily weight loss of 0.8 kg during three days of starvation on a constant fluid intake. A water diuresis was not noted in their studies and they attributed the bulk of unaccounted for weight loss to insensible fluid loss. A large natriuresis and kaliuresis were observed by Day 2 of starvation, with Na^+ excretion of 70 mmol/day and K^+ excretion of 90 mmol/day. Serum Na^+, K^+ and osmolality remained relatively constant during the three days of starvation.

Isotope techniques and balance studies have provided reliable data regarding body water loss during starvation (Smith and Drenick, 1966; Drenick, 1980). By far the greatest part, probably two-thirds, of the early water loss originates in the ECF compartment. Accordingly, the pre-existing size of this compartment will, in large measure, determine the magnitude of the early weight loss. In lean subjects the rate of body water loss is highest in the first five days; it diminishes rapidly, and after 10 days a fairly stable average loss is maintained, though fluctuations from one day to the next can be substantial. Using Na^+ loss as a measure, a fall of 2.5 litres in ECF in six days of starvation was calculated by Gamble (1946); while using direct

fluid balance measurements a 3.3 litre fall in ECF was found (Consolazio et al., 1967).

There is evidence that in lean subjects ECF, relative to the diminishing size of the remaining body mass, may slowly increase. Total body tissue mass continues to decrease while total body Na^+ is maintained at a constant level. Therefore, in order to preserve stable electrolyte concentrations in plasma and interstitial fluids, the fluid compartment may have to expand (Drenick, 1980).

During starvation, intracellular water is liberated from many tissues as a result of breakdown of glycogen and of body protein stores. In addition, water is produced daily from the oxidation of endogenous substrate components. These contributions to total body water pool have already been alluded to in Section 1.31 of this thesis.

The mobilisation of body water from various compartments during starvation is reflected in the urine output. Urine volume and osmolality are maximal in the first two days and diminish gradually thereafter if a constant quantity of water is given daily. When ad libitum water intake is allowed, urine volume may fall to very low levels (less than 400 ml) in the later phases of starvation, because intake is spontaneously reduced (Kleitman, 1927; Cizek, 1959; Bloom, 1967). With prolonged starvation, a degree of impaired renal concentrating ability may develop.

The pattern of urinary Na^+ excretion shows it to be highest on the first day following the onset of starvation; thereafter it diminishes rapidly. The major portion of the Na^+ excreted in the first six days of starvation probably originates in the ECF compartment. Cumulative Na^+ excretion in the urine corresponds fairly closely to the isotonic contraction of the ECF compartment (Drenick, 1980). Additionally, some evidence exists that bone Na^+ is mobilised during the acute early phase of starvation before Na^+ excretion ceases. Na^+ excretion declines to a level of 1 to 15 mmol/day following starvation of 10 to 15 days (Strauss et al, 1958; Stinebaugh and Shloeder, 1966).

The mechanisms responsible for renal Na^+ conservation during starvation have been investigated (Bloom and Mitchell, 1960). Though decreased plasma volume should stimulate renin and aldosterone secretion, these have not been consistently found (Kjellberg et al., 1971). In addition to decreased glomerular filtration, increased proximal Na^+ reabsorption undoubtedly contributes to Na^+ retention. More recently, the reduction in plasma insulin levels and the rise in glucagon concentrations has been found to play a role in the genesis of the initial natriuresis of starvation (Saudek et al., 1973). Glucagon has been shown to rise in early starvation in proportion to Na^+ excretion, and exogenous glucagon effected an increase in urinary Na^+ loss.

The kaliuresis of starvation is particularly marked during the initial phase (Drenick et al., 1966) and, on the whole, the ratio of K^+ to nitrogen in the urine tended to exceed that found in lean tissue (Winkler et al., 1944). Ratios of 2 mmol of K^+ to 1 g of lean tissue nitrogen are considered to prevail for whole body lean tissue. In muscle, the ratio is closer to 3 mmol of K^+ to 1 g muscle nitrogen. If 1 g of lean tissue is catabolised in starvation, about 60 mmol of K^+ may be released. In the first month's starvation, lean tissue catabolism may furnish as much as 300 mmol of K^+ to the body pool. Actual depletion of the remaining tissues would occur only if the rate of excretion exceeded the rate of release of K^+ from catabolised tissue. In addition to release from protoplasmic sources, K^+ is released from glycogen stores. Assuming a glycogen consumption of about 400 g in the first two to three days and a ratio of 3 g of glycogen to 1 mmol of K^+, then about 130 mmol of this cation will be released and made available from glycogen stores in liver and muscle (Drenick, 1980).

The magnitude of daily urinary K^+ loss varies. After one month's starvation K^+ loss in lean subjects remains about 15 mmol/day, whereas obese subjects at this stage lose less than one-half that amount. This difference may represent more efficient protein sparing in the obese fasting subject who is able to utilise the ample adipose tissue stores.

Although overt manifestations of K^+ depletion are uncommon

during short-term starvation, certain clinical events are probably ascribable to tissue K^+ deficit. It has been postulated that K^+ depletion may account for the inability of the kidney to maintain an appropriately low urine pH during starvation, though a metabolic acidosis persists. Furthermore, K^+ depletion may account for the inability of the kidney to effect appropriate concentration of the urine (Rubini, 1961).

1.512 Effects of re-feeding on water and electrolyte metabolism.

During re-feeding following a period of starvation, most of the changes described above are reversed. Acid-base abnormalities are corrected concomitant with the disappearance of ketosis. Positive balances are observed for all minerals which have been excreted during starvation.

If glucose and water are given orally after three days of starvation and before Na^+ excretion has become minimal, a marked diminution of renal Na^+ excretion follows. This is associated with a reduction of water excretion (Gamble et al., 1923; Bloom, 1967). A similar effect has been noted following re-feeding with protein, but not with fat (Katz et al., 1968). Intravenous glucose infusions effect a lowering of Na^+ excretion within two hours and simultaneously raise renal concentrating capability. No adequate explanation has been found for the mechanisms by which Na^+ excretion is increased during a fast but then reduced on

subsequent carbohydrate feeding. One major factor proposed is a failure of ammonium excretion to keep pace with the changing output of organic acid (North et al., 1974). Re-feeding with fat will not inhibit protein catabolism or ketogenesis, and therefore not bring about a sharp reduction in anion excretion; whilst re-feeding with protein is presumably only effective in terms of the proportion of its amino acids which are ultimately metabolised through carbohydrate pathways and are therefore able to inhibit ketogenesis.

During nutritional rehabilitation following prolonged starvation, phenomena involving abnormal water and salt retention tend to develop. These events are variable depending on the type and quantities of food ingested and the salt content. Also, the length of the preceding period of starvation and the degree of obesity at the time of re-feeding seem related to the severity of "re-feeding oedema" (Drenick, 1980).

If there has been water deprivation, some degree of increase in body water content is expected and represents simple restoration of normal hydration of tissues. ECF and plasma water are repleted. Positive water balances have been noted during nutritional rehabilitation following a period of starvation with free access to water. These averaged 1.8 litres/day for the first two days of rehabilitation (Consolazio et al., 1967). Re-feeding with carbohydrate in particular causes a reduction in daily urine volume (Veverbrants and Arky, 1969). It has long been known that

carbohydrate diet causes the largest water retention (Puckett and Wiley, 1932; Mackay and Bergman, 1932) and that water is obligated to intracellular glycogen storage (Fenn and Haege, 1940; Olsson and Saltin, 1970; Bergstrom and Hultman, 1972). In addition, protein is re-synthesised if as little as 30 g of protein is given daily following starvation. This occurs even when the entire diet does not exceed a total of 300 calories and despite a continuing negative calorie balance. However, the period of a positive nitrogen balance is only transient unless caloric intake is increased to approximately 1000 calories. During protein synthesis, 3 g of water is bound in newly formed protoplasm with every gram of protein re-synthesised.

The repletion of glycogen plus bound water represents a weight gain of approximately 1.5 kg. In Part III of this thesis, a physiological model is described that distinguishes the water obligated to glycogen storage from that due to possible changes in body Na^+. With nutritional rehabilitation, a marked weight gain is generally observed. As mentioned above, the initial phase is the result of expansion of ICF and ECF space - total body re-hydration if water has been deprived. However, further short term and sometimes startling weight gains in patients who are challenged by either enteral or parenteral nutrition have, in the past, been largely ascribed to 'water retention' (Hill et al., 1978; Yeung et al., 1979). In Part III the mechanism of glycogen, water and electrolyte deposition in recovery from

starvation and after injury will be further developed and evidence will be presented that glycogen obligated water accounts for a large proportion of the early weight gain during nutritional rehabilitation.

P A R T I I

POST-OPERATIVE HYPONATRAEMIA

C H A P T E R 2

RE-STUDY OF THE DISTRIBUTION OF A LARGE WATER LOAD IN MAN

2.1 INTRODUCTION

Water balance is a central feature in the adaptation of an animal to its environment. Any discussion of water balance requires consideration of the movement of water across cells. The swelling or shrinkage of a cell when placed in a non-isotonic solution is usually taken to indicate that the cell contents are enclosed in a semipermeable membrane (Fettiplace and Haydon, 1980).

The distribution of Na^+ within the body can only be meaningfully considered in relation to the distribution of water. Thus, the fundamental division of body fluids into ICF and ECF spaces coincides with an equally fundamental division between Na^+-poor and Na^+-rich fluid (see Fig. 1.1). The high concentration of Na^+ in the ECF is largely responsible for maintaining the osmotic pressure of this fluid, performing a similar role to that played by K^+ in the ICF; in addition, the ECF-Na^+ prevents disastrous cell swelling resulting from the colloid osmotic pressure exerted by ICF-protein which is present in higher concentration than in ECF. Any change in ECF-Na^+ concentration, therefore, produces important changes in ICF and ECF volumes. It is at the interface between the two, the cell membrane, that this vitally important electrolyte gradient occurs. It is the integrity of the cell membrane and its transport mechanisms which preserve the fluid compartments of the body from distortion by osmotically induced water movements (Sweadner and Goldin, 1980).

Until recently a great deal of controversy centred upon two problems: whether, at equilibrium, the osmotic pressures of the ECF and ICF were equal; and whether tissues possessed regulating mechanisms whereby their degree of hydration could be controlled by mechanisms other than the passive movement of water in the direction of its chemical gradient (Wynn, 1978). Until this controversy could be resolved there was no possibility of giving a uniform description either of normal physiological regulation of body fluid homeostasis, or of the effect upon it of disease. In fact many illnesses, such as surgical trauma, heart failure, and renal disease, were each held at one time to affect body fluid distribution in quite a specific way, and new theories were earnestly propounded to explain certain facts which were thought not to fit in with classical views (Wynn, 1957).

2.2 Osmoregulation and Renal Excretion of Water

Each day 180 litres of plasma are filtered at the glomerulus, and of this, 1.5 litres appear in the urine. As the concentration of solute in the plasma is some 290 mOsm/kg the net effect of the renal tubule is to concentrate glomerular filtrate by reabsorbing, proportionately, more water than solute.

Osmoregulation is achieved in man by the ability to adjust intake and output of water. In response to water restriction, conscious man increases intake to satisfy thirst. Although usually stimulated by plasma hyperosmolality, thirst may also be induced by a reduction in body fluid volume without an increase in osmolality. The excretion of water is determined by the kidney's ability to excrete a concentrated or dilute urine. Among the vetebrates only mammals, and to a lesser extent birds, are able to excrete hypertonic urine (Bentley, 1972).

The ability of the kidney to change the concentration of urine is the cornerstone of osmolar balance. As long as the kidney's concentrating and diluting ability remains intact, osmolar control can be finely modulated by the action of ADH. Maximal concentrating ability and the capacity to reabsorb solute-free water while excreting large solute loads reside upon the anatomical configuration of the renal tubule, that is, the counter-current multiplier (Wirz and Dirix, 1973). Man is able to conserve water by producing urine five times as concentrated as plasma before osmoregulation fails (Wesson, 1969). Lindeman et al (1960) found the maximum urine osmolality to average 1189 mOsm/kg in 14 young men after 24 hours of water deprivation.

If water is drunk, it is soon absorbed from the gut into the bloodstream (within 30-60 minutes) and from there it diffuses through total body water (TBW), the osmolality of which declines. A decrease of about one per cent in osmolality stimulates certain cells in the anterior hypothalmus - the 'osmo-receptors' - and they in turn inhibit the secretion of ADH by the hypothalamo-neurohypophysial ADH-secreting mechanism (Verney, 1947; Bie, 1980).

The decrease in circulating ADH diminishes water re-absorption in the distal tubules of the kidney and a water diuresis follows. In the absence of ADH the fluid emerging from the collecting duct will be maximally dilute - osmolality being 50-100 mOsm/kg (Robertson, 1974). After drinking a litre of water, water balance

is restored within three to four hours in an adult. If the kidneys cannot freely excrete a dilute urine the stage is set for water retention and hyponatraemia.

Dilution of the isosmotic fluid delivered from the proximal tubule occurs by reabsorption of its Na^+ content under the influence of aldosterone. In the absence of ADH the distal tubules are virtually impermeable to water and the glomerular filtrate, with its Na^+ content reduced, remains as a hypotonic fluid in the tubules and is finally excreted. A water diuresis results. When ADH is present, however, water is reabsorbed from the hypotonic tubular fluid until isotonicity with plasma is re-established. A water diuresis cannot now occur. The lowest osmolality which can be achieved in the distal tubules is about 50 mOsm/kg. Under the influence of ADH the osmolality of the fluid in this segment rises to about 300 mOsm/kg.

The final concentrating process of the urine (which raises its osmolality above that of the plasma) occurs in the collecting tubules where water only is reabsorbed. Water reabsorbed in the distal and collecting tubules is referred to as "facultative" water reabsorption (Wirz and Dirix, 1973).

The urinary water may thus be divided into two moieties: (i) that volume necessary to excrete all the urinary solutes in isosmotic proportion - the osmolal clearance (C_{osm}), and (ii) that volume reabsorbed from the urine without solute during the concentrating process or freed of solute during the diluting

process - the free water clearance (C_{H_2O}).

(i) $$C_{osm} = \frac{U_{osm}}{P_{osm}} \times Vu$$

where: Vu = urine volume (ml/min);

U_{osm}, P_{osm} = urine and plasma osmolalities (mOsm/kg).

(ii) $$C_{H_2O} = Vu - C_{osm}$$

"Free-water clearance" (C_{H_2O}) termed by Wesson and Anslow (1952) is not a true clearance value, and free-water excretion would be a more appropriate term. C_{H_2O} will have a negative value when the urine is hypertonic, and a positive value when the urine is hypotonic.

2.3 Objective

That dilution is the sole consequence of addition of water to the body rests on the postulate that isotonicity is maintained between ICF and ECF (Maffly and Leaf, 1959) with the exception of the renal medulla and some secretory tissues. Therefore, when water is administered, dilution of the plasma and ECF is quickly followed by movement of water into the ICF along the osmotic gradient, until both ICF and ECF are equally diluted, that is, water is distributed over the whole body fluid (Leaf et al., 1954).

In circumstances in which the kidneys are prevented from correcting the dilution of ECF by the normal processes of water diuresis, a fall in serum Na^+ concentration occurs which is predictable from knowledge of net load and total body water (TBW). Dudley and his colleagues (1954) reported disproportionate Na^+ falls in the ECF after equilibration of a water load with TBW, but their observations did not allow for possible changes in non-ionic components of ECF, and therefore in total osmolality. By contrast Wynn (1955), by indirect methods, felt that dilution was proportional to body water in acute hyponatraemic states.

Thus the first object of the present study was:

To Establish Whether Or Not Large Water Loads Dilute Body Compartments Proportionally.

2.4 Subjects and Methods

Six healthy volunteers had their TBW determined by the administration of 100 μci of tritiated water (^3H_2O) given intravenously; at three-and-a-half-hours a venous sample was taken and TBW calculated from its dilution (Vaughan and Boling, 1961). The experiment was commenced after an overnight fast and after the volunteers had emptied their bladders.

They were then subjected to an oral water load of five per cent of their TBW with simultaneous administration (intramuscular 0.1 μg/kg of 1-desamino-8-D-arginine vasopressin (Desmopressin, Ferring) in order to suppress renal excretion of water. Antidiuresis was achieved in all six subjects during the study period, with a urine volume that was never in excess of 0.9 ml/min.

Their serum Na^+, K^+ (Corning 450 flame photometer), glucose and urea (SMA-12, Technicon) concentrations and serum osmolality (Advanced Osmometer) were measured hourly to and past theoretical equilibrium (3.5 hours) for six hours of the study (Appendix 2.1).

TABLE 2.1

Details of water loading experiment

SUBJECT	TBW (litres)	H_2O load (litres)	DDAVP (μg)	Total Urine (ml)	C_{H_2O} (ml/min)
1	35.5	1.8	5.9	220	-1.4
2	49.3	2.5	8.1	94	-0.6
3	40.2	2.0	6.7	50	-0.3
4	43.3	2.2	7.5	30	-0.2
5	36.3	1.8	6.7	324	-1.6
6	42.4	2.1	7.3	150	-0.7

2.5 Results

Following a retained water load, the theoretical dilution level of serum Na^+ is given by the following relationship:

$$(Na^+_1)(TBW_1) + \Delta Osm = (Na^+_2)(TBW_2) \quad \text{(Appendix 2.1)}$$

where the sub-scripts 1 and 2 refer to initial and to final values at equilibrium respectively. The change in total osmolality (ΔOsm) allows for possible alterations in urea and glucose (Wynn, 1972).

Figure 2.1 shows the results expressed as percentage reduction in serum Na^+ in each volunteer. At equilibration time of $3\frac{1}{2}$ hours, the percentage reduction in all six volunteers fell within their predicted dilution levels indicated by the hatched area.

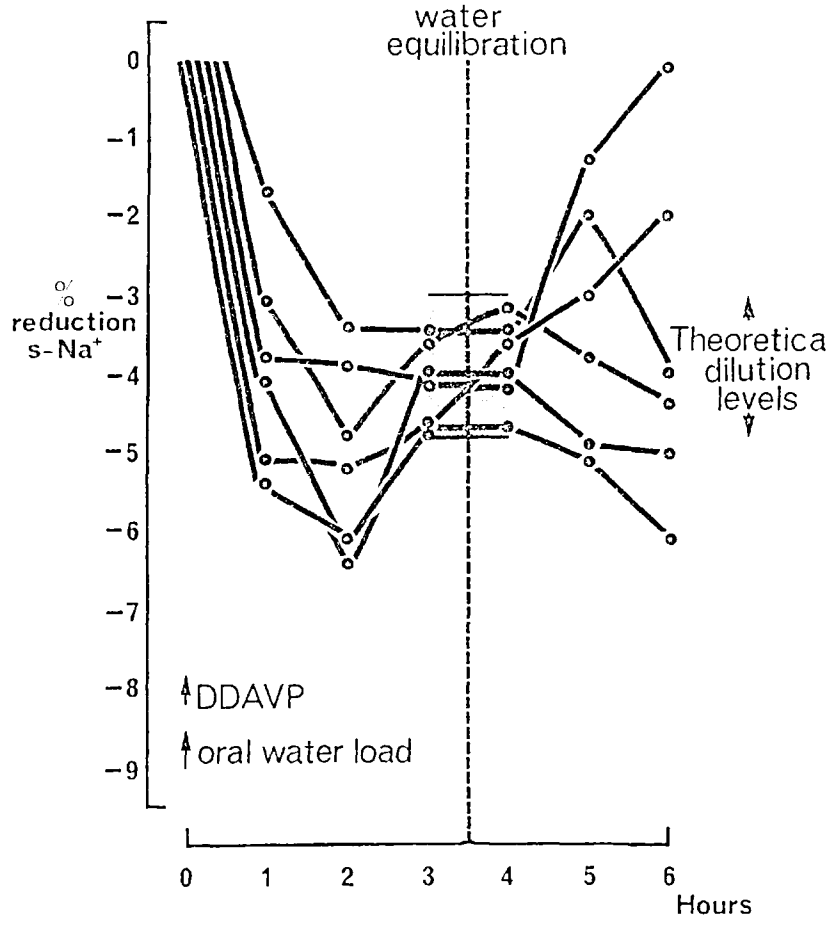


Figure 2.1

Effect of water load and desmopressin (DDAVP) antidiuresis on $s\text{-}Na^+$

TABLE 2.2

Data for each volunteer in water loading experiment

Name: STFC Age: 32 yr Sex: M

Weight: 58.6 kg TBW_1: 35.5 litres TBW_2: 37.3 litres

Water load: 1.8 litres DDAVP: 5.9 μg

Time (h)	s-Na^+ (mmol/l)	s-K^+ (mmol/l)	s-Urea (mmol/l)	s-Glucose (mmol/l)	s-Osm (mOsm/kg)	Calc-Osm*	% Δ s-Na^+
0	136.2	4.0	5.6	6.4	287.2	292.0	0
1	130.7	4.6	6.6	4.3	275.0	281.5	-4.0
2	127.5	4.1	6.5	6.9	271.9	276.6	-6.4
3	130.8	4.8	4.6	3.2	275.4	279.0	-4.0
4	130.6	4.2	6.5	5.6	275.3	281.7	-4.1
5	129.5	4.9	7.1	4.7	274.3	280.6	-4.9
6	129.4	4.3	6.8	4.6	273.3	278.8	-5.0

* Calc-Osm = $2(Na^+ + K^+)$ + urea + glucose

TABLE 2.2

Data for each volunteer in water loading experiment

Name: AR Age: 32 yr Sex: M

Weight: 81.4 kg TBW_1: 49.3 litres TBW_2: 51.8 litres

Water load: 2.5 litres DDAVP: 8.1 μg

Time (h)	s-Na^+ (mmol/l)	s-K^+ (mmol/l)	s-Urea (mmol/l)	s-Glucose (mmol/l)	s-Osm (mOsm/kg)	Calc-Osm*	% Δ s-Na^+
0	142.4	4.1	3.5	5.6	296.1	302.1	0
1	138.0	3.9	5.6	6.2	287.6	295.6	-3.1
2	135.6	3.7	6.0	6.4	282.2	291.0	-4.8
3	137.4	3.4	4.2	4.2	284.5	290.0	-3.5
4	137.9	3.8	6.4	5.9	287.1	295.7	-3.2
5	137.0	3.5	5.8	5.5	285.6	292.3	-3.8
6	136.2	3.3	4.9	5.0	275.8	288.9	-4.4

* Calc-Osm = $2(Na^+ + K^+)$ + urea + glucose

TABLE 2.2

Data for each volunteer in water loading experiment

Name: PE Age: 23 yr Sex: M

Weight: 67 kg TBW_1: 40.2 litres TBW_2: 42.2 litres

Water load: 2.0 litres DDAVP: 6.7 μg

Time (h)	s-Na^+ (mmol/l)	s-K^+ (mmol/l)	s-Urea (mmol/l)	s-Glucose (mmol/l)	s-Osm (mOsm/kg)	Calc-Osm*	% Δ s-Na^+
0	135.2	3.8	6.2	6.3	284.3	290.5	0
1	130.1	4.4	3.8	5.3	271.4	278.1	-3.8
2	130.0	4.2	3.8	6.3	270.3	278.5	-3.9
3	129.6	4.0	5.4	4.5	271.6	277.1	-4.1
4	129.5	3.7	4.0	4.9	272.5	275.3	-4.2
5	133.5	4.5	4.1	5.4	278.5	285.5	-1.3
6	135.1	4.5	4.2	4.4	280.1	287.8	-0.1

* Calc-Osm = $2(Na^+ + K^+)$ + urea + glucose

TABLE 2.2

Data for each volunteer in water loading experiment

Name: NMR Age: 25 yr Sex: M

Weight: 75 kg TBW_1: 43.3 litres TBW_2: 45.5 litres

Water load: 2.2 litres DDAVP: 7.5 µg

Time (h)	s-Na^+ (mmol/l)	s-K^+ (mmol/l)	s-Urea (mmol/l)	s-Glucose (mmol/l)	s-Osm (mOsm/kg)	Calc-Osm*	%Δ s-Na^+
0	140.0	4.4	4.0	5.3	283.7	298.1	0
1	132.4	4.4	5.3	4.8	277.0	283.7	-5.4
2	131.5	4.1	5.7	5.1	276.0	282.0	-6.1
3	133.5	4.0	4.4	4.3	271.5	283.7	-4.6
4	133.4	3.9	5.0	6.0	271.2	285.6	-4.7
5	132.8	3.7	5.3	5.1	273.5	283.4	-5.1
6	131.5	3.9	5.5	5.3	275.0	281.6	-6.1

* Calc-Osm = $2(Na^+ + K^+)$ + urea + glucose

TABLE 2.2

Data for each volunteer in water loading experiment

Name: AG Age: 60 yr Sex: M

Weight: 66.7 kg TBW_1: 36.3 litres TBW_2: 38.1 litres

Water load: 1.8 litres DDAVP: 6.7 μg

Time (h)	s-Na^+ (mmol/l)	s-K^+ (mmol/l)	s-Urea (mmol/l)	s-Glucose (mmol/l)	s-Osm (mOsm/kg)	Calc-Osm*	% Δ s-Na^+
0	137.5	4.1	6.3	5.0	281.7	294.5	0
1	135.2	4.0	5.8	4.6	275.6	288.8	-1.7
2	132.9	4.3	4.9	4.6	273.1	283.9	-3.4
3	132.7	4.5	5.5	3.0	273.5	282.9	-3.5
4	132.7	4.0	6.0	3.9	272.0	283.3	-3.5
5	134.9	4.4	5.8	4.5	280.1	288.9	-1.9
6	131.7	4.8	5.7	4.2	275.3	282.9	-4.2

* Calc-Osm = $2(Na^+ + K^+)$ + urea + glucose

TABLE 2.2

Data for each volunteer in water loading experiment

Name: CN Age: 26 yr Sex: M

Weight: 73.2 kg TBW_1: 42.4 litres TBW_2: 44.5 litres

Water load: 2.1 litres DDAVP: 7.3 μg

Time (h)	s-Na^+ (mmol/l)	s-K^+ (mmol/l)	s-Urea (mmol/l)	s-Glucose (mmol/l)	s-Osm (mOsm/kg)	Calc-Osm*	% Δ s-Na^+
0	139.4	4.3	4.2	6.7	289.5	298.3	0
1	132.3	3.8	4.1	4.3	274.0	280.6	-5.1
2	132.2	4.6	4.5	6.3	273.5	284.4	-5.2
3	132.5	4.5	4.0	6.6	272.9	284.6	-5.0
4	134.4	4.0	4.6	5.3	280.2	286.7	-3.6
5	135.2	4.2	4.5	5.6	279.9	288.9	-3.0
6	137.2	4.0	4.6	5.2	282.8	292.2	-1.6

* Calc-Osm = $2(Na^+ + K^+)$ + urea + glucose

2.6 Discussion

Sodium and the accompanying anions are 97 per cent of the osmotically active solute in ECF, and the serum Na^+ level is clearly correlated with serum osmolality. Because most body tissues are isotonic, the serum Na^+ level normally represents the degree of dilution or concentration of body fluids in health.

It is now well established that the ICF shares the same tonicity as the ECF (Conway and McCormack, 1953; Maffly and Leaf, 1959). Although the solute composition within cells is quite different from that of ECF, cell membranes do not constitute a barrier to the passage of water which, therefore, attains a uniform activity or osmotic equality inside and outside cells. Only in the renal medulla, where concentrated or dilute urine is formed, as well as certain secretory glands such as salivary glands, does tonicity differ from that of serum. The same mechanism, therefore, that serves to stabilise the total solute or Na^+ concentration of the serum also regulates the tonicity of the larger volume of ICF. The serum Na^+ concentration consequently serves as an index of the concentration or activity of water throughout the body fluids (Leaf, 1962).

In view of past reports to the contrary (Dudley et al., 1954), it was essential that the effects of water loading in the presence of a urine volume restricted by the use of

antidiuretic hormone was re-examined. The present study in normal volunteers has validated that water loading results in a proportional dilution of the two main body compartments - extra- and intracellular. Changes in serum Na^+ concentration and osmolality were those expected from equidistribution. One explanation of the previous conflicting reports might be erratic rates of exchange in the gastrointestinal tract.

The observation that fluid is distributed over the body cells according to calculable osmotic force has also been applied to fluid distribution in disease (Wynn, 1957; Flear et al., 1980). Armed with the information obtained in this chapter, the relationship between water balance and serum Na^+ concentration which could be predicted on the basis of dilution of ECF will be presented in Chapter 3 in relation to surgical operations.

2.7 Summary

In view of previous conflicting reports on whether or not the change in serum Na^+ was proportional to dilution, a re-investigation of the effects of water overload was done on six healthy volunteers who were experiencing maximal antidiuresis from desmopressin. The fall in serum Na^+ was predictable from prior measurement of total body water (tritium), confirming that the induced hyponatraemia was dilutional.

This study has demonstrated that a change in the osmolality on either side of the cell membrane is followed by a re-distribution of water, or solutes, or both, until equilibrium is re-established. The body cells behave passively like perfect osmometers, adapting their volume to the osmolality of their surroundings, at least in health. Whether this behaviour is affected by disease and, in particular, surgical injury will be the subject of the next Chapter. It is concluded that large water loads dilute body water compartments (extra- and intracellular) proportionally.

C H A P T E R 3

THE SERUM SODIUM CONCENTRATION AFTER SURGICAL OPERATION

3.1 INTRODUCTION

The serum Na^+ concentration is almost routinely determined in the context of major surgery as part of a profile of "urea and electrolytes" - ostensibly as a guide to progress. Presumably, clinicians feel that they are reassured when they find it "normal", and can make some inferences about the patient's physiological status if it is not. However, the evidence on which this conclusion is based is shaky. The interpretation of the serum Na^+ concentration in individual patients still remains confused and to know when to act or, more important, when not to act, remains a perplexing problem (Leaf, 1962; Editorial, Lancet, 1978; Flear et al., 1981).

A fall in serum Na^+ concentration is frequently seen after surgical injury and many papers have been written on hyponatraemia as a phenomenon of the acutely or chronically ill, particularly by Moore (Moore and Ball, 1952; Moore, 1962). However, normal response to injury under standard circumstances has never been adequately studied in spite of the millions of determinations that are routinely made in hospital laboratories. Furthermore, though the evidence is strong that most of the change observed after injury is dilutional and consequent upon water retention (LeQuesne, 1954; Wynn, 1960; Thomas and Morgan, 1979), the

literature on dilutional hyponatraemia is confusing.

In the surgical context, post-injury hyponatraemia has been widely ascribed to the predominant influence of ADH (Dudley et al., 1954; Hayes, 1968), and further exaggerated by misdirected fluid and electrolyte therapy (Moore, 1962). Many stimuli for the release of ADH are present. These include pre-operative oral intake restriction, pre-medication with narcotic agents, pain and emotional stimuli, incision and visceral stimulation, haemorrhage, positive pressure ventilation and anaesthesia (Deutsch et al., 1966).

The view that ADH release is important in post-operative hyponatraemia is supported by bioassay studies (Moran et al, 1964) and more recently by radioimmunoassay studies (Haas and Glick, 1978; Cochrane et al., 1981). Before the skin incision is made, circulatory ADH levels are mildly elevated; transient but very marked rises occur during operation. After operation, elevated levels plateau out for six to 12 hours, and then gradually return to normal over the next five days.

At the same time, other factors may be involved in the antidiuresis following injury. In a patient with diabetes insipidus, antidiuresis has been observed (Luttwak and Saltz, 1962) which only occasionally responds to the ADH inhibitory action of alcohol (Bennett et al., 1964). Irvin et

al. (1972) reported that giving balanced salt solution during, as well as after, surgery did not prevent the excess ADH (as assessed by free water excretion), although it prevented the fall in serum Na^+ in the patients given dextrose solution. This finding suggests that there is no simple relationship between hyponatraemia and increased ADH. Renal blood flow, glomerular filtration and renal tubular Na^+ reabsorption may all be altered by surgery, and it has been suggested that these factors play a role (Swales, 1975).

Moore et al. (1963) have demonstrated that important changes in body composition occur with cellular catabolism to produce a fall in the ratio of intracellular to total body water and a reduction in body potassium. This internal redistribution of water will, therefore, contribute to dilutional hyponatraemia. Furthermore, Flear (1970) has adduced evidence in support of the hypothesis that hyponatraemia is essentially a cellular event with widespread disturbance of membrane permeability, resulting in net gains of intracellular Na^+ and loss of K^+. The studies by Moore et al. (1963) have, however, shown no evidence of Na^+ movement into cells and moreover, physiological information is lacking on this concept of Na^+ "binding" - how and where? Alternatively, increased solute is generated within the cells, and then leaks out into the ECF, thus obligating water along with it - a redistributional phenomenon.

3.2 The Meaning of 'Normal' Serum Na^+ Concentration

The serum Na^+ concentration in health normally ranges between 135 and 145 mmol/l of serum in spite of large individual variations in the daily intake of salt and water (Widdowson and Dickerson, 1964). The constancy of the serum Na^+ concentration is the consequence of the fact that the salts of Na^+ comprise the major osmotically active solutes in the serum and that the body jealously preserves the total solute concentration of the serum in health within narrow limits of some 270 to 290 milliosmoles (mOsm) per kilogram of water. Maintenance of the constancy of total solute activity of serum is the function of the thirst-neurohypophysial-renal axis, about whose functional inter-relations there is now a considerable understanding (Leaf and Mamby, 1952).

Serum Na^+ values in man conform to a normal distribution, that is, values are evenly scattered about the mean (Wotton et al., 1951; Fawcett and Wynn, 1956). Earlier studies which relied upon chemical determinations yielded a wider range than later, more precise, flame photometer determinations.

It has been suggested that the normal range published for the concentration of Na^+ in serum seems high when compared with results from hospital laboratories (Henry, 1964). In most

illnesses which are known to affect the serum Na^+, its concentration is reduced. The low values seen in the majority of patients might therefore be interpreted as indicating that most of the patients for whom Na^+ analyses are requested suffer from such illnesses; the alternative interpretation being that they do not suffer from such illnesses and that their Na^+ levels should be judged against a lower norm. Payne and Levell (1968) suggested that control values should be obtained from hospital patients, in preference to healthy persons, so that degrees of hyponatraemia which are of clinical significance can be identified, while others have argued that this concept assumes the presence of two distinct sub-populations (control and abnormal) in respect of the parameter measured (Flear and Singh, 1973).

As Na^+ is accompanied by an equal number of anions, the contribution of Na^+ to serum osmolality can be obtained by doubling the Na^+ concentration. In other circumstances, abnormally high concentrations of additional solutes may be found in the ECF, such as glucose and urea. In practice, the serum osmolality can be calculated sufficiently accurately for clinical purposes if serum Na^+, K^+, urea and glucose concentrations are known.

$$\text{Calc-Osm} = 2(Na^+ + K^+) + \text{urea} + \text{glucose}$$

where the concentrations of Na^+, K^+, urea and gluocose are expressed in mmols per litre. Urea is not an "effective" solute,

since most body cells are quite freely permeable to the substance; it is, therefore, not a determinant of water distribution, except in certain circumstances in the renal tubule. Sudden changes in the concentration of glucose in the blood do, indeed, change water distribution between cells and ECF, as can be demonstrated by the marked dilutional hyponatraemia produced by sudden infusions of large amounts of concentrated glucose (Moore, 1962). This result is transient, however, as the glucose gains an intracellular position and is oxidised. There is thus a very close correlation between serum Na^+ concentration and serum osmolality, corrected for the contribution made by glucose and urea (Edelman et al., 1958) and fluctuations in effective tonicity are generally linear with fluctuations in Na^+ concentration. Exceptions occur commonly due to ingestion of alcohol (Robinson and Loeb, 1971, or due to administration of mannitol (Aviram et al., 1967).

Serum Na^+ level reflects only the ratio of Na^+ to water in the ECF. This ratio is determined by total body Na^+ (Na_e), total body water (TBW), and the distribution of the latter between ECF and ICF compartments. The distribution of TBW is also dependent on total body potassium (K_e), the principal intracellular cation. Thus, the serum Na^+ level depends on Na_e, K_e and TBW. Isotopic data from the study of body composition has confirmed this inter-relationship between Na^+, K^+ and water (Moore et al., 1956; Edelman et al., 1958). Of the three, the most important sudden fluctuations in serum Na^+ and tonicity

(of the type that produce changes in consciousness) are produced by sudden changes in body water content, because marked alteration in body content of the two ions is much more difficult to produce.

3.3 Objective

Major abdominal surgery is usually associated with parenteral water and electrolyte administration at a time when renal excretory capacity is reduced and water in excess of need will therefore be retained (Dudley et al., 1954). If the many thousands of serum electrolyte determinations done on surgical patients are not to be wasted efforts, we need for practical management some clear numerical directives on the significance of changes and on the effect, or otherwise, of dilution in relation to water and electrolyte administration to post-operative patients.

The objective of this study was:

To Delineate the Normal Pattern of Change in Serum Na^+ Concentrations After Uncomplicated Surgical Injury Managed on a Standard Fluid and Electrolyte Regimen.

The investigation was also aimed at answering the following questions:-

(a) What error limits should be taken into consideration before a decision is taken by the clinician that the serum Na^+ concentration <u>has</u> changed?

(b) How do these changes relate to changes in:

(i) other serum electrolyte concentrations;

(ii) total osmolal content of serum?

3.4 Subjects and Methods

3.41 Uncomplicated surgery

Fifty patients presenting for elective major abdominal surgery were studied from the day before operation (Day 0) until the sixth day after operation (Day 6). The surgical procedures included cholecystectomy, highly selective vagotomy, gastrectomy, and colectomy (Table 3.1). There was almost equal distribution of males (n = 26) and females (n = 24) with a wide range of ages (20-79 years) and a median age of 49.

Standard anaesthetic techniques were used, with intermittent positive pressure ventilation, nitrous oxide, oxygen, and muscle relaxants. Operative blood loss was measured by swab-weighing, and was replaced with whole blood. In addition, Hartmann's solution was infused at a rate of 5 ml/kg/h during the operative procedure. The standard post-operative intravenous fluid regimen provided 30 ml/kg of water per day, and 90 mmol of Na^+. Nasogastric tubes were not used and there were no other extrarenal fluid losses. Oral intake was allowed to resume as gastrointestinal tract function recovered. A blood sample was taken each morning at a standard time, and 24-hour urine collections were made for the seven days of the study (0900-0900h).

TABLE 3.1

Surgical procedures and intra-operative data of patients for post-operative s-Na^+ studies

Abdominal surgery:	Number:	IV-Hartmann's* (ml)	Na^+-load* (mmol)	Blood* units
Cholecystectomy	19	434.5 ± 32.7	57.0 ± 4.3	0.5 ± 0.2
Colectomy	9	1008.8 ± 65.5	132.3 ± 8.5	2.2 ± 0.1
Highly Selective Vagotomy	8	535.4 ± 35.1	70.1 ± 4.6	0.5 ± 0.3
Gastrectomy	5	1046.6 ± 86.4	137.4 ±11.3	2.2 ± 0.2
Small Bowel Resection	4	675.0 ± 85.7	88.5 ±11.2	1.0 ± 0.4
Laparotomy	4	510.8 ± 71.9	67.0 ± 9.3	1.8 ± 0.3
Excision Ovarian Tumour	1	500.0	66.0	2.0

* mean ± SEM

Serum Na^+ and K^+ concentrations were measured by a Corning 450 flame photometer and serum osmolality by freezing-point depression using an Advanced osmometer. Replicate determinations showed less than one per cent error. The Na^+ values determined by the photometer compared well with those of daily determination by the hospital chemical pathology laboratory (Table 3.2). The difference between the lower 95 per cent tolerance limits for the two determinations was less than 0.4 mmol/l (mean). Daily clinical balance measurements were done by careful charting of input and output of water and electrolytes.

3.42 Isotope studies

In 14 of the healthy patients total exchangeable Na^+ (Na_e) was measured by the administration of 20 μCi ^{24}Na intravenously (Forbes and Perley, 1951); total body water (TBW) was determined by the intravenous administration of 100 μCi of ^3H_2O (Vaughan and Boling, 1961). Total exchangeable potassium (K_e) was then calculated from the formula of Edelman and Moore, validated by Shizgal et al. (1977), thus allowing pre-operative quantitation of body composition. These values were corrected for external balance changes over the six post-operative days of the study. (Appendix 3.4).

TABLE 3.2

s-Na^+ values of photometer determinations compared with those of hospital pathology laboratory

DAY		0	1	2	3	4	5	6
Mean	A	139.96	134.16	133.57	135.15	136.27	137.35	138.74
	B	139.96	134.28	133.80	135.24	136.68	137.56	138.98
S.D.	A	2.21	2.74	2.91	3.38	3.23	3.38	3.02
	B	2.39	2.55	2.70	3.15	3.29	3.34	3.19
Difference between lower 95% tolerance limits		0.43	0.57	0.73	0.64	0.26	0.30	0.17

A - Surgical Unit Flame Photometry

B - Chemical Pathology Laboratory Analyses

3.43 Restricted regimen

Ten further patients, subject to the same magnitude of surgery, were studied on a more restricted fluid regimen providing 20 ml/kg of water and 60 mmol Na^+/24 h (Table 3.3).

Informed consent was obtained from each person and the investigation was approved by the local Ethical Committee. Tolerance limits were determined from standard tables (Documenta Geigy, 1970). Statistical comparisons have been made using the Student's t test (paired and unpaired as appropriate) for normally distributed data.

3.5 Results

3.51 Uncomplicated surgery.

In 50 patients who followed an uncomplicated post-operative course (Fig. 3.1) a statistically significant reduction in serum Na^+ was present, in comparison with pre-operative values, on all six post-operative days, being maximal over the first two days following surgery ($p < 0.001$ first five days, $p < 0.005$ Day 6).

The serum Na^+ concentrations at any epoch were always normally distributed in this population studied, so permitting 95 per cent tolerance limits with 95 per cent confidence probability to be drawn (Fig. 3.2). Normality of distribution was established by using the third moment of the mean (Appendix 3.5).

TABLE 3.3

Patients given a restricted regimen and intra-operative details

Patient:	Procedure:	Wt (kg):	Duration (h):	IV-Hartmann's (ml):	Na^+-load (mmol):	Blood (units):
1	Cholecystectomy	59	1.0	295	39	0
2	Cholecystectomy	68	1.3	442	58	0
3	Cholecystectomy	65	1.5	488	64	1
4	Cholecystectomy	72	1.3	468	61	0
5	Colectomy	69	2.3	794	104	2
6	Colectomy	67	2.5	838	110	2
7	Colectomy	71	2.3	817	107	2
8	Hepatic Artery Ligation	62	1.3	403	53	2
9	Laparotomy	70	2.0	700	92	1
10	Laparotomy	72	1.5	540	71	2
	Mean $\pm$ SEM	67.5 $\pm$ 1.4	1.7 $\pm$ 0.2	578.5 $\pm$ 61.3	75.9 $\pm$ 8.0	1.2 $\pm$ 0.3

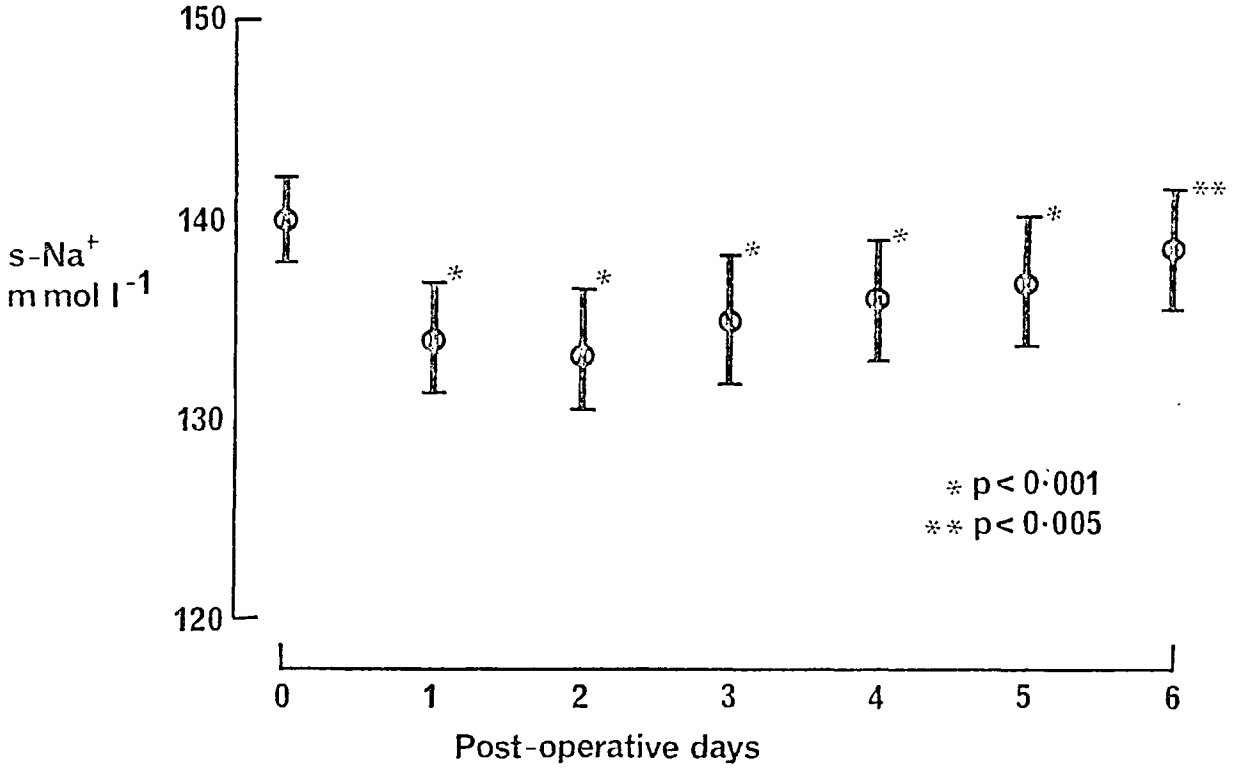


Figure 3.1

The s-Na^+ concentrations over 6 post-operative days (mean ± SD) following uncomplicated abdominal surgery compared with pre-operative values (day 0).

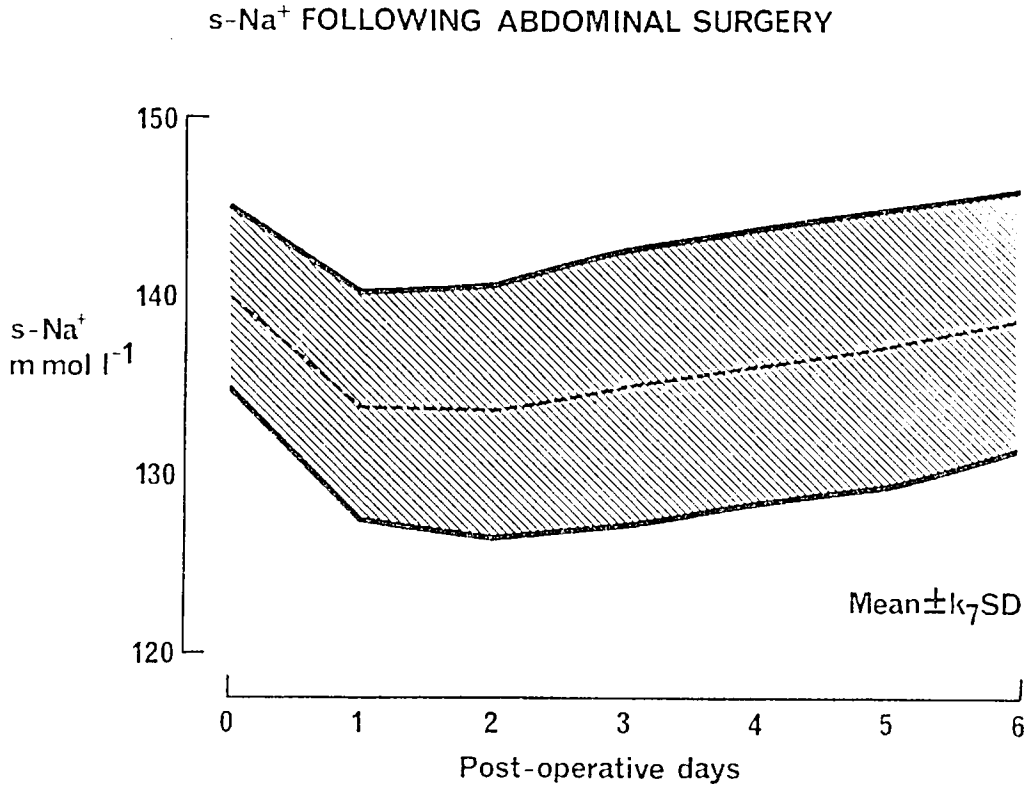


Figure 3.2

Ninety-five per cent tolerance limits for s-Na^+ data following uncomplicated surgery

The serum osmolality after uncomplicated surgery followed a similar pattern. A strong linear relationship exists between serum osmolality and Na^+ concentration (Fig. 3.3), the equation of the regression line of serum osmolality on serum Na^+ being:

$$s\text{-}Osm = 1.86(s\text{-}Na^+) + 18.74; \quad p < 0.001$$

A similar relationship exists between observed and calculated serum osmolality (Fig. 3.4):

$$Obs\text{-}Osm = 0.97[Calc\text{-}Osm] + 15.11; \quad p < 0.001$$

Unlike the serum Na^+, there was no consistent pattern in the serum K^+ levels.

3.52 Isotope studies.

In 14 uncomplicated patients, by measuring Na_e and TBW and deriving K_e with corrections of these values for external balance over six post-operative days, a linear regression (Fig. 3.5) was demonstrated between serum Na^+ concentration and the sum of Na_e and K_e divided by TBW corrected for external balance:

$$s\text{-}Na^+ = 0.85 \frac{Na_e + K_e}{TBW} + 22.11; \; p < 0.001$$

(Appendix 3.4)

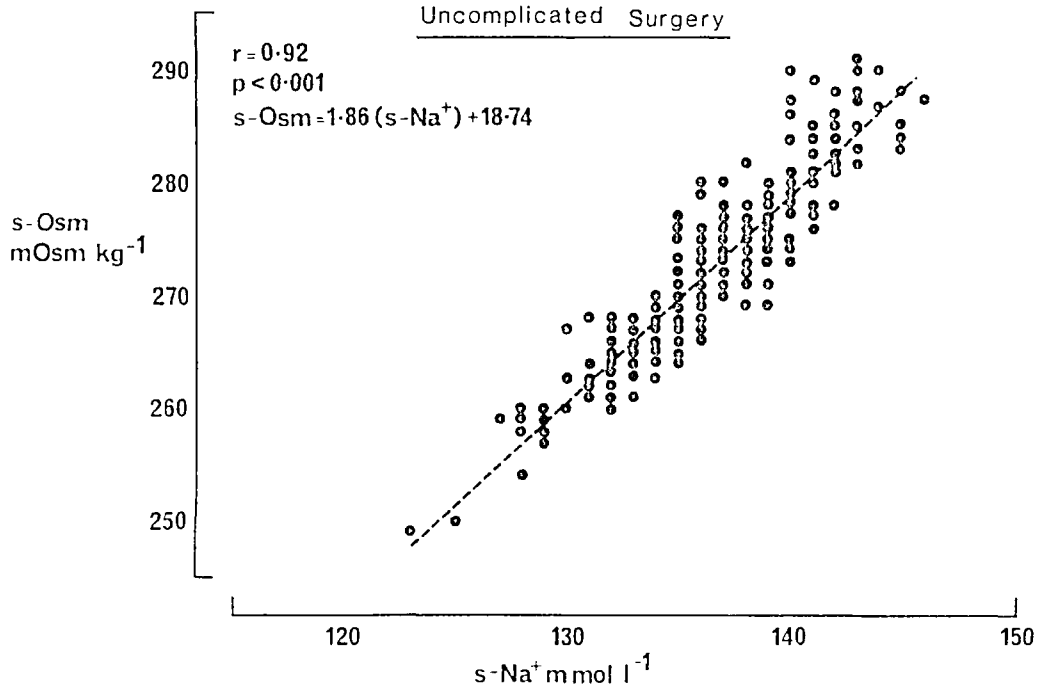


Figure 3.3

Regression plot of the relationship between serum osmolality and serum Na^+ following uncomplicated surgery in 50 patients.

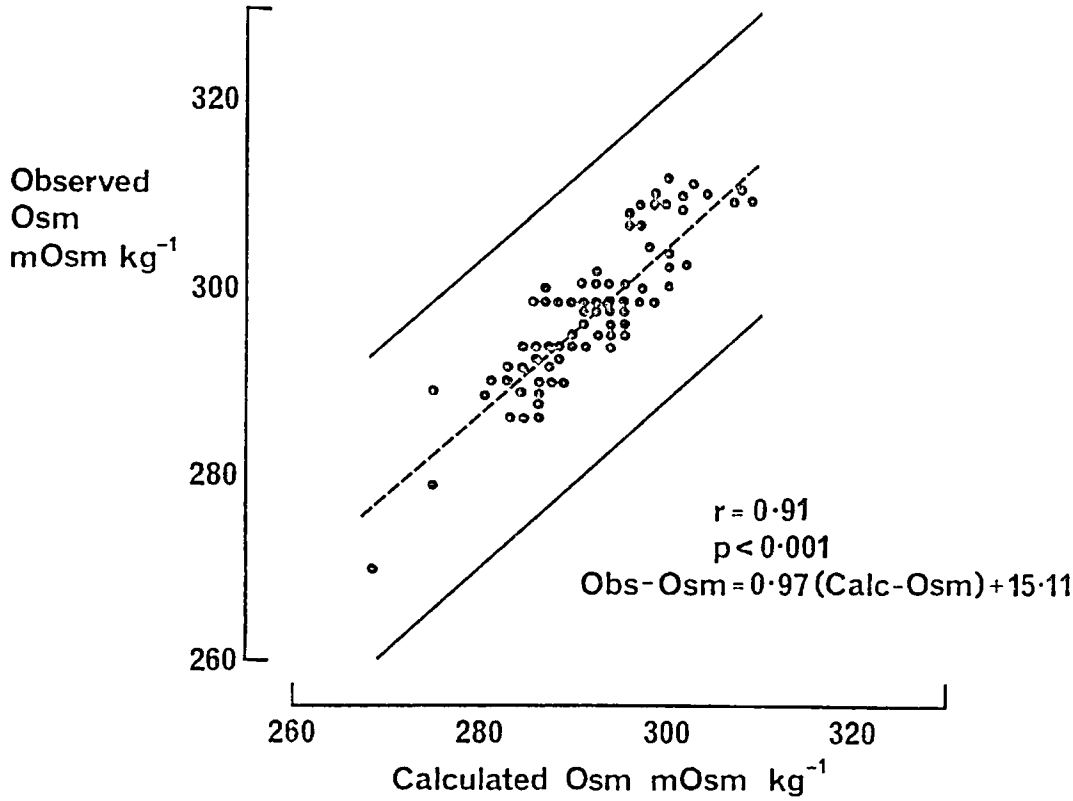


Figure 3.4

Regression plot of the relationship between observed serum osmolalility and calculcated serum osmolality.

Calculated serum osmolality = $2(Na^+ + K^+)$ + urea + glucose

Ninety five per cent tolerance limits are constructed for the patients folowing uncomplicated surgery

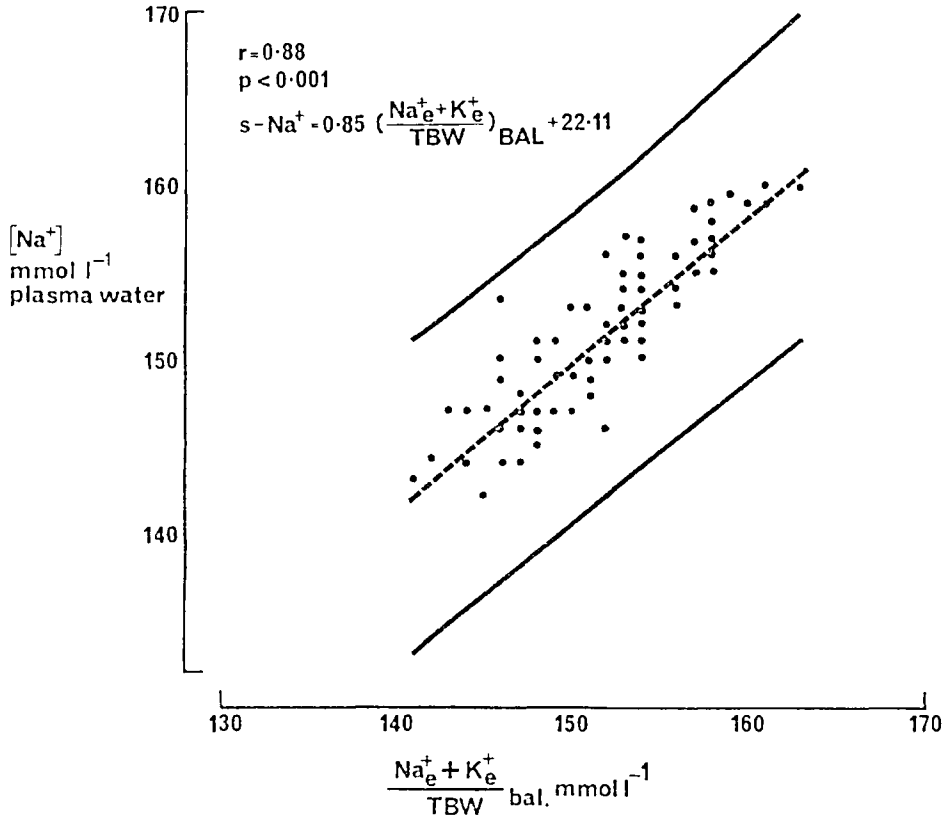


Figure 3.5

The relationship between s-Na^+ concentrations per litre of plasma water and the ratio of exchangeable sodium plus exchangeable potassium per total body water corrected for daily balance over 6 post-operative days. Ninety-five per cent tolerance limits defined the uncomplicated population studied.

3.53 Restricted regimen.

Figure 3.6 compares the group on a restricted fluid regimen with the group on a conventional fluid regimen. On a more restricted fluid regimen there was no significant difference in serum Na^+ concentration by post-operative Day 5 in comparison with pre-operative values. There was a significant difference in the fall of serum Na^+ on post-operative Day 2 between the groups ($p < 0.001$). The clinical course of the patients on a more restricted regimen was unremarkable.

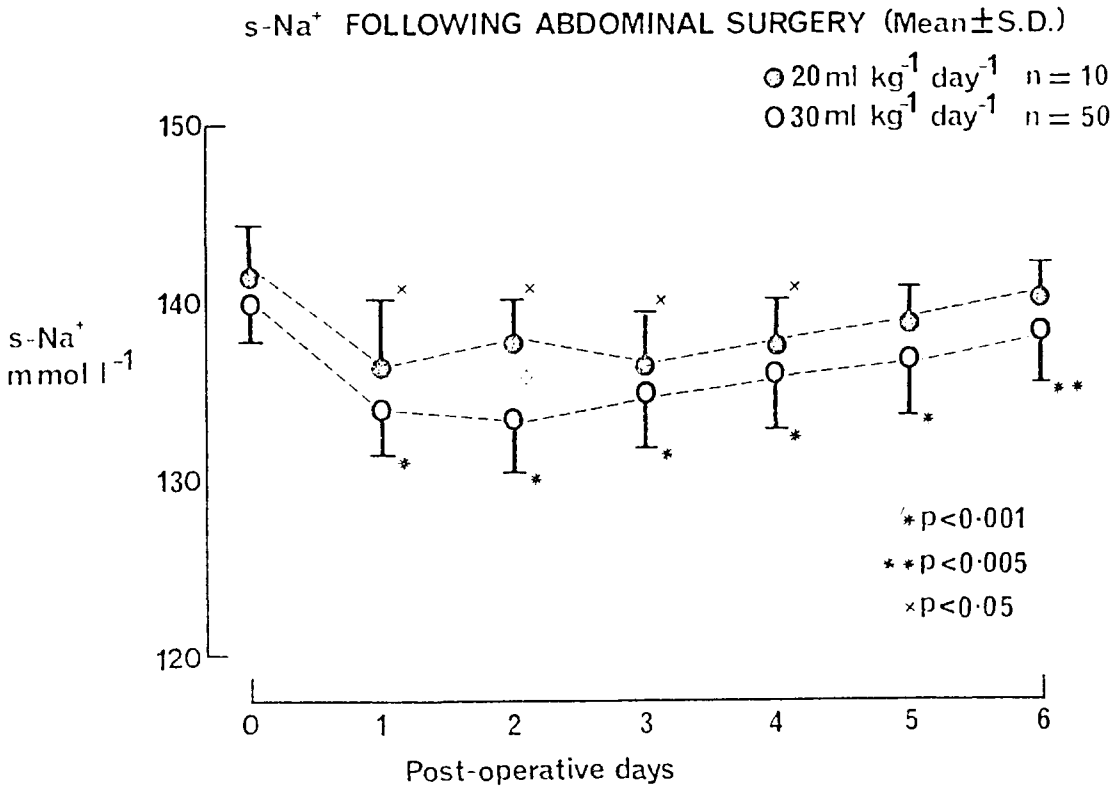


Figure 3.6

The mean (± SD) values of serum Na^+ concentration over 6 post-operative days compared with pre-operative values (day 0). The patients given a 'conventional' fluid regimen (o----o) are compared with those given a restricted fluid regimen (●----○).

3.6 Discussion

The finding of a serum Na^+ concentration below the normal range (135 to 145 mmol/l) is arbitrarily taken as the level below which hyponatraemia exists. Hyponatraemia is often unsuspected clinically and only comes to light when blood urea and electrolytes are measured routinely.

The magnitude of the problem is reflected in the incidence of finding a low serum Na^+ concentration in hospital patients variously reported to be between 20 and 50 per cent (Flear and Singh, 1973). It has been suggested that a decrease in serum Na^+ concentration results from disturbances caused by illness, the extent of which determines the size of the reduction (Weston et al., 1958). Danowski, Fergus and Mateer (1955) reported that of patients who developed hyponatraemia, 33-50 per cent died.

From this viewpoint, it would appear that any lowering of serum Na^+ concentration must be considered to reflect illness. This is supported by the observations that serum Na^+ concentrations do not decrease in healthy persons admitted to hospital (Deitrick et al., 1948; Moore and Ball, 1952).

On the one hand, correction of hyponatraemia is often both unnecessary and hazardous, but on the other hand severe

hyponatraemia may contribute to patient morbidity and mortality. Severe hyponatraemia of rapid onset can be fatal - headache and fatigue progressing to cramps, nausea, vomiting, diarrhoea and delirium; the symptoms can progress to convulsions, unconsciousness and death. A gradual reduction in serum Na^+ concentration over several days or weeks may pose little, if any, threat to survival.

In the context of injury, during the phase of Na^+ retention there is often a paradoxical fall in serum Na^+ concentration (Moore and Ball, 1952). This is usually slight and begins soon after injury, and recovers spontaneously after several days. In severe injury, however, and especially after extensive burns or where sepsis is a complication, hyponatraemia may be prolonged and severe. In most patients it appears to be of no clinical importance, but the more severe changes often cause concern. Patients with marked hyponatraemia are usually very ill, but the extent to which hyponatraemia contributes to the illness is not clear, and opinions differ as to the cause of hyponatraemia (Hunt, 1972).

Though many thousands of serum electrolyte investigations are done after surgical procedures, little attempt has been made to define the normal pattern of change in serum Na^+ concentrations after injury. Restriction on the excretion of water by the kidneys after injury is one factor in causing a fall in serum Na^+ concentration and osmolality if water

administration is continued (LeQuesne and Lewis, 1953). The extent of this after standard surgical insult under general anaesthesia using a conventional fluid regimen has never been rigorously defined. The data in this chapter provide firm information on normals. Only when it can be definitely stated that in the surgical patient the serum Na^+ concentration should be within a particular range can abnormalities be confidently identified. With reference to a confidence band (Fig. 3.2) we can state that if any other single sample should lie outside these limits, it has a defined probability of coming from a different population of co-variables (Ludbrook and Dudley - in press).

The strong correlation between serum Na^+ concentration and serum osmolality indicates that dilution is the major factor in the hyponatraemia of uncomplicated surgical insult. The similar relationship between observed and calculated osmolality suggests that no new ions were entering the ECF space and carrying water with them to cause dilution.

Studies of body composition using isotope dilution techniques indicate the following relationship:

$$s\text{-}Na^+ = k.\frac{Na_e + K_e}{TBW}$$

(Moore et al., 1956; Edelman et al., 1958).

These techniques do not permit the frequent determinations which are necessary to test this relationship during the acute changes which follow injury in a given patient. Serial

determinations are possible when daily balance measurements are used to revise Na^+, K^+, and water content so that a value for serum Na^+ can be calculated for each day:

$$s\text{-}Na^+ = k\frac{(Na_e + Na^+_{BAL}) + (K_e + K^+_{BAL})}{TBW + \text{water balance}}$$

In the wide range of surgical procedures studied, the linear regression between serum Na^+ concentration and the sum of Na_e and K_e divided by TBW (an indicant of body tonicity) over six post-operative days provides further independent evidence that dilution accounts for the changes.

The final evidence to support dilutional hyponatraemia is that changes are proportionately less in patients given a restricted fluid regimen. That their clinical course was unremarkable indicates that 'conventional' fluid regimens are almost certainly too liberal.

This study has provided firm information on normal behaviour in standard circumstances. Current post-operative fluid regimens cause dilutional changes which persist for longer than has been previously thought. If these are the consequence of ADH activity, they cannot easily be overcome and this is an argument for more restricted fluid regimens than are currently practised.

In the surgical patient, there are potentially other factors that could alter the serum Na^+ concentration. A reduced serum Na^+ level has been observed following a period of starvation (Consolazio et al., 1967; Johnson et al., 1982); pre-

operative serum Na^+ levels were all within the normal range in the patients presented in the present study. Evidence also exists that changes in the "setting of the osmostat" may occur (Orloff et al., 1959; Earley and Sanders, 1959) to preserve a less than normal level of serum Na^+ concentration. The mechanism proposed is that osmotic gradients also affect the "osmoreceptors" causing shrinking or swelling of the latter which might serve as the afferent impulse for regulating release of ADH (Verney, 1947). In the new steady state, there would be a normal cell volume but a low ICF and ECF osmolality; ADH levels would appear excessive when related to the serum Na^+ and osmolality levels. Though much has been written on ECF volume expansion and contraction allowing stretch receptors in the capacitance vessels to alter ADH secretion (Zehr et al., 1969; Johnson et al., 1970) the evidence for "osmostat re-setting" is still largely circumstantial.

Though there may be more than one cause of a low serum Na^+ concentration, the results presented in this chapter indicate that the dominating cause is simple dilution, at least following uncomplicated surgical injury. The possibility of release of intracellular solutes and a decline in Na^+ concentration gradient across cell membrane in the genesis of hyponatraemia will be the subject of the next two chapters.

3.7 Summary

Using a standard intravenous fluid regimen (30 ml/kg of water and 90 mmol of Na^+/24 h), a prospective study for six days on 50 patients undergoing major abdominal surgery established a confidence band for change in serum Na^+ concentration. On this management serum Na^+ concentration and osmolality always fell, and even at six days had not uniformly returned to pre-operative levels. There was a strong linear relationship between serum osmolality and Na^+ concentration (s-Osm = 1.86 [s-Na^+] + 18.74; $p < 0.001$) indicating that dilution is the major factor following uncomplicated surgery. A similar relationship existed between observed and calculated serum osmolality (Obs-Osm = 0.97 [Calc-Osm] + 15.11; $p < 0.001$) which suggests that no new ions were entering the ECF space and carrying water with them to cause dilution. More detailed investigations of 14 patients by isotope dilution provided independent evidence of dilutional change: a linear regression was demonstrated between serum Na^+ concentration and the sum of Na_e and K_e divided by TBW corrected for external balance changes.

Ten further patients, subject to the same magnitude of surgery, were next studied on a more restricted fluid regimen (20 ml/kg of water and 60 mmol of Na^+/24 h). Dilutional changes were proportionally less in such patients and their clinical course unremarkable.

It is concluded that following uncomplicated surgery, simple dilution accounts for the changes in serum Na^+ and osmolality. The range of change in serum Na^+ concentrations has also been established for a standard fluid regimen. The utility of such an approach will be the subject of the next Chapter.

C H A P T E R 4

IDENTIFICATION OF OSMOLAL GAPS IN POST-SURGICAL HYPONATRAEMIA

4.1 INTRODUCTION

The work presented in Chapter 3 of this thesis has established that if a standard fluid and electrolyte regimen is administered to the patient after injury, dilution of body water takes place -that is, unlike the normal response to a hypotonic load which is the excretion of the excess, the post-surgical patient retains water. This is a precise confirmation of the long-held interpretations of LeQuesne and Lewis (1953) and Dudley et al. (1954) that non-osmotic secretion of ADH takes place after injury.

Though the evidence already cited is strong that post-surgical hyponatraemia is caused chiefly by water retention, others (Tindall and Clark, 1976) have reported some instances of disproportionate dilution in surgical patients with consequent large 'osmolal gaps', supporting the view that there may be change in the permeability of the cell membrane (Flear and Singh, 1973). Furthermore, these 'non-dilutional' trends have been supported by observations that a discrepancy was found between changes in serum Na^+ and external balance of water during recovery from hyponatraemia (Jaenike and Waterhouse, 1959) and when ADH was noted to increase the apparent exchangeable Na^+ lying outside

the ECF space of muscle (Kaye, 1966).

These observations have been sporadic rather than systematic and were made, at least in part, on patients who were seriously ill. Nor were the changes observed standardised with respect to total body water or fluid and electrolyte therapy in the post-operative phase.

4.2 Osmolal Gaps and Hyponatraemia

Osmolality is simply a convenient way of expressing osmotically active solute concentration. It is measured commonly by freezing point depression techniques with an osmometer which measures one of the colligative properties of a solution (Bevan, 1978). Osmolality is expressed in milliosmoles (mOsm) per kilogram of water - not of serum or urine, but of serum or urine water.

Na^+ is dissolved in only about 93 per cent of a given volume of plasma, the remaining seven per cent being occupied by protein and lipid. If the serum Na^+ concentration is expressed more rigorously as per litre of serum water, rather than per litre of serum, it is some seven per cent higher; in the absence of an abnormally raised lipid-protein fraction of blood the correction factor for serum Na^+ is small, and in most examples of hyponatraemia it is valid to equate changes in serum Na^+ concentration with changes in serum water concentration (Swales, 1975).

Osmolality is a measure of particle numbers, irrespective of size or weight; the smallest ion has the same osmotic effect as the larger fat or protein particle. Thus, ions and small molecules, because of their relatively large numbers, determine osmolality. Serum osmolality can be calculated as follows:

$$\text{Calc-Osm} = 2(Na^+ + K^+) + \text{urea} + \text{glucose}$$

where the concentrations of Na^+, K^+, urea and glucose are expressed in mmols per litre. Normally, glucose and urea contribute no more than 10 mOsm/kg, so that serum osmolality is usually only slightly higher than twice the serum Na^+ (Edelman et al., 1958; Burke, 1978).

Occasionally, the measured or observed osmolality (Obs-Osm) is higher than the calculated osmolality (Calc-Osm) in non-lipaemic serum, and may be abnormally high. This discrepancy between Obs-Osm and Calc-Osm - "osmolal gap" - indicates the presence of other osmotically active particles not accounted for by the above equation of Calc-Osm. These osmolal gaps have been reported during the administration of mannitol (Aviram et al., 1967), the ingestion of ethanol (Robinson and Loeb, 1971) and other, often toxic, substances (Glasser et al., 1973).

There is a view that many cases of hyponatraemia arise because of a shift of Na^+ ions from the extracellular to the intracellular compartment - in contrast to the dilutional hyponatraemia found when water excretion is defective. Two lines of evidence support the concept of Na^+ re-distribution. Firstly, intracellular Na^+ levels are increased in the cells of patients with various grave illnesses (Smith et al., 1963; Welt et al., 1967; Cunningham et al., 1971). Secondly, if hyponatraemia were caused by simple dilution, there should be a direct relation

between falls in Na^+ level and serum osmolality, accompanied by a gain in total body water. In many cases of hyponatraemia there was no evidence of a gain in body water, and falling serum Na^+ was not matched by low serum osmolality (Flear and Singh, 1973).

It has been suggested that a disturbance in the relationship between serum Na^+ concentration and serum osmolality affords an indication of increase in cell membrane permeability (Flear, 1970; Flear and Singh, 1973). The escape of normally non-diffusible solutes from cells through leaky membranes and the attendant isosmotic redistribution of water is held to account for the hyponatraemia and resultant osmolal gaps (Flear et al., 1980). In vitro studies by these workers have suggested that there is a considerable net leak of amino acids and that the greater the osmolality, the greater the amino acid leak.

Boyd and Mansberger (1968) reported osmolal gaps in animal studies and in a small group of patients with haemorrhagic shock. In ill patients with major injuries, Boyd and co-workers (1970) noted that the observed osmolality (Obs-Osm) on admission was substantially greater than that calculated (Calc-Osm) from measured serum levels of Na^+, urea and glucose, and that it fell on resuscitation. In patients with haemorrhagic shock the osmolal gaps were more marked and these authors suggested that such measurements of osmolalities might serve as a prognostic index in shock following major trauma.

4.3 Objective

Though the presence of an osmolal gap has been taken as supportive evidence that there may be change in cell membrane permeability, only sporadic reports of osmolal gaps have been made in relation to the hyponatraemia of surgical injury (Boyd et al., 1970; Tindall and Clark, 1976; Flear et al., 1980). Furthermore, a systematic approach for its precise identification and interpretation in sick hyponatraemic patients is lacking in clinical practice.

The data presented in Chapter 3 of this thesis demonstrate that following uncomplicated injury, changes are dilutional and a normal range for serum Na^+ concentrations established under standard circumstances. To investigate the utility of this approach, the following question was posed:

Given the Understanding that Changes are Dilutional and Having Established the Range of Change, What Value Does This Have at the Bedside Should We Find Departures from the Normal Range?

4.4 Subjects and Methods

Figure 4.1 shows the chart attached to the bedside of patients presenting for major abdominal surgery. Departures from the normal range signalled to us abnormal behaviour.

In seven patients who were ill before surgery (weight loss greater than 10 per cent, chronic sepsis) (Table 4.1), and whose post-operative course was complicated, the serum Na^+ concentration, osmolality and body composition were matched against the 'normal' information derived and presented in Chapter 3.

Serum Na^+ and K^+ concentrations were measured (Corning 450 flame photometer) and glucose and urea (SMA-12, Technicon) determined. Observed serum osmolality (Obs-Osm) was determined by the freezing point depression method (Advanced Osmometer). Calculated serum osmolality (Calc-Osm) was obtained as follows:

$$\text{Calc-Osm} = 2(Na^+ + K^+) + \text{urea} + \text{glucose}$$

All extrarenal fluid losses were recorded and daily clinical balance measurements were charted. (Appendix 4.1).

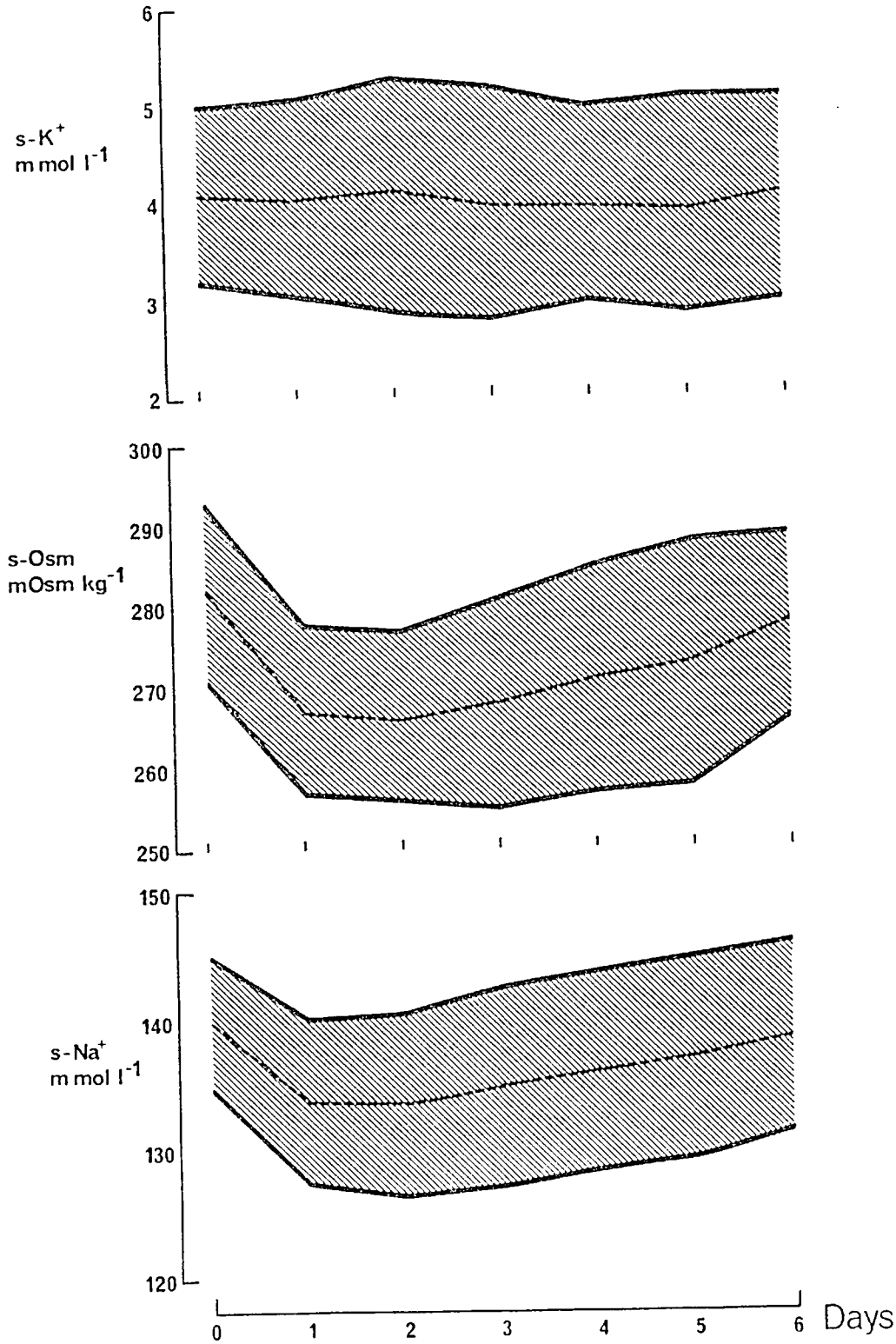


Figure 4.1

Bedside diagnostic chart : ninety five per cent tolerance limits for serum Na^+, osmolality and K^+ following uncomplicated surgery

TABLE 4.1

Patients with 'Osmolal Gaps' and their course

Patient:	Sex:	Age (yr):	Diagnosis:	Operation:	Post-op complications	Weight loss (% Ideal body wt)	Sepsis:	Outcome:
1 FC	M	56	Ca-Stomach	Total Gastrectomy	Anastomotic leak; Respiratory Failure	12%	Subphrenic Abscess	Discharged
2 GW	F	75	Ampullary Ca	Whipple's Procedure	Cardio-Respiratory Failure	15%	Septicaemia	Died
3 SBR	M	55	Ca-Colon	Colectomies	Obstructive Jaundice	11%	Septicaemia	Died
4 RB	F	59	Ca-Stomach	Total Gastrectomy	Failure to thrive	18%	-	Discharged
5 FA	M	64	Ca-Stomach	Total Gastrectomy	Respiratory Failure	12%	Subphrenic Abscess	Discharged
6 HJ	M	87	Small Bowel Obstruction	Small Bowel Resections	Recurrent Obstructions	13%	-	Died
7 VP	M	59	Ca-Rectum	Abdomino-perineal excision	Recurrence	14%	-	Discharged

4.5 Results

In seven critically ill surgical patients, deviations of serum Na^+ concentration from the 95 per cent tolerance limits established from the data of healthy patients were observed (Table 4.2).

Furthermore, when the ill patients' data were matched against those of isotope and osmolality studies established for the uncomplicated patients, there were two important findings. First, in sick surgical patients the observed osmolality was higher than the calculated osmolality (Fig. 4.2). This difference could be expressed in terms of osmolal gaps ranging from 20-30 mOsm/kg.

Second, for each value of serum Na^+ concentration there was a higher value in the ratio of Na_e, K_e and TBW (Fig. 4.3).

TABLE 4.2

Data for observed and calculated osmolalities

Patient:	s-Na^+ (mmol/l)	S-K^+ (mmol/l)	s-Urea (mmol/l)	s-Glucose (mmol/l)	Obs-Osm (mOsm/kg)	Calc-Osm (mOsm/kg)	Osmolal Gap (mOsm/kg)
1	124.2	3.1	6.2	4.5	291	265	26
2	125.6	4.0	7.5	5.2	299	272	27
3	125.0	3.5	7.3	6.4	299	271	28
4	126.5	3.7	6.0	4.2	297	271	26
5	128.3	4.0	8.2	5.0	303	278	25
6	127.4	3.6	7.5	4.0	301	274	27
7	129.9	3.2	7.0	4.2	303	277	26

Figure 4.2

In critically ill surgical patients (x) 'osmolal gaps' (Observed osmolality > calculated osmolality) ranging from 20 - 30 mOsm/kg were identified.

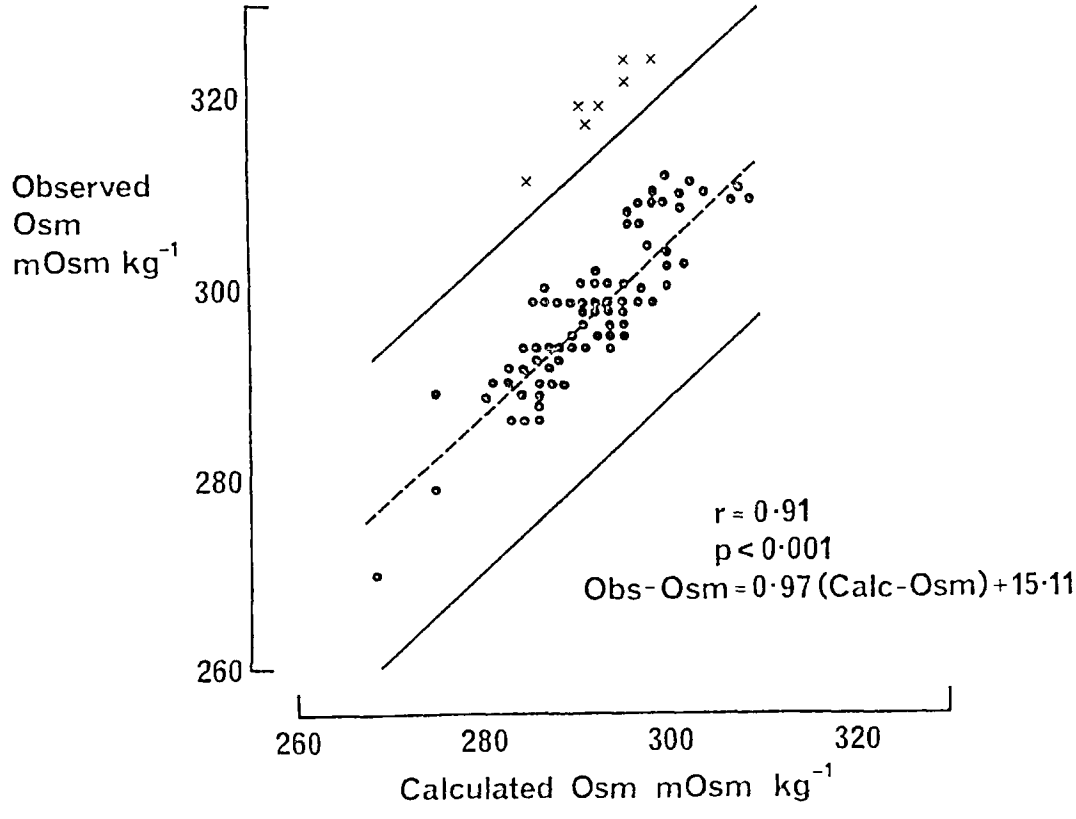
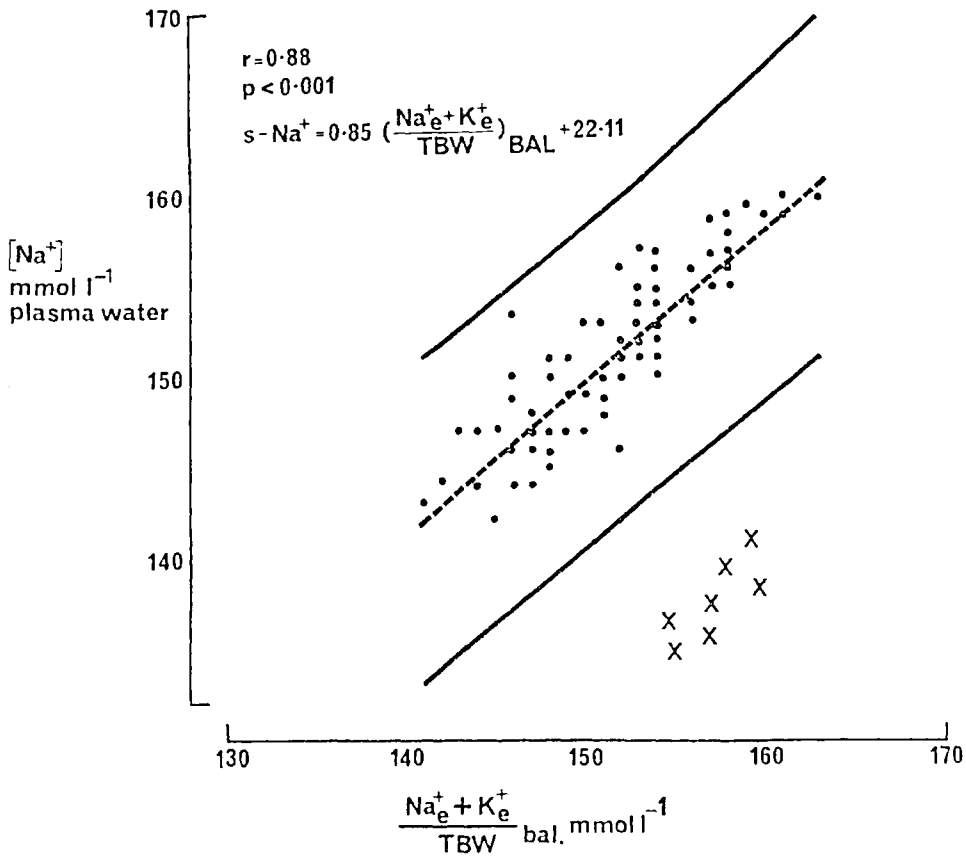


Figure 4.3

Relationship of serum Na^+, Na_e, K_e, TBW in sick surgical patients (x)



4.6 Discussion

Low serum Na^+ in a seriously ill patient is a bad sign, whatever the underlying illness (Danowski et al., 1955). The cause of this biochemical complication is usually said to be obscure, and various mechanisms have been proposed to explain post-traumatic hyponatraemia (Welt et al., 1967; Cunningham et al., 1971; Flear and Singh, 1973). However, the level of serum Na^+ at which "non-dilutional" abnormalities may operate has never been well defined. Departures from the confidence band have signalled to us "non-dilutional" trends, and osmolal gaps were identified.

In severe illness, particularly if there is tissue hypoxia, it has been suggested that adenosine triphosphatase (ATP) dependent active transport of Na^+ across cell membranes is impaired. Consequently, membrane permeability to Na^+ ions is increased and Na^+ ions can then leak back into cells down their concentration gradient (Welt et al., 1967). Na^+ is thus lost from ECF to ICF and hyponatraemia results. In such cases, there is no concomitant fall in serum osmolality which would be expected if the hyponatraemia was purely dilutional as a result of water retention (Flear and Singh, 1973). However, opponents of this view have pointed out that Na^+ entry into cells would result in a concomitant shift of water to the ICF, so hyponatraemia would

not result (Leaf, 1962) unless there was an 'osmotic inactivation' of intracellular Na^+ preventing water entry.

In the extensive studies of Edelman et al. (1958) and Moore et al. (1963) there was no indication for such Na^+ binding. That disturbances of Na^+ transport occur in some conditions, such as uraemia, has been carefully demonstrated (Welt et al., 1967); there is, however, no suggestion that such abnormalities can account for hyponatraemia in clinical situations.

Even if Na^+ migration were to cause hyponatraemia, the renal response would normally be to correct the serum hypotonicity (Swales, 1975). It is therefore necessary to postulate an additional renal abnormality which would produce hyponatraemia without Na^+ shifts.

In that the observed osmolality was higher than the calculated osmolality in sick hyponatraemic patients, support is provided for the alternative explanation of "non-dilutional" hyponatraemia, that is, the release of osmotically active solutes with their water from the cells of these sick surgical patients. Furthermore, deviations from the normal relationship between serum Na^+ and body spaces, as defined by isotope studies, suggest that in these patients the ratio

$$\frac{Na_e + K_e}{TBW}$$

no longer accounts for total body fluid tonicity.

Although the exact nature of these non-ionic molecules associated with osmolal gap remains unknown, the identification of such osmolal disturbances in post-surgical hyponatraemia may have treatment implications. This will be further developed in Chapter 8 of this thesis, when the rational use of glucose-potassium-insulin therapy in hyponatraemia is discussed.

4.7 Summary

Though the evidence is strong that post-surgical hyponatraemia is caused chiefly by water retention (see Chapter 3), instances of disproportionate dilution in surgical patients with consequent osmolal gaps have been reported. These observations have been sporadic rather than systematic and the changes observed were not standardised with respect to total body water or fluid and electrolyte therapy in the post-operative phase.

In seriously ill patients, various mechanisms have been proposed to explain post-traumatic hyponatraemia but the level of serum Na^+ at which non-dilutional abnormalities may operate has never been well-defined. Departures from the confidence band (established in Chapter 3) have signalled to us non-dilutional trends in seven critically ill patients whose post-operative course was complicated. In this group osmolal gaps of 20-30 mOsm/kg were identified.

Furthermore, deviations from the normal relationship between serum Na^+ and body spaces, as defined by isotope studies, suggest that either Na^+ migration or, more likely, an expulsion of water and non-ionic solutes from the cells of sick surgical patients can explain these results.

This study, taken together with those in Chapter 3, has clearly demonstrated the utility of having at hand firm information on normal behaviour in standard circumstances. It is concluded that current post-operative fluid regimens cause dilutional changes; these are predictable and prolonged and provide a yardstick for use in management of both the healthy and the ill surgical patient.

C H A P T E R 5

TRANSCELLULAR MOVEMENT AND INTRACELLULAR CONCENTRATION OF SODIUM IN ERYTHROCYTES AFTER SURGERY

5.1 INTRODUCTION

It is now evident that the diffusion of Na^+ into, and K^+ out of the cell down their concentration gradients is balanced by the active transport of these cations against the same concentration gradient (Sweadner and Goldin, 1980). This gradient can be abolished by cooling, or by metabolic inhibitors; it is therefore maintained by an active process which requires metabolically-derived energy. It follows that the ratio between ICF and ECF Na^+ represents a steady state resulting from leakage of Na^+ into the cells, along an electrochemical and concentration gradient, and active pumping of Na^+ from the cells.

The most elegant and quantitative characterisation of active transport of Na^+ and K^+ employed re-sealed red cell ghosts (Glynn, 1968). The metabolic energy required can be derived from glucose (Harris, 1941) via the anaerobic glycolytic pathways which are available to the human erythrocyte.

The energy stores of the cell are primarily in the form of the high energy phosphate bonds of adenosine triphosphate (ATP), and the work of Post et al. (1960) and Dunham and Glynn (1961) has shown that the release of energy from ATP could be brought about by the action of an enzyme system (an ATPase) located within the transporting membrane itself. Further evidence has amply confirmed that this enzyme is, indeed, the main energy transducer concerned with Na^+ transport across cell membranes (Skou, 1965). The cell volume is thus regulated indirectly by the activity of the Na^+-K^+ pump.

5.2 Disorders of Na^+ Transport - "The Sick Cell Syndrome"

The work of Leaf (1959; 1970) has demonstrated that cellular swelling could be prevented by incorporating a non-diffusible, osmotically active solute in the culture medium. Leaf suggested that cellular swelling was produced by impairment of the Na^+ pump mechanism which normally maintains the Na^+ gradient across the cell membrane. Normally, this counterbalances the osmotic pressure exerted by intracellular non-diffusible colloid. Impairment of this pump allows Na^+ to diffuse into the cell, which consequently swells until a new steady state is reached.

Welt et al. (1964) demonstrated that a proportion of uraemic subjects had a high concentration of Na^+ in their red blood cells. Considered in isolation, Na^+ efflux from these cells was normal. However, in normal red cells, increased intracellular Na^+ stimulates Na^+ efflux. When considered in relation to the cell Na^+ content, efflux was therefore depressed (the fraction of cell Na^+ transported in unit time -the fractional Na^+ efflux). Leucocytes from uraemics have also been shown to share the same abnormality of Na^+ efflux (Patrick and Jones, 1974). Subsequently, a similar defect has been found in other disease states.

The diagnosis of extracellular/intracellular Na^+ shifts is a popular one. Cunningham et al. (1971) studied the skeletal

muscle of a group of patients with severe debilitating disease. Transmembrane potential was reduced in these patients and "intracellular" Na^+ (assessed by Cl^- distribution) increased. They suggest that there is a close analogy with Welt's studies of red cells in uraemia. For proponents of the view that such shifts give rise to hyponatraemia, it is disconcerting to note that serum Na^+ was normal in most of these patients.

The term "sick cell syndrome" has been loosely applied, generally with the explicit or implicit suggestion that hyponatraemia can be attributed to migration of Na^+ into the intracellular fluid as a consequence of a disturbance of membrane transport (Swales, 1975). Flear et al. (1980) promote the view that the primary underlying event in hyponatraemia is alteration of the normal characteristics of the outer membranes of cells provoked by such events as impaired tissue perfusion, systemic or tissue hypoxia, and bacterial endo- or exotoxins. Although there is evidence for such Na^+ migration in certain disorders (Hoffmann and DeNardo, 1968), its relevance to the development of common clinical hyponatraemia remains doubtful.

5.3 Objective

Amongst the many metabolic alterations associated with major trauma or surgery is a transient state of extracellular hypotonicity with hyponatraemia (Moore, 1959; 1962; Thomas and Morgan, 1979). The evidence is strong that such acute disorders of tonicity following uncomplicated surgery are chiefly dilutional and consequent upon water retention (Dudley et al., 1954; Chan et al., 1980). However, when injury is protracted or where sepsis is a complication, hyponatraemia may be severe and prolonged, and in this situation Danowski et al. (1955) have suggested that hyponatraemia is associated with a bad prognostic signficance, whatever the underlying illness.

It has been postulated that change in transmembrane Na^+ flux is a possible cause of hyponatraemia (Flear and Singh, 1973). Changes in Na^+ flux have also been suggested as the cause of the "sick cell syndrome" - a condition said to be characterised by a low ECF and a high ICF Na^+ concentration (Welt et al., 1964). Though impairment of cellular integrity and membrane transport has been documented in experimental models of low flow states (Shires et al., 1972), its relevance to the development of hyponatraemia in the clinical situation is doubtful (Leaf, 1962).

The present study was undertaken:

To Establish If There Is Any Evidence of Membrane Changes in Relation to Surgery by Measuring Intracellular Na^+ Concentration and Transmembrane Flux After Uncomplicated Surgical Insults and in Seriously Ill Surgical Patients.

5.4 Materials and Methods

Nine healthy patients undergoing uncomplicated elective abdominal surgery - vagotomy and pyloroplasty, cholecystectomy and colonic resection - were studied (Table 5.1). Fourteen seriously ill patients with gross sepsis, weight loss in excess of 10 per cent of healthy weight, were also studied serially. At the time of study no patient was alkalotic, hypokalaemic, jaundiced, had renal failure or any other disease states previously associated with decreased Na^+ efflux. None was receiving digoxin. Informed consent was obtained from all patients studied.

A. Preparation of erythrocytes: Venous blood was collected in a heparinized syringe before pre-medication and 24 hours after the beginning of surgery or, in the sick patients, at intervals as appeared indicated. Measurements were made within 30 minutes of collection. The red cells were separated in a refrigerated centrifuge (4^oC) at 3000 G, plasma retained and buffy coat discarded.

Flux in this text refers to the total amount of Na^+ actively pumped out of or flowing into the cells per hour, the unit of measurement being mmol per litre cells per hour. Na^+ flux was measured in Krebs' solution to which glucose (5 mmol/l) had been added, and/or in the patients' own plasma. The Na^+ influx and efflux were calculated from a modified method

TABLE 5.1

Clinical details of patients for Na^+ flux studies

(a) Uncomplicated elective surgery and intra-operative details

Patient:	Operation:	IV-Hartmann's (ml):	Na^+ load (mmol):	Blood (units)
1 (D)	Anterior Resection	950	125	2
2 (W)	Abdo-perineal excision	1020	134	3
3 (M)	Laparotomy	460	60	0
4 (H)	Right hemicolectomy	850	112	2
5 (H)	Cholecystectomy	500	66	0
6 (D)	Vagotomy and Pyloroplasty	460	60	0
7 (B)	Vagotomy and Pyloroplasty	500	66	0
8 (M)	Cholecystectomy	500	66	0
9 (O)	Cholecystectomy	420	55	0

(b) Seriously ill patients and their course

Patient:	Sex:	Age (yr):	Diagnosis:	Operation:	Complication:	Wt. loss: (% healthy wt)	Sepsis:	Outcome:
1 (M)	M	34	Gall-stones	Cholecystectomy	Pyrexia	29%	Subphrenic abscess	Dishcarged
2 (H)	F	65	Ca-colon	Colectomy	Anastomotic leak	18%	Septicaemia	Discharged
3 (D)	M	62	Ca-oesophagus	Oesophagectomy	Failure to thrive	18%	-	Dead
4 (H)	F	72	Ca-stomach	Total Gastrect.	Respiratory failure	12%	-	Dead
5 (C)	M	57	Ca-stomach	Total Gastrect.	Cardio-resp.failure	20%	Septicaemia	Dead
6 (D)	M	65	Ca-oesophagus	Oesophagectomy	Respiratory failure	16%	-	Dishcarged
7 (P)	F	69	Gastric ulcer	Gastrectomy	Respiratory failure	12%	-	Dead
8 (H)	M	19	Road traffic accident	Multiple ops.	Respiratory failure	14%	-	Dishcarged
9 (H)	F	62	Carcinomatosis	Laparotomy	Cardiac failure	16%	-	Dead
10 (M)	F	68	Ca-ovary	Laparotomy	Respiratory failure	18%	-	Dead
11 (C)	F	56	Ulcerative jejunitis	Laparotomy	Failure to thrive	22%	-	Discharged
12 (T)	F	64	Ca-rectum	Abdomino-perineal excision	Pelvic abscess	15%	Septicaemia	Dead
13 (A)	M	64	Ca-stomach	Total Gastrect.	Respiratory failure	12%	Subphrenic abscess	Dishcarged
14 (L)	M	34	Road traffic accident	Multiple ops.	Failure to thrive	17%	-	Discharged

(Appendix 5.1) based on that described by Smith and Samuel (1970).

B. Na^+ influx: The volume of packed cells was added to Krebs' solution or plasma to give a haematocrit value of 3 per cent and then incubated at 37°C for 15 minutes. After 15 minutes' equilibration period, 5 μCi ^{22}Na were added to the red cell suspension and samples taken at 30 and 90 minutes thereafter. The samples were immediately centrifuged at 4°C and the red cells washed three times in cold potassium-free Hartmann's solution (Levin et al., 1968). The red cell mass from each sample was haemolysed by making to 5 ml with water and then the activity of the red cell mass measured along with the supernatant prior to the first wash (Wallac gamma counter, LKB, Sweden) to at least 10^4 counts. The red cell mass was calculated from the haemoglobin and packed cell volume (Makarema, 1974). Influx was estimated by expressing the fraction of counts entering the cells from the supernatant per hour and correcting for Na^+ pumped out of the cells during the study period (Smith and Samuel, 1970).

C. Na^+ efflux: Red cells were incubated at 37°C in plasma containing 25 μCi ^{22}Na for three hours. The cells were washed three times in Hartmann's solution at 37°C. Immediately thereafter cells were added to Kreb's solution or plasma to give a haematocrit of 0.2 per cent. Samples of erythrocytes were then taken immediately and at 20, 40 and 60 minutes. At time zero the

total activity of the samples was determined. The other samples were centrifuged at $4^{o}C$ and the activity of the supernatant determined, together with the haemoglobin concentration (Makarema, 1974). Fractional haemolysis was calculated for each supernatant by comparison with the haemoglobin content of a haemolysed specimen taken at time zero. The flux was then calculated from the equation which is valid for haematocrits less than 0.3 per cent (Smith and Samuel, 1970):

$$\text{Efflux} = \log_n \frac{1 - Na^*_s/Na^*_h}{1 - \text{fractional haemolysis}}$$

where: Na^*_s is the activity of the supernatant in counts/ml/min

Na^*_h is the activity of the haemolysed sample in counts/ml/min.

The fraction of intracellular Na^+ pumped out of the cells per hour (rate constant efflux) can be calculated by plotting the Na^+ efflux value obtained from the above equation against time. The slope of the line is the rate constant for efflux. The total Na^+ pumped per hour is then calculated by multiplying the rate constant by the intracellular Na^+ concentration.

The flux values obtained from the seriously ill patients were, whenever possible, those determined in the patients' <u>own</u> plasma. This may seem arbitrary, but it can be argued that it more truly reflects what is happening in vivo. To a degree, this is confirmed by the results from the two patients with the lowest

plasma Na^+ concentrations, who showed abnormalities in flux values when these were estimated in Kreb's solution, but near normal values in their own plasma (Table 5.2). However, because there was no difference between the flux values obtained in Krebs' solution and plasma in the other seriously ill patients, plasma values were used when available: hence the two patients with severe hyponatraemia were included in analyses using their plasma flux values.

D. Intracellular Na^+ concentration: The osmolality of all the patients' plasma was measured by freezing point depression (Advance Osmometer, Advanced Instruments, Massachusetts, U.S.A.). The erythrocytes were washed in a standard solution containing (mmol/l): KCl (100), $MgCl_2$ (7), $MgSO_4$ (7), NaCl (5), $CaPO_4$ (2) and glucose (6). This solution approximates to human erythrocyte intracellular concentration except that of magnesium which is lower than the solution used. The pH was 7.35, giving an osmolality of 255 mOsm/kg. The final osmolality of the wash was adjusted to that of the patients' plasma by varying the K^+ content. 25 μCi ^{51}Cr EDTA was added to estimate extracellular contamination. This solution was used for three main reasons: (1) to reduce the extracellular contamination by using low Na^+ levels in the wash solution, (2) to reduce to a minimum Na^+ flux during the period of measurement (Schneider, 1974), and (3) to prevent the movement of water across cell membranes due to osmotic pressure differences, thus

TABLE 5.2

Erythrocyte flux values (influx and efflux) from two patients with severe hyponatraemia (plasma sodium 109,119 mmol/l) in comparison to the values obtained from the remaining 12 seriously ill patients. (Mean ± SEM)

	Seriously Ill Patients		Severe Hyponatraemia	
	Krebs'	Plasma	Krebs'	Plasma
INFLUX (mmol/l cell/h)	2.13 ± 0.85	2.75 ± 0.51	5.48 ± 0.17	3.01 ± 0.92
EFFLUX (mmol/l cell/h)	2.81 ± 0.53	2.90 ± 0.46	5.30 ± 0.31	3.45 ± 0.97

preventing dilutions or concentration of intracellular Na^+.

Packed red cells were added to the individually tailored solutions to give a haematocrit of 40 per cent. The red cell suspension was thoroughly mixed and then centrifuged at 3000 G for five minutes at $4^{o}C$. 50 µl of supernatant was added to 4.9 ml of 15mM lithium chloride solution. The remaining supernatant was discarded. Three 50 µl samples of mixed packed cells were treated as per the supernatant sample. All samples were then counted for a minimum of 10^4 counts before Na^+ estimation by flame photometry (Corning 450, U.K.). Cellular Na^+ content was corrected for trapped extracellular fluid.

E. Statistical analysis: These are non-parametric: Wilcoxon signed-rank test for paired data and Mann-Whitney U statistics for unpaired data. Linear regression analysis between Na^+ efflux and intracellular Na^+ was performed by the least squares method.

5.5 Results

Figure 5.1 shows the plasma Na^+ values of all patients studied. The plasma Na^+ levels in the nine healthy patients fell within the 95 per cent tolerance range established for our surgical population following uncomplicated surgery, and these are dilutional trends (Chan et al., 1980).

In the 14 critically ill surgical patients, departures of plasma Na^+ values from this tolerance range were found, and thus were considered unequivocally hyponatraemic.

The flux results of all patients studied are shown in Table 5.3 and the individual results for the uncomplicated patients are shown as paired data in Figure 5.2. There was no significant change between pre- and post-operative Na^+ flux (influx or efflux) in erythrocytes after uncomplicated surgery (Wilcoxon signed-rank test).

When considering the Na^+ flux estimations obtained from the seriously ill patients there was again no difference between influx and efflux (Wilcoxon signed-rank test) and no significant difference between influx and efflux of pre-operative patients and the influx or efflux of the seriously ill patients (Mann-Whitney U statistic).

The erythrocyte intracellular Na^+ concentrations obtained for the above patients are represented in Table 5.4 and Figure 5.3. There is no statistical difference between the pre-

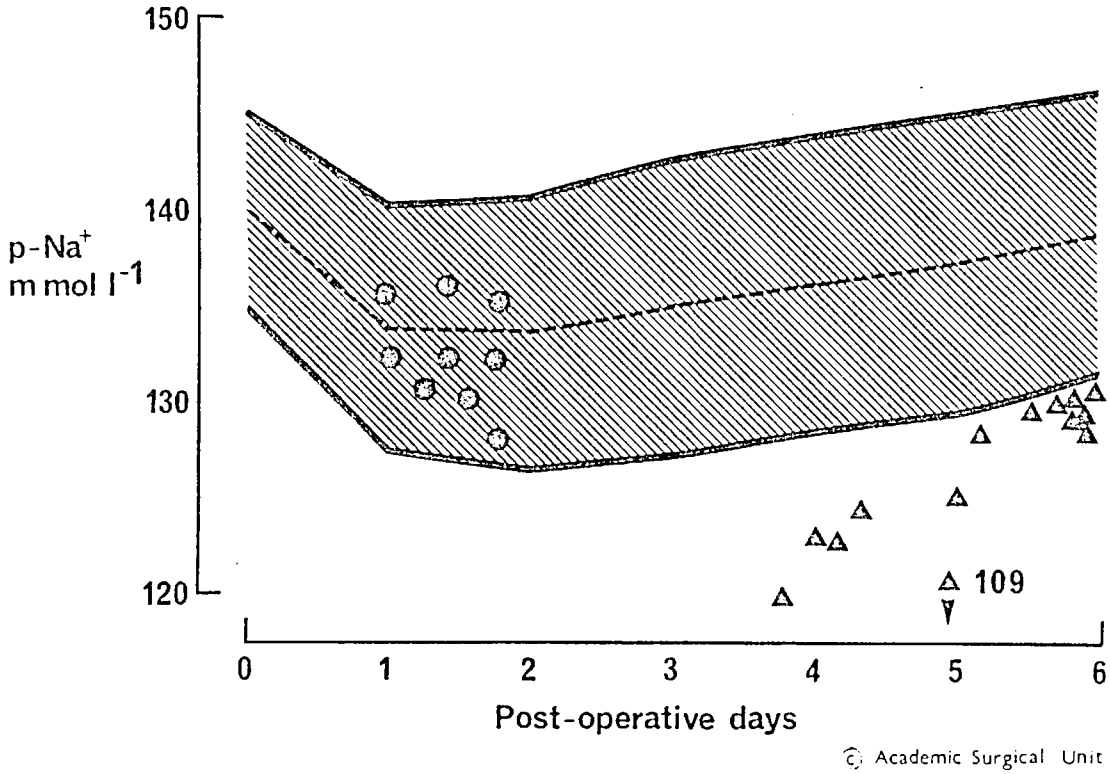


Figure 5.1

Plasma Na^+ values in 9 patients following uncomplicated surgery (o) and in 14 critically ill surgical patients (Δ). The shaded area is the 95 per cent tolerance range for our hospital surgical population

Table 5.3

Flux results (influx and effux) from all patients studied during the trial (Mean ± SEM)

	Influx:	Efflux:
Pre-operative (n = 9)	3.03 ± 0.24	2.90 ± 0.22
Post-operative (n = 9)	3.18 ± 0.24	2.82 ± 0.28
Seriously ill patients (n = 14)	2.80 ± 0.13	3.02 ± 0.24

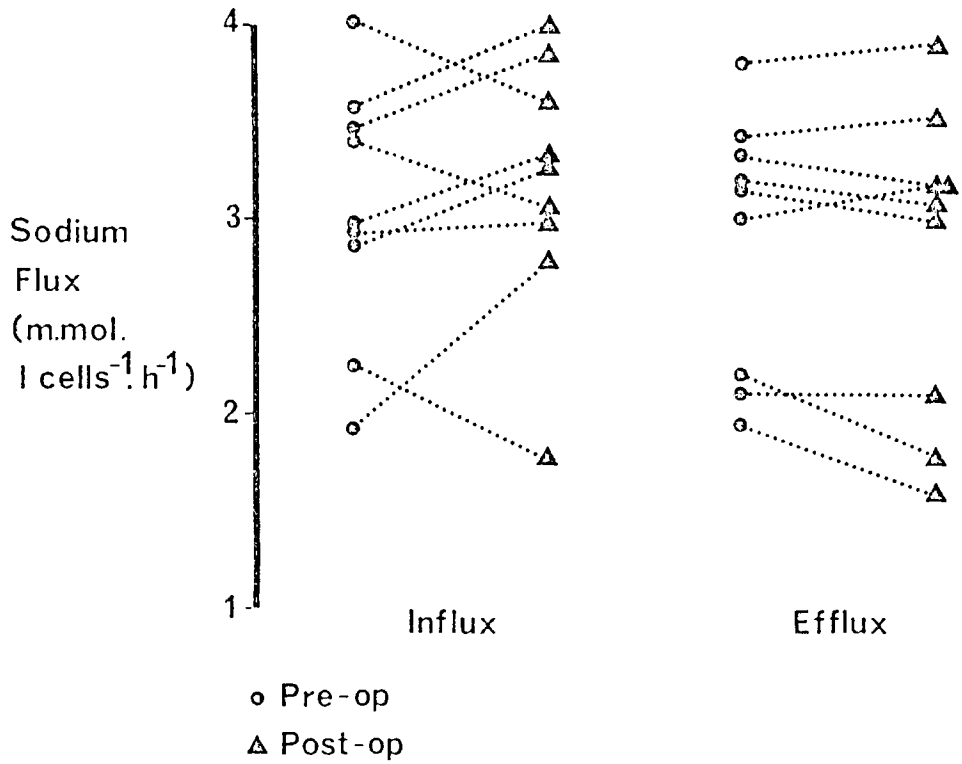


Figure 5.2

Values for Na^+ influx and efflux for each patient during the pre- and post-operative periods (paired data) - uncomplicated surgery

Table 5.4

The mean intracellular Na^+ concentration from each group of patients studied (Mean ± SEM)

Intracellular Na^+ concentration (mmol/l cells)		
Pre-operative:	Post-operative:	Seriously ill:
8.16 ± 0.54	8.43 ± 0.54	7.45 ± 0.42

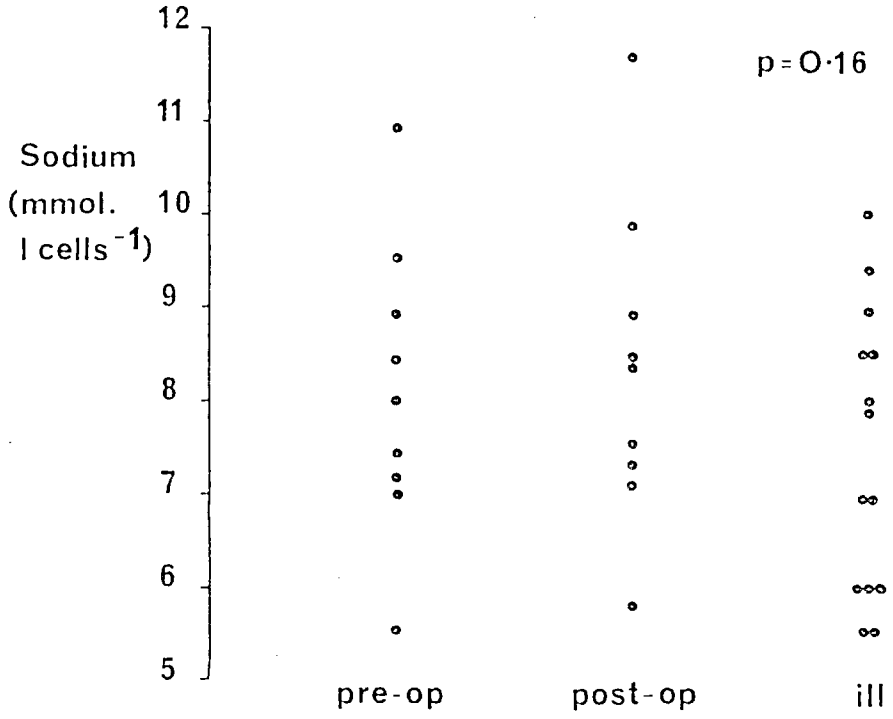


Figure 5.3

Erythrocyte intracellular Na^+ concentrations from all the patients studied

and post-operative measurements (Wilcoxon signed-rank test) but there is a lower numerical value for the seriously ill patients which does not reach statistical significance (Mann-Whitney U) when compared with pre-operative ($p = 0.32$) or post-operative ($p = 0.16$) values.

5.6 Discussion

Overwhelming evidence now exists for a $Na^+ - K^+$ activated ATPase component of the cellular pump (Glynn, 1968; Sweadner and Goldin, 1980). In erythrocytes the energy for this pump is generated from glycolysis providing the necessary ATP. Welt has adduced evidence that in the 'sick cell syndrome' a deficiency in energy in the form of ATP leads to a decrease in Na^+ efflux and in consequence a raised intracellular Na^+ concentration (Welt et al., 1964; 1967). Based on measurements in erythrocytes, decreased efflux has been suggested as the basis of an increased intracellular Na^+ content in many diseased states, including uraemia (Welt et al., 1964), malnutrition (Khalil et al., 1974) and liver disease (Owen and McIntyre, 1978). Additionally, ATPase activity may be compromised in the clinical situation of a generalised decrease in cellular metabolism, anoxia, hypothermia, depressed thyroid function and cardiac glycoside therapy (Repke, 1965).

An increased Na^+ content may also arise by increased Na^+ influx through a change in membrane permeability (Cunningham et al., 1971). Such an increase in cell membrane permeability has been proposed with elevated circulating catecholamine as in endotoxic shock (Batey et al., 1970). Membrane changes in muscle

have also been found in response to haemorrhagic shock (Shires et al., 1972).

This study has investigated the postulate that similar conditions apply after elective surgery and in critically ill surgical patients, and found no disturbance in either total Na^+ flux or intracellular Na^+ concentration. The flux values reported here agree well with those in the literature for the normal state (Levin et al., 1968). In addition, seriously ill patients showed no diminution of flux when this was measured in their own plasma. Both influx and efflux measured in Krebs' solution were generally higher in the severely hyponatraemic patients, reflecting the greater concentration gradient in which the cells were suspended. This suggests, therefore, that those patients' cells could respond to a greater influx of Na^+ down the concentration gradient by raising the efflux rate. When Na^+ efflux values are plotted against intracellular Na^+ concentration (Fig. 5.4) there is no difference between the regression lines for healthy or seriously ill surgical patients. The inference is that in seriously ill patients the normal relationship of increasing efflux with increasing extracellular Na^+ concentration is maintained.

The discrepancy between the results here and those reporting high intracellular Na^+ concentration in other critically ill states can be related to differing methods of calculating erythrocyte ionic concentrations. The major source of error in

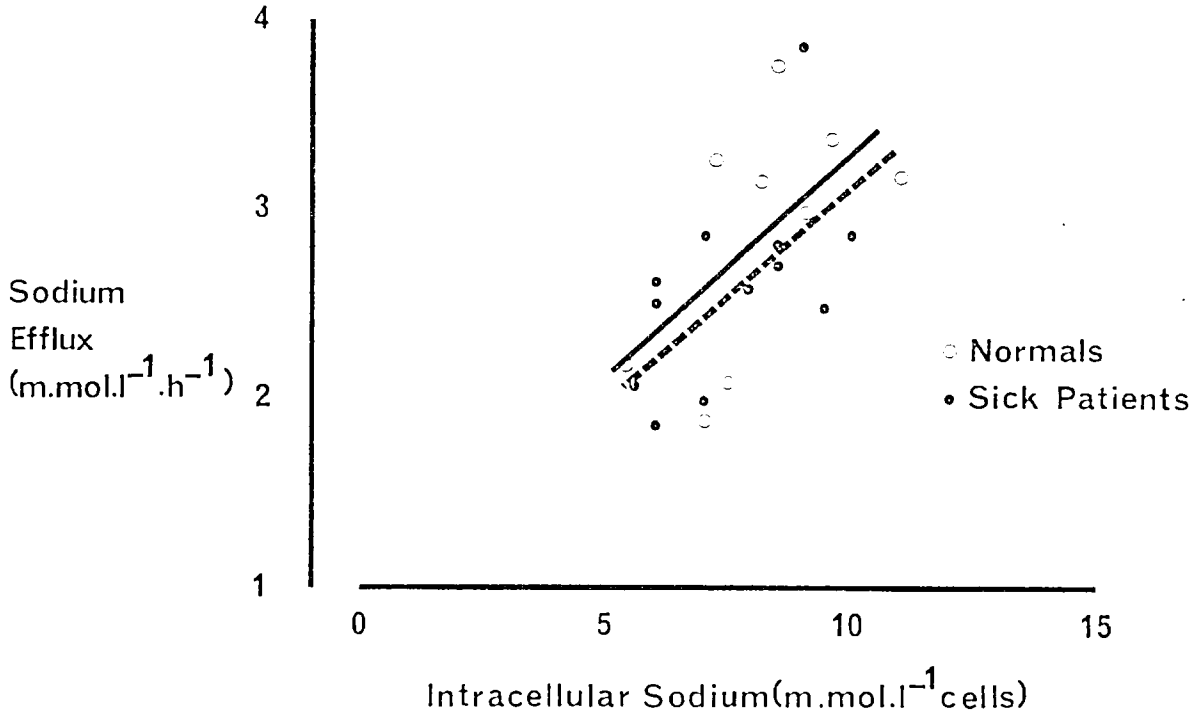


Figure 5.4

Na^+ efflux plotted against intracellular Na^+ for normal patients (---) and sick patients (——)

estimating intracellular concentration is the amount of extracellular contamination present: any small error in the calculation of contamination will result in a falsely high value for intracellular concentration. This potential source of error can be overcome by washing the cells in a solution containing intracellular amounts of Na^+. A further factor of importance is the osmolality of the wash solution. A hypertonic wash medium relative to the patient's plasma will result in a high intracellular Na^+ concentration. In this study, isotonic wash solutions were used.

In the seriously ill patients with severe hyponatraemia this study has found a lowered intracellular Na^+ concentration (Table 5.4). Though not statistically significant, this is consistent with more recent observations of red cell Na^+ content in ill cirrhotic patients (Astrup et al., 1980). Although changes in flux mechanism have been implicated to explain these data, the results here do not support that idea in surgical patients with hyponatraemia. The observation that intracellular Na^+ content was found to be related to serum values suggests the alternative that there is dilution of both intra- and extracellular compartments. An additional possible explanation of the failure to find a raised intracellular Na^+ concentration might be that most of our seriously ill patients had received adequate total parenteral nutritional support and thus were not energy substrate

deficient. They could be expected to have restored their low glycolytic rates to normal. In studies on severely burned patients with provision of a high calorific diet, Helmkamp et al. (1973) have failed to find any evidence of a raised intracellular Na^+, although others have documented increased intracellular Na^+ in erythrocytes falling to normal after provision of a 3000 kcal diet for several days (Curreri et al., 1971). It could be argued that erythrocyte studies may not be pertinent because of the highly specialised nature of these cells and that a normal Na^+ flux in red cells does not exclude changes in flux and other organs leading to hyponatraemia. Evidence exists that they are well representative of body cells and metabolic disorders appear in them much earlier than in the plasma (Bojanovicz, 1979; Ellory and Lew, 1977). Shires et al. (1972), by measuring transmembrane potential difference in muscle, have suggested that in haemorrhagic shock there is a raised intracellular Na^+ both in the experimental model and in clinical practice. At the same time, erythrocyte Na^+ content was found to be raised. Clinically evident haemorrhagic shock may not be comparable to the patients in this study. None was suffering from hypovolaemia.

Studies in erythrocyte Na^+ content of patients with liver disease and hyponatraemia led Astrup and his colleagues (1980) to conclude that abnormalities found were not due to liver disease *per se* but to secondary complications of cirrhosis. It would seem

likely that the same situations apply in surgical practice. The 'sick cell syndrome' with hyponatraemia in surgical patients is dominated by hypothesis rather than measurement. In that this study has found no support for the significant changes in membrane function in the surgical circumstances associated with hyponatraemia, it is concluded that the major cause of hyponatraemia for this group is extracellular dilution. This may be the consequence of whole body dilution on the basis of a disturbance of water homeostasis, or is the result of unidentified molecules in the ECF which obligate the presence of water so as to maintain extra-intracellular isotonicity. Both factors may be involved in individual circumstances.

5.7 Summary

The possibility of the decline in the Na^+ concentration gradient and in flux across cell membrane has been proposed as an explanation for post-traumatic hyponatraemia. Direct evidence of this was sought by measuring erythrocyte intracellular Na^+ concentration and transmembrane Na^+ flux in nine healthy patients undergoing uncomplicated elective abdominal surgery.

Intracellular Na^+ concentration was determined by in vitro washing of cells in a solution approximating to intracellular constituents and measuring extracellular Na^+ contamination with ^{51}Cr EDTA. Na^+ flux was determined by radioactive ^{22}Na tracer, both as influx and efflux. No change in erythrocyte intracellular Na^+ concentration or in Na^+ flux was found post-operatively.

In 14 seriously ill surgical patients, all of whom had plasma Na^+ levels outside the tolerance range of our surgical population, erythrocyte intracellular Na^+ concentration decreased, but not significantly compared with patients undergoing uncomplicated surgery ($p = 0.16$). Furthermore, Na^+ flux in seriously ill patients was proportional to intracellular Na^+ concentration. These results are at variance with the hypothesis of 'sick cell syndrome', which is said to be typified by a high

intracellular Na^+ concentration and a reduced Na^+ efflux.

Hyponatraemic extracellular hypotonicity in surgical patients must be assumed to be dilutional, though the source of the excess extracellular water in the sick patient remains to be defined.

CHAPTER 6

URINARY SOLUTE AND ELECTROLYTE EXCRETION IN THE POST-OPERATIVE PERIOD

6.1 INTRODUCTION

Restriction on the excretion of water by the kidney after injury is one factor in causing a fall in serum Na^+ concentration and osmolality if water administration is continued. The data presented in Chapter 3 of this thesis show that the dilutional changes persist for longer than had been previously thought. If these are the consequence of antidiuretic hormone (ADH) activity, they cannot easily be overcome.

Though it had been observed that urine volume was reduced after injury since Claude Bernard's time, it was in 1953 that LeQuesne and Lewis first suggested that the renal response to water loading in the two days immediately after major trauma (without overt circulatory disturbance) resembled that seen following the release or administration of near maximally effective amounts of ADH. These observations were confirmed by Dudley et al. (1954) using acute water loading. Other collateral evidence then accumulated that ADH was involved: varying the solute load produced the characteristic responses which are seen during ADH activity; alcohol administered post-operatively changed the degree of water reabsorption in a manner that would be expected from its antidiuretic action (Bennett et al., 1964); finally, and perhaps most importantly, bioassay and radioimmuno-

assay demonstrated that increased quantities of circulating ADH-like substance were present in blood and urine during the post-operative period (Ukai et al., 1968; Haas and Glick, 1978; Cochrane et al., 1981).

It is tempting to suggest a cause-and-effect relationship between the increased plasma ADH concentration and post-traumatic oliguria. During surgery, when plasma ADH concentration is greatest (Moran et al., 1964), the urine produced is of small volume and poorly concentrated (Gullick and Raisz, 1960; Zideman et al., 1978). Even if ADH is administered to patients during surgery, the urine seldom becomes more concentrated than plasma.

The absence of any renal response to ADH and the oliguria of surgery have been ascribed to factors such as the intense renal vasoconstriction (Eng and Stahl, 1971) initiated by catecholamine secretion (Price et al., 1959), and accompanied by a considerable decrease in glomerular filtration rate (Hayes et al., 1959). The decreased delivery of solute to the loop of Henle prevents the generation of a hyperosmotic renal medulla. Alternatively, high concentrations of ADH may divert renal blood flow from the superficial cortex to the medulla and thus decrease urine concentrations (Johnson et al., 1977).

6.2 Renal Functional Changes Following Injury

It has been a common clinical observation that the volume of urine remains small for 48 hours after injury (25 ml per hour or 600 ml per 24 hours) and then slowly increases towards the pre-operative volume about 800-1000 ml per 24 hours, which is reached after about a week (Pringle et al., 1905; Wilkinson, 1973). Occasionally, post-traumatic alterations in renal function become severe enough to compromise essential excretory needs with the result that renal failure ensues. Arbitrary limits for hourly urine production rates or concentration, either in terms of urea concentration (Molloy, 1962) or urine:plasma urea (Perlmutter et al., 1959) or osmolality ratios (Eliahou and Bata, 1965) have been suggested as indices to detect the development of renal dysfunction following injury. All suffer from ignorance of, or assumptions about, the normal pattern of solute and electrolyte excretion in the peri-operative period.

Following injury, urine osmolality rises almost immediately and remains high for a week or 10 days (Wilkinson, 1973). As already alluded to in Section 2.2, renal concentrative capacity is better reflected by osmolal clearance measurements which indicate the rate of removal of solutes from the plasma and are calculated as:

$$C_{osm} = \frac{U_{osm}}{P_{osm}} \times Vu$$

where: V_u = urine volume (ml/min), and

U_{osm}, P_{osm} = urine and plasma osmolalities (mOsm/kg).

Free water excretion (usually designated C_{H_2O}, though it is not in fact a 'clearance') takes more explicit cognizance of the rate of urinary output:

$$C_{H_2O} = V_u \left(1 - \frac{U_{osm}}{P_{osm}}\right)$$

If the kidneys are excreting maximally concentrated urine (V_u = 0.7 ml/min; U_{osm} = 1400 mOsm/kg; P_{osm} = 300 mOsm/kg):

$$C_{H_2O} = 0.7 - \frac{(0.7)(1400)}{300}$$

$$= 2.6 \text{ ml/min}$$

a negative free water excretion is achieved and implies that the kidneys are conserving water only at a rate of 2.6 ml/min.

Osmolal excretion (O_{osm}) is the product of urine volume and urine osmolality:

$$O_{osm} = V_u \times U_{osm}$$

(mOsm/h) (l/h) (mOsm/kg)

A 70 kg man on an 8.5 MJ (2000 kcal) diet produces, for renal excretion, 800 mOsm/day (Hilden and Svendsen, 1975). With maximal urine concentration (U_{osm} = 1400 mOsm/kg), 800 mOsm can be excreted in 800/1400 kg urine = 600 ml. In situations where metabolic end-products, such as urea, are produced in excess, e.g. burns, osmolal excretion may rise to 1000 mOsm/day (Settle, 1975). The normal post-operative patient excretes a solute load of 600 mOsm/day (Zideman et al., 1978).

The production of urine more concentrated than plasma depends upon the anatomical configuration of the renal tubule, that is, the counter-current multiplier (Wirz and Dirix, 1973,. As long as the kidneys' concentrating and diluting ability remains intact, osmolar control can be finely modulated by the action of ADH (Berliner et al., 1958). The medullary hypertonicity and the osmotic gradient, essential for the functional integrity of the counter-current system, results from the interstitial accumulation of solutes, mainly Na^+ and urea (Levinsky et al., 1959; Kokko, 1970).

Reduction in the urinary output of Na^+ from the pre-operative daily quantity of 100 mmol or more begins soon after operation and may fall to as little as 25 mmol or less from the third to fifth post-operative days (Wilkinson et al., 1949; Cochrane, 1978). Wilkinson et al. (1949) demonstrated that Na^+ conservation occurs regardless of the type of post-operative treatment provided and, at least in the first 48 hours, is as

intense in the patient to whom large quantities of Na^+ are administered as it is in those who receive none at all. Subsequently, however, the effect of thus loading the body with Na^+ modifies to some extent, but does not entirely obliterate, the normal pattern of post-operative Na^+ conservation which commonly lasts for up to a week after an operation such as partial gastrectomy.

The urinary excretion of K^+ is usually markedly increased during the first 24 hours after injury (Moller, 1949) from less than 50 mmol per day before operation to 75-125 mmol per day, and this increase may last for three or four days. The urinary output then usually falls below the daily pre-operative level and remains low for more than 10 days. It has also been noted that the increase in urinary K^+ excretion following injury precedes that of the excretion of increased nitrogenous material (Wilkinson et al., 1950(b)). The loss of cellular K^+ is presumably accompanied by or follows the mobilisation of water from the ICF.

6.3 Objective

In the peri-operative period, a series of hormonal and cellular changes results in Na^+ and water conservation. Relative oliguria and a reduced urinary excretion of Na^+ are normal consequences of major surgery (LeQuesne and Lewis, 1953; Dudley et al., 1954) even if peri-operative fluid-loading regimens are utilised (Shires et al., 1961; Jenkins et al., 1975).

It has appeared to many that it is possible to manipulate urine volume with ease, using either exogenous osmotic diuretics, such as mannitol, endogenous osmotic diuretics acting on the loop of Henle, such as frusemide (Powers et al., 1964; Baek et al., 1973) or by Na^+ loading with saline or Hartmann's solution. This practical ability has diluted interest in the underlying physiology.

Furthermore, virtually all the work that has suggested a restriction on water and electrolyte excretion in the post-traumatic period has been done on pooled urine samples, with little attempt made to separate temporal phases of the intra- and post-operative response. Although a considerable fetish is made of measuring hourly urine output (and, less frequently, its concentration) in many ill patients, little attention has been paid as to how these changes might be interpreted in terms of renal physiology.

Thus, the aim of the study was:

To Establish the Pattern of Hourly Urinary Excretion of Solute and Electrolytes Following Severe Single Surgical Trauma.

6.4 Patients and Methods

6.41 Patients

Seven patients undergoing severe surgical trauma were studied. The operations ranged from radical total gastrectomy to total oesophagectomy (Table 6.1). All the patients were starved overnight.

Pre-medication, approximately one hour pre-operatively, consisted of a papaveretum-atropine (15mg/0.6mg) combination which was administered intramuscularly. Anaesthesia was induced with thiopentone, intubation facilitated with suxamethonium, and anaesthesia maintained using controlled ventilation with 70 per cent nitrous oxide in oxygen and supplemented with intermittent phenoperidine. Post-operative analgesia was provided by continuous morphine infusion (Rutter et al, 1980). During the operation, blood loss was measured by swab-weighing and replaced with whole blood. In addition, Hartmann's solution was infused at the rate of 5 ml/kg/h during the operative procedure. The standard post-operative intravenous fluid regimen provided 30 ml of 5% Dextrose/kg/24 h.

TABLE 6.1

Patient clinical data and intra-operative details

Patient:	Sex:	Age:	Weight: (kg)	Operation:	Duration: (h)	IV-Hartmann's: (ml)	Na^+ loading: (mmol)	Blood (units):
1 (MO)	M	32	60	Oesophago-gastrectomy	5.0	1500	197	3
2 (JR)	M	61	58	Total gastrectomy	4.5	1305	171	2
3 (MF)	F	64	58	Oesophago-gastrectomy	5.0	1450	190	3
4 (JQ)	M	75	61	Oesophago-gastrectomy	5.5	1678	220	4
5 (TM)	M	53	55	Total gastrectomy	5.5	1513	198	3
6 (MK)	F	56	64	Total gastrectomy	4.5	1440	189	2
7 (MB)	F	63	68	Oesophago-gastrectomy	5.0	1700	223	4
Mean ± SEM:					5.0 ± 0.2	1512.3 ± 52.2	198.3 ± 6.9	3.0 ± 0.3

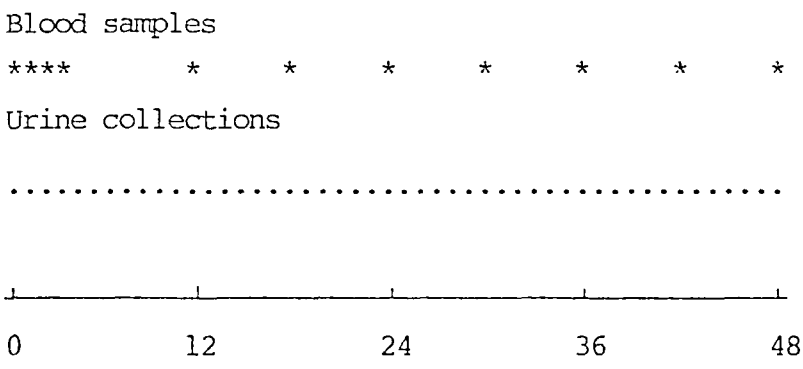
No patient was included if the pre-operative serum electrolyte or urea concentrations were outside normal limits. Nasogastric tubes were not used and there were no other extra-renal fluid losses.

The study commenced at the start of the operation and was terminated at 48 hours (Fig 6.1). All patients were catheterized and the bladder emptied by abdominal compression after induction of anaesthesia but before commencement of surgery. All urine passed subsequently was collected hourly, the volume recorded (Appendix 6.1) and aliquots reserved for measurement of osmolality (U_{osm}) using an Advanced 3L osmometer (Medical Scientific Equipment Ltd) and urinary Na^+ and K^+ concentrations (Corning 450 flame photometer). Blood samples were taken two-hourly for the first six hours, and then at six-hourly intervals thereafter, plasma osmolality measured (P_{osm}) and free water excretion (C_{H_2O}) calculated.

Blood urea was measured pre-operatively and twice within 72 hours post-operatively.

Figure 6.1

Protocol for urinary volume, solute and electrolyte excretion



6.42 Volunteers

In order to separate the changes due to starvation and those due to injury, 12 healthy volunteers of both sexes were also studied to mimic post-traumatic conditions. After overnight starvation, 6 volunteers consumed hourly 5% dextrose, and 6 volunteers 0.4% dextrose in 0.18% saline at the rate of 30ml/kg/24h. Urinary volume and osmolality were determined from hourly voided specmens, and Na^+ and K^+ concentrations measured. Blood samples were taken for plasma osmolality as in the patients.

Informed consent for the study was obtained from each patient and volunteer. All the patients' data are expressed as means ± SEM. In the diagrams, the mean of the results of the patients has been superimposed on those of the volunteers for ease of comparison.

6.5 Results

6.51 Patients

All 7 patients followed an uncomplicated post-operative course. There was no significant difference between the means of the pre-operative blood urea concentration ($\bar{x}$: 4.74 mmol/l) and the maximum post-operative values ($\bar{x}$: 4.94 mmol/l) measured within 72 hours of surgery ($t = 0.48$; $p > 0.10$; paired t-test; Table 6.2).

Figure 6.2 shows the hourly pattern of urine osmolality, free water excretion, Na^+ excretion, K^+ excretion and osmolal excretion following uncomplicated severe single surgical trauma. The following observations are relevant:

Urine osmolality (U_{osm}). Urine is hypertonic at the beginning of surgery (mean: 434 mOsm/kg). At 18 hours, the mean urine osmolality reaches 660 mOsm/kg and falls after 24 hours.

Free water excretion (C_{H_2O}). As expected from U_{osm} values free water excretion is negative for the first 24 hours, and

thereafter becomes positive although a sharp return to negative values occured after 40 hours.

Sodium excretion ($U_{Na}+$). There is a marked increase in Na^+ excretion during surgery and in the immediate post-operative period. This is followed by a steady decline to minimal values, commensurate with the Na^+-free intravenous regimen.

Potassium excretion (U_K+). K^+ excretion increases 4 hours post-operatively. U_K+ was approximately 4 mmol/h for the first 24 hours. There was then a reduction in its ecretion in the ensuing 24 hours, despite a reduced Na^+ excretion.

Osmolal excretion (O_{osm}). As a result of the early rise in Na^+ excretion and with a modest contribution from the increase in K^+ excretion, there is an initial rise in osmolal excretion. Following this, it varies between 20 and 40 mOsm/h.

TABLE 6.2

Pre-operative and maximum post-operative blood urea level

Patient	Pre-op. (mmol/l)	Post-op. (mmol/l)
1	3.7	4.9
2	4.0	3.8
3	5.8	7.2
4	5.9	6.4
5	3.7	4.6
6	6.1	4.5
7	4.0	3.2
$\bar{x}$	4.74	4.94
SD	1.12	1.41
SEM	0.42	0.53
t	-	0.48
p	-	NS

($p > 0.10$; paired t-test)

6.52 Volunteers

Figure 6.3 shows the composite data for volunteers and patients with the mean of the patients' data superimposed upon

those of the volunteers.

Urine osmolality (U_{osm}). The urine osmolality of the volunteers is higher at the beginning of the experiment than that of the patients', even though both groups had been starved overnight. After 24 hours there is no difference discernible between volunteeers and patients. The diurnal rhythm of U_{osm} is preserved in the volunteers.

Free water excretion (C_{H_2O}). As a consequence of starvation C_{H_2O} is initially negative. It rises slowly to become positive, and then swings around the base-line.

Sodium excretion ($U_{Na}+$). The pattern of Na^+ excretion in both volunteer groups show no discernible difference from the operated group, except in the early peri-operative period.

Potassium excretion (U_K+). By contrast, both volunteer groups showed a reduction in K^+ excretion, and appeared to maintain a diurnal rhythm.

Osmolal excretion (O_{osm}). The pattern of hourly osmolal excretion appeared similar between patients and volunteers.

Figure 6.2

Hourly pattern of U_{osm}, C_{H_2O}, U_{Na^+}, U_{K^+} and Oosm following surgical trauma

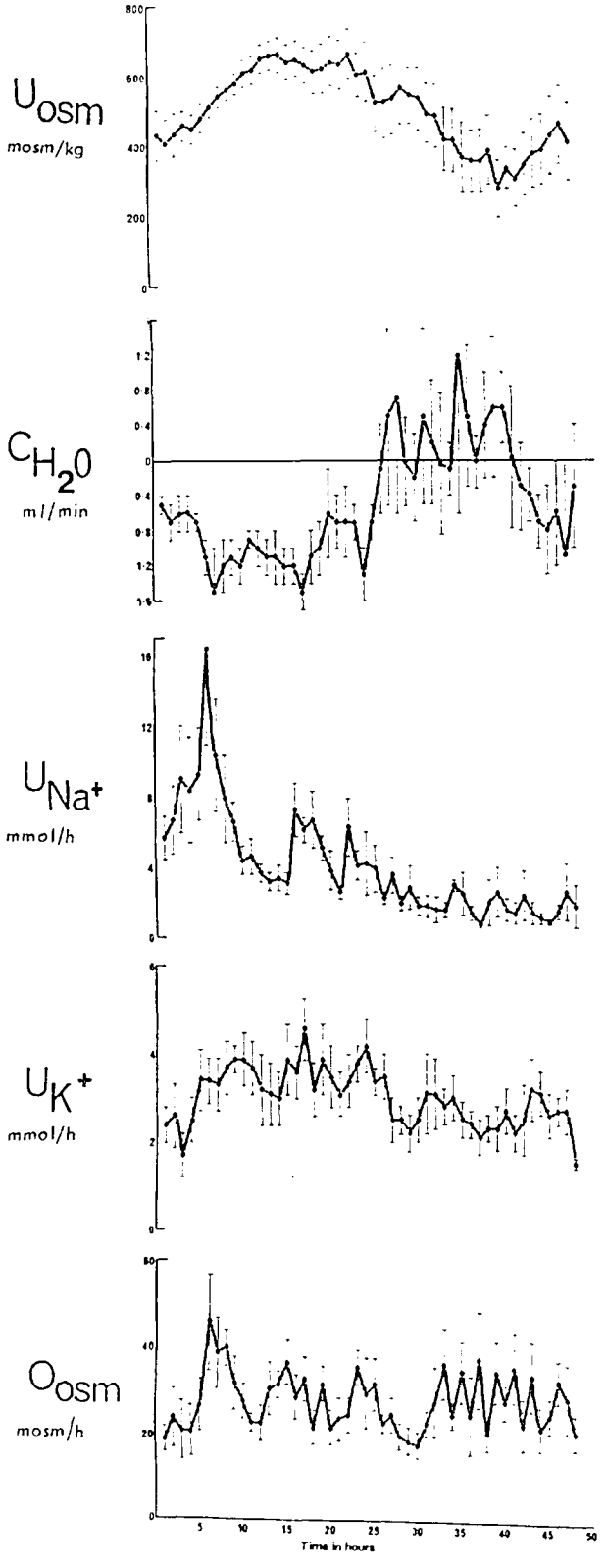
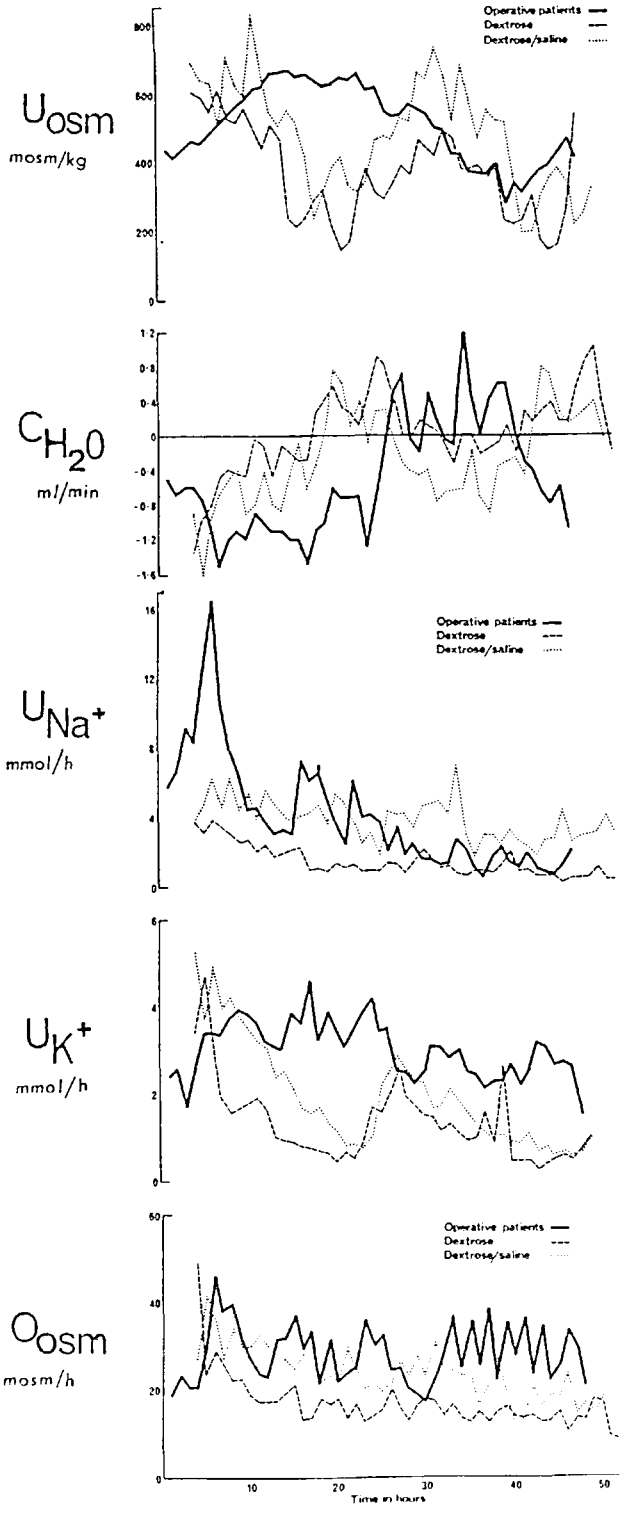


Figure 6.3

Composite pattern of hourly excretion of U_{osm}, C_{H_2O}, U_{Na^+}, U_{K^+}, O_{osm} in volunteers and patients



6.6 Discussion

Renal functional changes are a common sequel to major trauma, and renal failure still occurs after injury (Leading Article: Br.Med.J., 1980). Though numerous studies have attempted to describe the pathophysiology of acute renal failure and its clinical management (Rosenberg et al, 1971; Hayes et al, 1974), its prevention is still very much based on pragmatism - the use of diuretics such as mannitol and frusemide. Both urine volume and concentration are widely used to 'monitor' the adequacy of renal function and a considerable fetish is made of measuring hourly urine output in many ill patients. However, there is insufficient data on the temporal changes in urine volume and concentraton in the intra- and immediate post-operative periods after uncomplicated, but major, trauma to sustain decisions about fluid replacement or diuretic administration.

This study has established the hourly pattern of solute and electrolyte excretion following such surgical intervention. The marked rise in Na^+ excretion in the first five hours would seem contrary to expectation. However, further examination of the data reveals that this almost certainly reflects the large intra-operative Na^+ load insisted upon by our anaesthetists - the average Na^+ load being 200 mmol (Table 6.1). Increased delivery of Na^+ to the renal tubules by saline infusion decreases fractional reabsorption of the Na^+ load so that $U_{Na}+$ increased. Furthermore, the expanded ECF volume inhibits Na^+

reabsorption, especially in the proximal tubules (Hayslett et al, 1967; Backalew et al, 1970). The progressive diminution in Na^+ excretion is commensurate with the post-operative Na^+-free intravenous regimen. The prolonged Na^+ conservation conforms with the work of Cochrane (1978) who observed the same phenomenon in spite of only a seven-and-a-half-hour rise in plasma aldosterone; factors other than aldosterone must play a part in the high cumulative balance of Na^+ following injury. Although K^+ excretion was raised for the first 24 hours, it does not account for a prominent part of the solute output.

Another striking feature of this study is that the intra-operative urinary concentration (U_{osm}) is not that normally seen with the action of antidiuretic hormone (ADH). The volume and concentration of the urine during and immediately after surgical injury have been widely ascribed to the predominant influence of ADH (LeQuesne and Lewis, 1953; Dudley et al, 1954; Moran et al, 1964).

Peri-operative oliguria is a well-recognised entity (Snyder et al, 1952; Mackenzie and Donald, 1969). Major surgery, with its accompanying pre-medication, anaesthesia, skin incision, traction on viscera, decrease in blood volume and cardiac output, and finally post-operative pain creates a constellation of non-osmotic stimuli which leads to operative and post-operative

release of ADH. It therefore seems, at first sight, likely that the oliguria and posterior pituitary hypersecretion are related causally, particularly because in the peri-operative period ADH activity is greatest during the operation (Moran and Zimmermann, 1967).

Though in our patients urine volume (Fig 6.4) is low and within the range associated with maximal antidiuresis, U_{osm} ($\bar{x}$: 434 mOsm/kg) is only moderately in excess of plasma. Both volume and osmolality do increase in the immediate post-operative period, but maximal values are achieved only at 18 hours. Furthermore, although in this group of patients undergoing severe single surgical trauma we would expect maximal value in response to ADH to be in excess of 1000 mOsm/kg, in fact the highest value achieved was just below 800, and mean 660 mOsm/kg. Free water excretion (C_{H_2O}) is a measure of water excreted free of solute. Thus, when C_{H_2O} is zero, urine is isotonic with plasma. C_{H_2O} is positive with hypotonic urine, and negative when urine is hypertonic. As would have been expected from U_{osm}, C_{H_2O} is negative for the first 24 hours but not greatly so. C_{H_2O} becomes positive after 24 hours, but of interest is the unexplained sharp return to negative values after 40 hours.

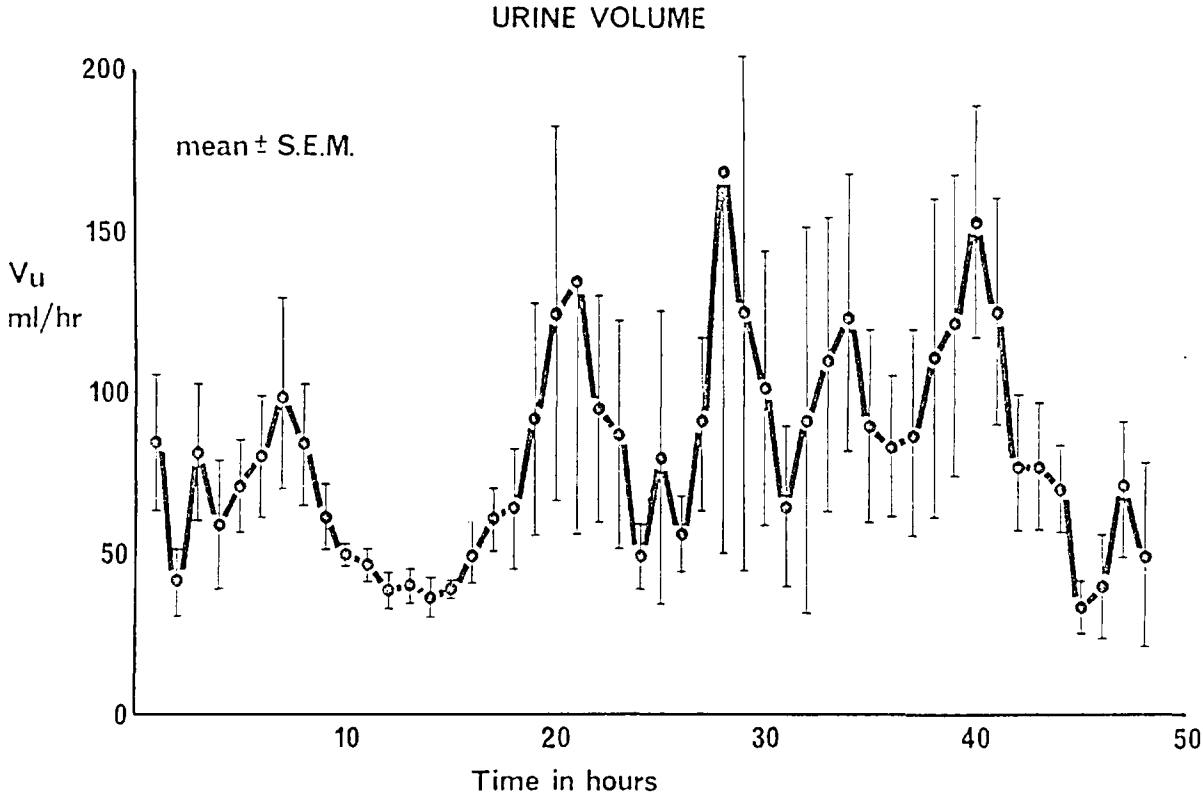


Figure 6.4

Hourly pattern of urinary volume from patients group (Mean ± SEM)

Though antidiuresis is one factor in post-traumatic oliguria, these observations suggest that the kidney does not respond to high circulating ADH activity in the intra-operative and the immediate post-traumatic period. A further possibility is that ADH has an additional role affecting the kidney, perhaps by an effect on renal perfusion (Fisher et al, 1970; Johnson et al, 1977) as well as on the production of a concentrated urine. Whilst ADH modulates the fine control of urine concentration, it can be effective only in the presence of an hypertonic medulla. The counter-current multiplier mechanism operates optimally if the loop of Henle is supplied with a sufficient amount of solute, and if glomerular filtration rate is normal.

Similarly, medullary blood flow should be relatively low (Wirz and Dirix, 1973). Changes in any of these factors limit the production of an hypertonic medulla and, therefore, urine in the post traumatic period. Previous work has demonstrated that even if ADH is administered to patients in the post-traumatic period, renal concentrating ability is usually lower than that achieved pre-operatively, (Gullick and Raisz, 1960; Dudley et al, 1980). It has also been demonstrated that during surgery grossly elevated ADH concentrations are associated with a decrease in glomerular filtration rate and renal perfusion (Moran et al, 1964). Furthermore, in the intra- and immediate post-operative period renin production is high (Cochrane, 1978). This would

reduce renal plasma flow and glomerular filtration rate (Bock and Krecke, 1958) thus throttling concentrating ability.

The observations in the volunteers indicate that the changes in urinary volume and composition seen in the uncomplicated post-injury patient, even after major surgery, are similar to the adaptations seen in altered intake. Though the volunteer group lost an average of 1.58 $\pm$ 0.21 kg in weight during the course of the study, there is no discernible difference in the temporal pattern of their urinary volume (Fig 6.5) when compared to those of the patient group (Fig 6.4). Both groups had undergone overnight starvation and the changes seen in the post-injury patient after major surgery are largely adaptive. This is particularly striking in relation to Na^+ excretion at 24 hours. The differences in K^+ excretion between the volunteers and patients in the first 24 hours could be partly accounted for by causes both known and unknown, including hormonal and intra-renal mechanisms. When starvation begins, the urinary output of K^+ falls to about 50 mmol/day and then further declines (Wilkinson, 1973). Part of this excreted K^+ comes from cell metabolism, but some may follow the movement of water out of the cells, thus allowing the endogenous provision of water for insensible water loss and the formation of urine. Glycogen mobilisation may also release K^+. After injury, urinary K^+ usually ranges from 75 to 125 mmol/day, and thereafter falls

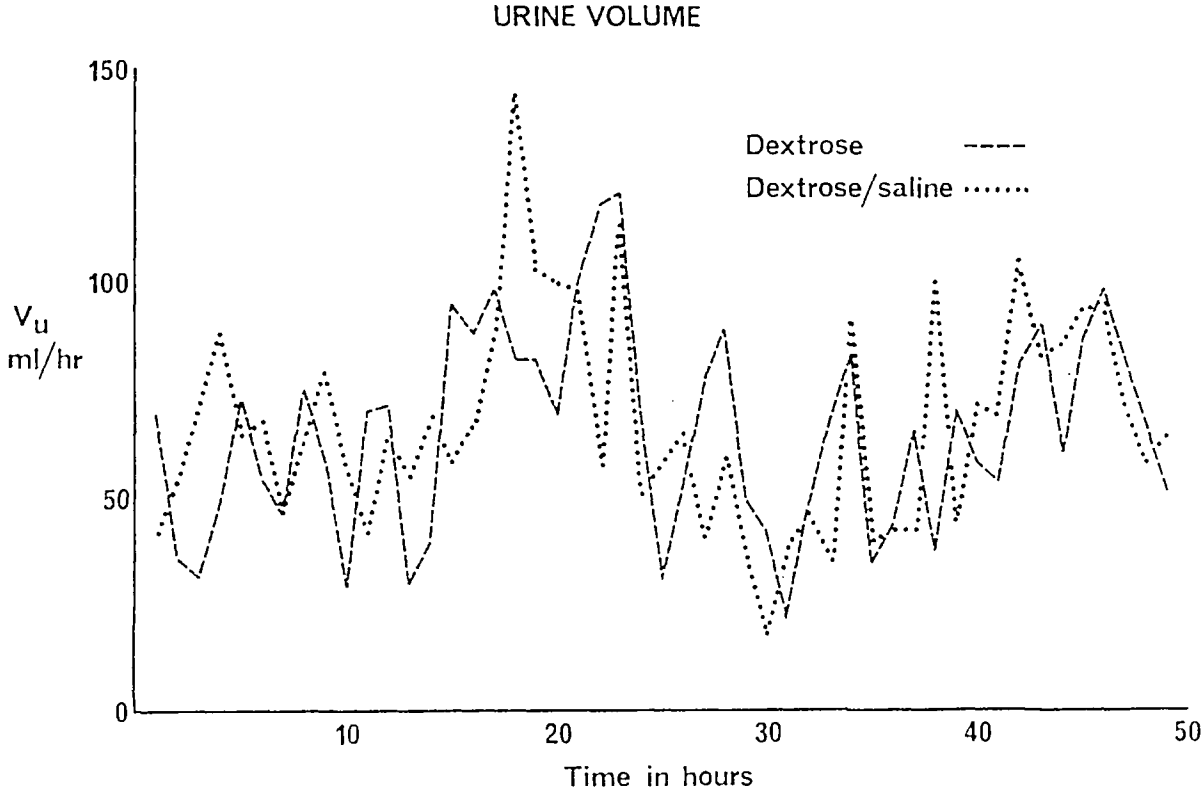


Figure 6.5

Hourly pattern of urinary volume
from volunteer group (mean)

below the daily pre-operative level (Moore, 1959). The small fluctuations in osmolar output (the product of volume and concentration) throughout the study period are similar to those previously found; the obligatory solute output of a 70 kg man undergoing major abdominal surgery is approximately 700 mOsm/day (Zideman et al, 1978). Thus an hourly urinary solute excretion of at least 28 mOsm would appear to be indicative of adequate renal function in the peri-operative period.

That the volunteers preserved some of the diurnal rhythm in their pattern of water and electrolyte excretion despite drastic alterations in habits of eating and sleeping (awakening hourly to void) has been well documented (Mills and Stanbury, 1952; Mills et al, 1954). Thus, the events seen following uncomplicated injury are largely identical to those which take place when intake of water and electrolytes is modified or withdrawn, though in the case of injury they are driven by stimuli additional to those involved in normal homeostasis.

This study has confirmed the decrease in renal excretory function during major surgical trauma although, at least for the first 18 hours after injury, ADH is not the major determinant of volume and concentration. The temporal pattern of solute and electrolyte excretion established for standard severe trauma and shown to be largely an adaptive phenomenon should enable a more

rational approach towards preventive management for renal insufficiency. In that urine volume and occasionally its concentration is used to detect the development of renal dysfunction, data from the present study provides a yardstick for the interpretation of these measurements in surgical patients managed on a similar regimen under standard circumstances; provided the solute output falls within these limits, urinary manipulation with exogenous or endogenous diuretics may be unwise and unnecessary and only serves to complicate the picture. Further work is needed to elucidate the effects of diuretics in circumstances of standard surgical trauma.

6.7 Summary

Though urine volume (and, less frequently, concentration) is often measured in the peri-operative period, little attempt has been made to separate temporal phases of the intra- and post-operative response to surgery. In seven patients undergoing standard severe single trauma and managed by a conventional regimen which included intra-operative Hartmann's solution, this study has investigated the hourly pattern of urine solute and electrolyte excretion over the first 48 hours. Contrary to expectation, in the first five hours Na^+ excretion increases in association with overall solute excretion, and thereafter progressively diminishes. K^+ excretion increases four hours post-operatively and remains elevated for 24 hours, after which it returns to normal, even though Na^+ excretion remains low. Free water excretion is negative for the first 24 hours, though urine osmolality does not suggest a maximal antidiuretic response by the kidney - the highest concentration achieved being just below 800 mOsm/kg. In order to distinguish between the physiological adaptive changes due to starvation and those due to injury, the hourly pattern of urine solute and electrolyte excretion was further investigated in 12 healthy volunteers mimicking post-operative conditions. Apart from the early post-operative period, the hourly pattern of Na^+, K^+ and osmolar

excretion show no discernible difference from the operated group. These results show that, particularly in relation to Na^+, the changes seen in the post-injury patient, even after major uncomplicated surgery, are largely adaptive, and this is especially striking at 24 hours after surgery.

THE STUDY OF WATER AND SODIUM HOMEOSTASIS IN THE SURGICAL PATIENT WITH PARTICULAR REFERENCE TO HYPONATRAEMIA AND SODIUM FLUX

V O L U M E I I

P A R T I I I

METABOLIC SUBSTRATE AND SODIUM AND WATER MOVEMENTS AFTER SURGERY

C H A P T E R 7

GLYCOGEN OBLIGATED WATER: ITS CONTRIBUTION TO EARLY WEIGHT GAIN DURING NUTRITIONAL REHABILITATION

7.1 INTRODUCTION

The work presented in Part II of this thesis has concentrated on that part of the metabolic response relating to ECF, Na^+ and water homeostasis following injury. It is now widely recognised that the metabolic response after severe injury is characterised by catabolism, loss of body weight, negative nitrogen balance, and accelerated fluxes of substrates among organs (Moore, 1959). As noted in Section 1.5 of the historical review, in the '60s there was a renewed interest in the details of changes in energy metabolism of the critically ill and catabolic patient (Kinney et al, 1970); since then, with the development of techniques for enteral and parenteral nutrition, patients with severe injuries would now receive vigorous nutritional support during their catabolic illnesses (Ellis et al, 1976; Grant, 1980). Currently nutritional support of patients who have suffered injury has evolved to at times complex regimens of enteral or total parenteral nutrition comprising amino acids, carbohydrates, fat, electrolytes and water, trace elements and vitamins.

Despite widespread clinical acceptance, nutritional therapy has recently come under increasing clinical and financial scrutiny (Goodgame, 1980; Michel et al, 1981). This is particularly so with parenteral nutrition, as techniques for maintaining nutritional integrity intravenously are now available almost regardless of the severity of the illness or the organ system failure which may supervene.

The broader issue is a need for more carefully defined and controlled studies to demonstrate specific benefit from such treatment, although ethical considerations, finding a comparable group of patients and assessment of outcome in a complex situation, virtually preclude that any such clinical studies can be truly 'controlled'.

The problem is further bedevilled by the many indices recommended to assess the benefits of nutritional therapy (Michel et al, 1981). Even such a simple yardstick as weight gain has been alleged to be mostly 'water retention' (Hill et al, 1978; Yeung et al, 1979; Macfie et al, 1981).

Another major unsettled problem is the formulation of precise guidelines for administration of the macronutrients: amino acids, carbohydrates and fat (Elwyn, 1980). While the body's catabolic response to injury could theoretically be offset by

high-calorie, high-nitrogen feedings,the relative merits of carbohydrate and fat as the non-protein energy source remain controversial.

Though several investigators have shown that the provision of large quantities of non-protein calories can diminish nitrogen excretion, it was Gamble (1946) who first demonstrated clearly that 100g of glucose with ample water resulted in a prompt decrease in urinary nitrogen excretion during the starved state. This small amount of glucose stimulates insulin secretion which limits proteolysis and gluconeogenesis (Fig 7.1). Insulin also decreases ketogenesis. The available glucose is utilised by glycolytic tissues while the remainder of the body continues to oxidise fat. Subsequent to Gamble's work, it has been shown that there is a progressive effect on protein sparing by increasing amounts of glucose in starving man. Infusion of 400-700g of carbohydrate per day markedly diminishes nitrogen loss by signalling for increased insulin elaboration (O'Connell et al, 1974). More recently, the effect of high carbohydrate intake alone after surgery has been studied. Radcliffe et al, (1980) studied nitrogen excretion after surgery at three calorific levels: 6, 25 and 40 kcal of glucose/kg body weight/day for the first two days post-operatively. Serum insulin levels were highest in the 40 kcal/kg group. Carbohydrate infusion was found to have a progressive nitrogen sparing effect

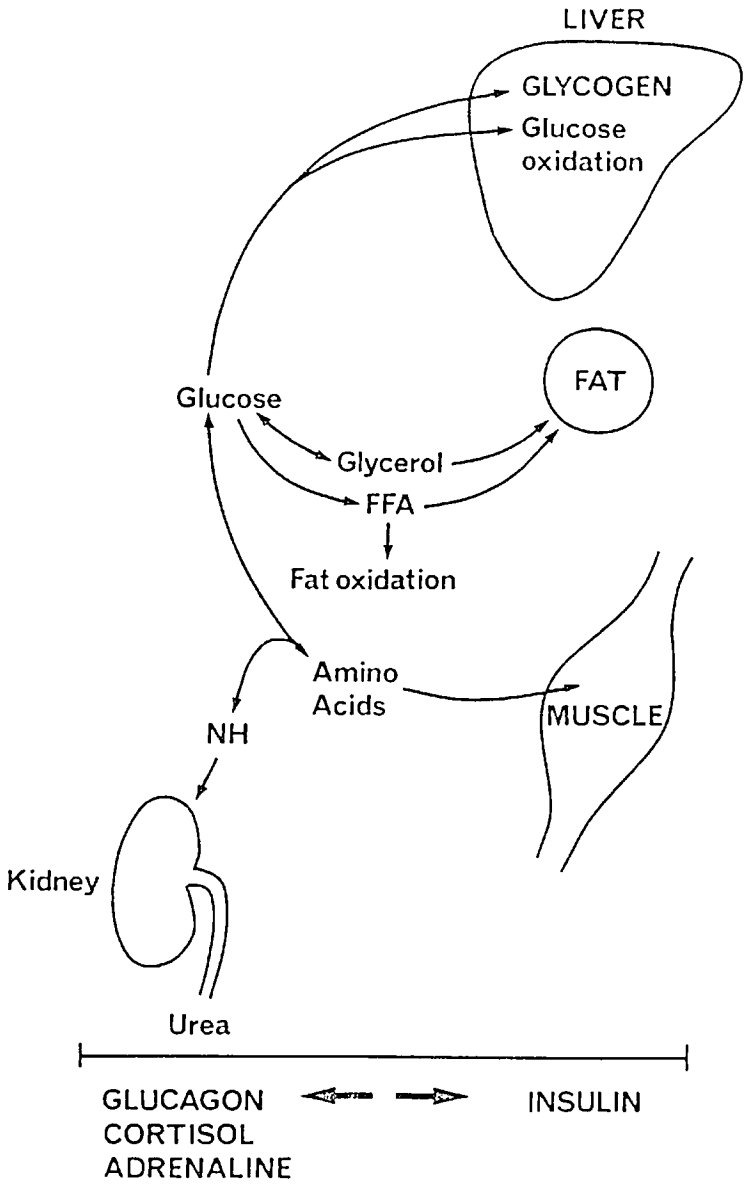


Figure 7.1

Hormone-Substrate Interaction

quantitatively comparable to that achieved by intravenous amino acid infusion (Blackburn et al, 1973). However, the increased negative nitrogen balance associated with surgical stress could not be prevented completely.

In that negative nitrogen balance persists in the face of carbohydrate infusion above requirements, emphasises the need to suppy nitrogen to reverse this. Blackburn et al (1973) have proposed that positive nitrogen balance can be obtained with infusion of amino acids alone. These workers inferred that the infusion of glucose (in hypocaloric amounts) may even be deleterious. The infused glucose stimulates insulin production which in turn inhibits lipolysis, thus depriving the body of endogenously produced energy substrates, free fatty acids, glycerol and ketones (Fig 7.1). In order to compensate for this there is an increase in protein breakdown and amino acid metabolism to provide carbon chains for gluconeogenesis.

These observations have not been confirmed (Kinney et al, 1980) and studies have failed to demonstrate postive nitrogen balance with amino acid infusions in the post-operative period (Hoover et al, 1975; Greenberg et al, 1976). It would appear that the protein sparing effect of amino acids is a function of the infused amino acids alone and is not related to the degree of endogenous fat mobilisation.

More recently, the deleterious effects of high carbohydrate loads on respiratory function have been emphasised. The Respiatory Exchange Ratio (RER) and carbon dioxide (CO_2) production is different for each type of fuel that is oxidised and is very high for conversion of glucose to fat (Appendix 7.1).

TABLE 7.1

Process	RER
Glucose oxidation	1.00
Protein oxidation	0.80
Fat oxidation	0.71
Lipogenesis (glucose to fat)	9.67

The work of Elwyn et al (1981) has demonstrated that as carbohydrate intake is increased until there is no net fat oxidation, the non-protein RER approaches 1.0, CO_2 production increases steadily, while oxygen (O_2) consumption decreases slightly due to its increased caloric equivalence. Further increments of carbohydrate are converted to fat with increasing RERs together with marked increase in CO_2 production. This effect is avoided to the extent that fat replaces carbohydrate in

the feeding regimen. Furthermore, high carbohydrate loads also increase resting energy expenditure (REE) and in the severely injured and septic patient, high glucose loads have been reported to precipitate respiratory distress secondary to increased CO_2 production (Askanazi et al, 1980 (a)(b)). However, many of these ill patients reported may already have compromised pulmonary reserve, and the amounts of glucose given were excessive.

Finally, studies of body composition in surgical patients have focussed upon the water retaining effect of glucose (Hill et al, 1978; Yeung et al, 1979). In a study of two groups of patients who received intravenous nutrition for 2 weeks, significant weight gain occurred in both groups (Macfie et al, 1981). The only difference in the intravenous nutrition regimen between the group was the non-protein energy source. Less water was found to be retained when part of the non-protein energy source was provided in the form of fat while there was a significant gain in total body water in the patients fed with glucose alone even though there was no protein gain. These authors inferred that the water retaining effect of glucose 'can sometimes be a problem'.

7.2 Carbohydrate, Na^+ and Water Balance

Claude Bernard (1865) was the first to draw attention to the importance of a stable and constant composition of the ECF compartment. Ten years earlier, he had made fundamental studies of the physiology of glycogen and described that during fasting, or when non-carbohydrate fuel was ingested, the blood sugar level was kept normal because of the breakdown of liver glycogen (Bernard, 1855). Around 1890, it was demonstrated that liver glycogen could be formed from ingested sugar by a direct conversion of sugar to glycogen (Otto et al, 1891).

During this period the role of carbohydrates in relation to water and Na^+ balance was first recognised. The phenomenon of rapid weight change with alterations of diet composition was demonstrated by Bischoff and Voit (1860) and confirmed by Benedict and Milner (1907). Studies of fasting - in effect, a low carbohydrate diet at the cellular level - demonstrated that 'the body loses more water than is set free by the destruction of tissue' (Hammarsten and Mandel, 1909). Benedict (1915), in his classical studies, showed that early in a fast, weight loss exceeds that which can be explained on a caloric basis and this was attributed to a change in water balance.

When a healthy adult is deprived of both water and food, the small carbohydrate reserve which exists as glycogen is soon exhausted. The continuing oxidation of body fat and protein will provide some 300 ml of water per day while the remaining 1300 ml of the theoretical minimal daily water requirement must be provided from water already in the body. The quantities of Na^+ and K^+ excreted in the urine indicate the degree to which the ECF and ICF are used to provide the continuing daily requirements of water. Gamble et al (1923) confirmed this observation and demonstrated that there was definite Na^+ loss related to the water loss of fasting. The loss of Na^+ and of ECF is greatest on the first day, declines during the next 3 days and is small from the fifth day onwards (Gamble, 1947).

If ample water is provided for the fasting subject, the loss of body water is greatly reduced. The renal conservation of Na^+ limits the loss of ECF and the urinary output of Na^+ and K^+ indicates that only about 500 ml of body water are lost per day. Gamble's subjects drank freely and in excess of their basal requirements of water; they excreted about 800 ml of urine per day which he therefore concluded was the minimum urine volume for fasting subjects under basal conditions. Observations on surgical patients under similar conditions agree closely with this figure (Wilkinson, 1973).

Gamble (1946-7) also showed a striking difference in Na^+ excretion when experimental 'life raft survivors' were supplied water with or without 100 g of glucose. Those volunteers receiving glucose excreted far less Na^+ than their fasting counterparts despite the fact that there was only a 400 calorie difference in their energy balance. The administration of glucose reduces the loss of Na^+ in the urine by about half but the K^+ loss is reduced by only about one-sixth. The experiments of Hervey and McCance (1952) yielded comparable data and indicated the important role of carbohydrate in conservation of water and Na^+ in men without food or sufficient water. No adequate explanation has been found for the Na^+ sparing action of carbohydrate (see Section 1.512) although many facets of hormonal regulation and Na^+ metabolism have been implicated (Bloom, 1967).

On the other hand, a more direct biochemical explanation exists for carbohydrate and water balance. It has been demonstrated that a carbohydrate diet caused storage of glycogen in the liver and that water was bound to liver glycogen at the time of storage (Pavy, 1860; Bridge and Bridges, 1932). Biochemical analysis of liver slices from animal studies have shown that the deposition of 1 g of glycogen is associated with

1-3 g of water (Puckett and Wiley, 1932; Fenn and Haege, 1940). Similar figures were obtained from muscle and liver glycogen in humans by using needle biopsy techniques under conditions of starvation and re-feeding with carbohydrates (Olsson and Saltin, 1970; Bergstrom and Hultman, 1972; Nilsson and Hultman, 1973). Reference has already been made in Sections 1.31 and 1.511 that the water that is obligated to glycogen storage is liberated from many tissues during starvation. When carbohydrate is the main fuel, the human body reqires 2-4 kg of water in the tissues more than when fat is being utilised. This water is rapidly lost when the carbohydrate reserves begin to run down and the metabolism becomes dependent on exogenous or endogenous fat (Passmore, 1961). As a consequence of glycogen consumption, this portion of intracellular water will contribute to the total body water pool.

7.3 Objective

It has been repeatedly observed that patients who are being nutritionally rehabilitated by enteral or parenteral means gain weight rapidly over the first three or more days of therapy. The nature of this weight gain, however, whether water retention or increased body cell mass, is still debated (Elwyn et al, 1975; Brans et al, 1976; Polley et al, 1979; Jeejeebhoy, 1979). Recent studies of body composition in surgical patients suggest that short-term and sometimes startling weight gains are caused mostly by water retention without corresponding increase in lean body mass (Hill et al, 1978; Yeung et al, 1979; Macfie et al, 1981), and it has been inferred that in consequence there is no advantage gained and even that the increased body water may be deleterious.

The alternative hypothesis is that because feeding in such circumstances is usually of a high carbohydrate nature and because the starving patient has exhausted his storage glycogen (Fig 7.2) the weight gain reflects glycogen repletion which is known to obligate water (Puckett and Wiley, 1932; Fenn and Haege, 1940; Olsson and Saltin, 1970; Bergstrom and Hultman, 1972). An additional possibility is that most feeding regimens also contain

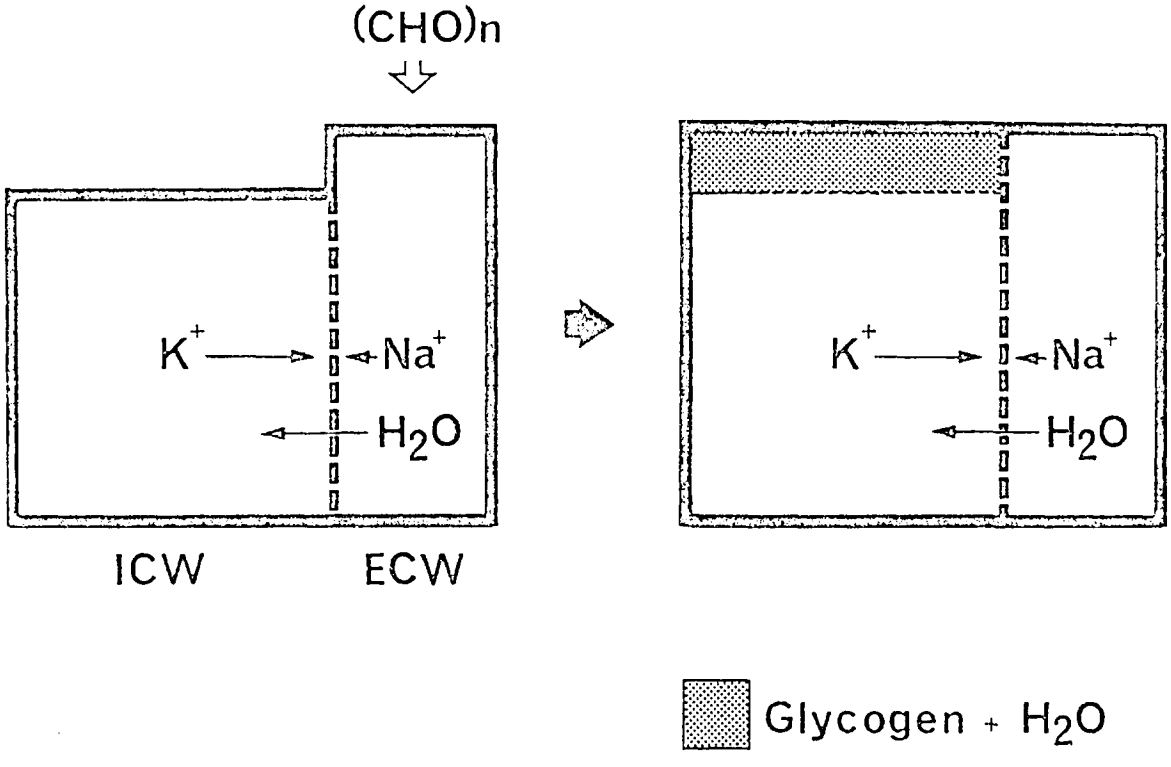


Figure 7.2

Possible weight gain from high carbohydrate feeding

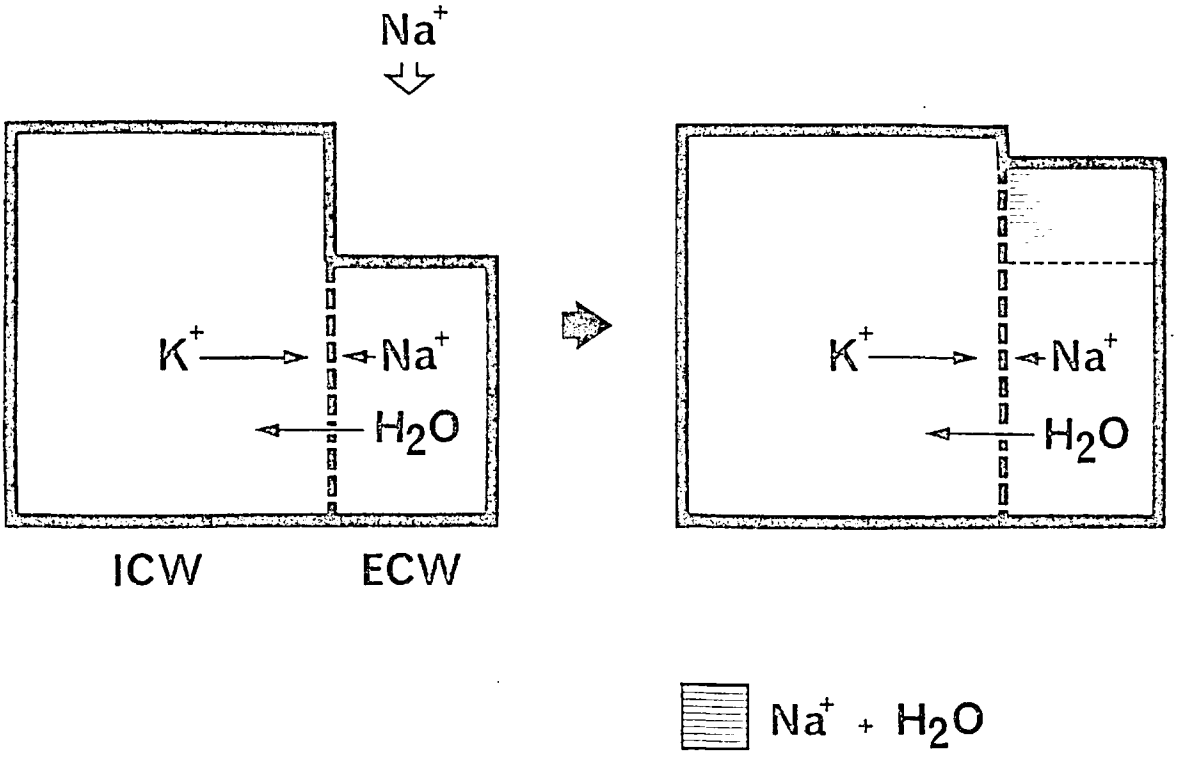


Figure 7.3

Possible weight gain from resumption of Na^+ intake

Na^+ (Fig 7.3) and patients who are starving absorb little or none of this ion, so that the accumulation of fluid during nutritional rehabilitation represents a return to the midpoint of Na^+ homeostasis, with consequent re-expansion of ECF volume towards its median value (Strauss et al, 1958).

Thus the objective of this study was :

To Differentiate the Weight Gain Associated with Repletion of Glycogen Stores and That Which Might Be Consequent Upon Resumption of a Na^+ Intake.

7.4 Subjects and Methods

Volunteers

Eight young healthy volunteers (four male and four female medical students and nurses) were studied over a period of 14 days. All were within 10 per cent of their ideal body weight. A preliminary dietary analysis was done to establish normal nitrogen-energy intakes for each individual (Appendix 7.2). Meals conforming to these were prepared and provided by the Hospital Dietetics Department: total daily energy ranged from 6.28 MJ to 12.55 MJ (1500 to 3000 kcal). During the first 7 days all the volunteers consumed a low Na^+ (4.7 mmol Na^+ and 56 mmol K^+) 'ketogenic' diet of the same composition each day consisting of 67 per cent fat, 26 per cent carbohydrate and 7 per cent protein, calculated from standard food tables and designed to deplete body glycogen stores (Jette et al, 1978). These were taken in three meals daily at 08:30, 12:30 and 18:30 h. Over the next 7 days, in order to replete glycogen stores, 6 of the volunteers consumed an isoenergetic diet with a similar Na^+ restriction and K^+ intake, but daily carbohydrate intake was increased to 86 per cent of the total energy (fat 7 per cent, protein 7 per cent). The 2 remaining volunteers received an identical intake except that K^+ was limited to 5 mmol/day.

Daily fluid intake was kept constant at 30 ml/kg of deionised water throughout the study period.

Patients

During the course of this study, 2 patients presented to the Unit with total dysphagia (weight loss of 26 per cent and 44 per cent of ideal body weight) as a result of malignant and benign oesophageal stricture respectively. Both patients were studied pre-operatively for 8 days after admission while being prepared for surgery and both then underwent successful resections. The intravenous regimens simulated the dietary intakes of the volunteers: low-Na^+ low-carbohydrate feeding was provided in the form of zero Na^+ input and 5% dextrose for 3 days, and low-Na^+ high-carbohydrate feeding in the form of zero Na^+ input and 20% dextrose for the next 5 days. K^+ intake was sustained at 60 mmol/day throughout the study. Conventional total parenteral nutrition with dextrose, amino acids, electrolytes and minerals was then given at the end of the study period to complete preparation for surgery (Appendix 7.2).

General Investigations

In all volunteers and patients, 24-h urine collections were made for the 14 days (09.00 - 09.00 h). Concentrations of electrolytes in urine and plasma were measured daily by flame photometry (Corning 450). Body weights were determined each

morning with a weighing scale accurate to ± 50g after the subjects had emptied their bowel and bladder and before any food or fluid intake.

Respiratory Exchange Ratio (RER)

RER measurements were determined on alternate days in order to identify net substrate oxidation and energy source during low- and high-carbohydrate feeding periods. RER was measured by indirect calorimetry by the standard Douglas bag method (Appendix 7.1). A conventional nose-clip and mouthpiece were used and 10-min calibration period was allowed before the collection of exhaled air for 6 min in a Douglas bag. This standard method is reproducible to 5 per cent. $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were calculated from the bag volume and analysis of P_{O_2} and P_{CO_2} by paramagnetic O_2 analyzer (OA 272 Taylor Servomex Ltd) and by infra-red CO_2 analyzer (17070 Godart-Statham Ltd).

Total Body Water (TBW)

TBW was measured with tritium-labelled water (^3H_2O) as the tracer substance (Vaughan and Boling, 1961) at the beginning of the study, at the end of the low-Na^+ low-carbohydrate feeding and again at the end of low-Na^+ high-carbohydrate feeding. Before intravenous injection of a weighed quantity

containing 50 μCi (1.85 MBq) ^3H_2O, a blood sample was taken for background radioactivity of plasma and another blood sample taken 3.5 h later when the tracer substance was equilibrated in body water. No fluid was allowed during this period. The tritium activity of duplicate samples was counted in a liquid scintillation counting system after vacuum distilation. The scintillation solution was toluene-based. Samples were counted for 10^4 counts which gave ± 1 per cent variation of the measured radioactivity. The accuracy for TBW with this method is within ± 2 per cent (Appendix 2.2).

Data Analysis

All data are expressed as means ± SD. Significance between means was calculated by the t-statistics, paired or unpaired as appropriate. Linear regression analysis for correlation between weight and water changes was performed by the least squares method and significance calculated using the t-distribution.

Informed consent for the study was obtained from each volunteer and patient and the investigations were approved by the Hospital Ethics Committee.

7.5 Results

Low-Na^+ low-carbohydrate diet in volunteers

The response of Na^+ excretion to a severe dietary salt restriction in the 8 normal volunteers was as expected. Sodium conservation developd gradually; 5 to 6 days were required before Na^+ balance was achieved at the low level of intake and output (Fig 7.4). By day 5, urinary Na^+ levels had reached less than 10 mmol/day. The mean plasma Na^+ and K^+ concentrations for the group did not change signficantly (paired t-test; $t = 0.93$, $p > 0.10$) during these 7 days (Appendix 7.2).

During this period of carbohydrate restriction, RER values fell from those of the subjects on a mixed diet, 0.84 ± 0.02, to a mean value of 0.75 ± 0.04 on day 7 (Fig 7.5).

The percentage weight changes of the 6 volunteers who received a sustained K^+ intake throughout the study are shown in Fig 7.6. The initial period of Na^+ restriction and low-carbohydrate feeding was accompanied by a mean weight loss of 2.67 ± 0.63 kg (4.23 ± 0.79 per cent) by day 7 (Table 7.2). Concomitant with this was a fall in TBW of 2.33 ± 0.20 litres (6.29 ± 1.48 per cent). A diuresis and negative water balance was most marked for the first 4 days. A nadir of change in weight was achieved by day 6.

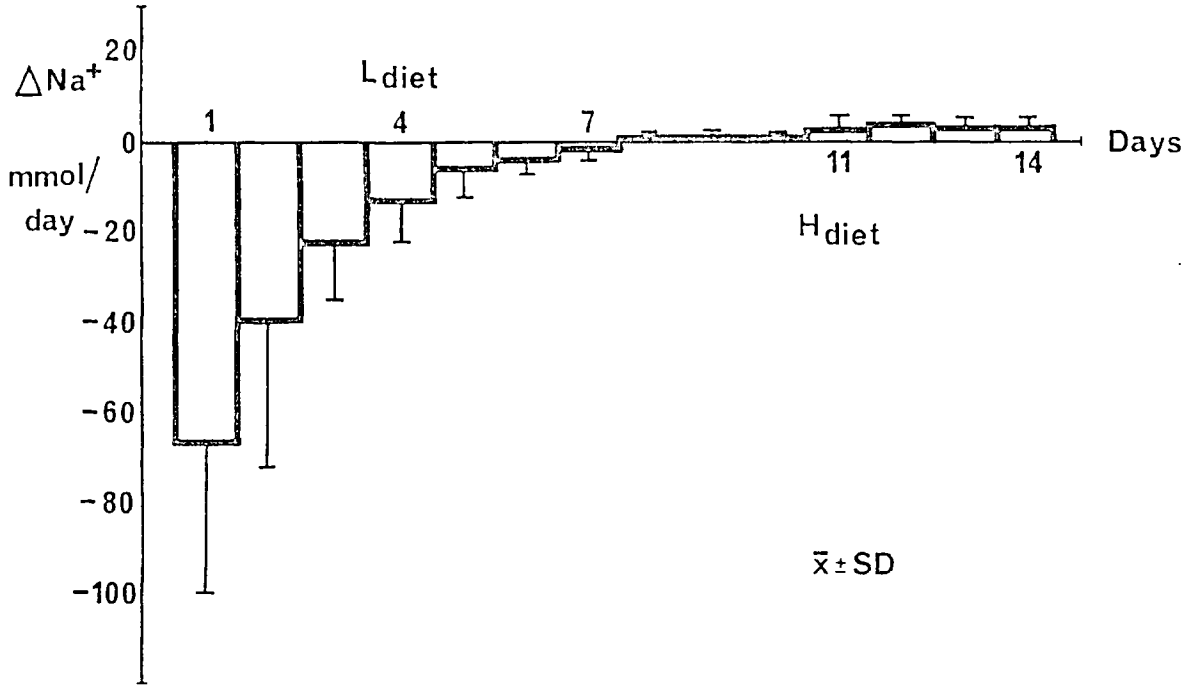


Figure 7.4

Na^+ balance during low-Na^+—low-carbohydrate (L_{diet}) and low-Na^+—high-carbohydrate (H_{diet}) feeding in volunteers

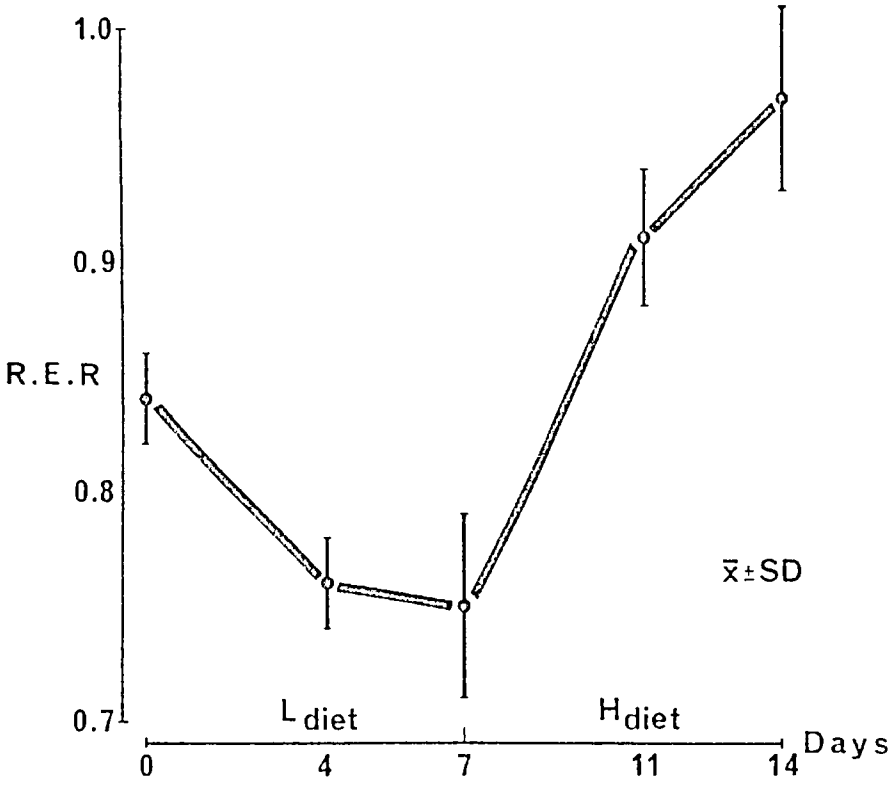


Figure 7.5

RER during test diets in volunteers

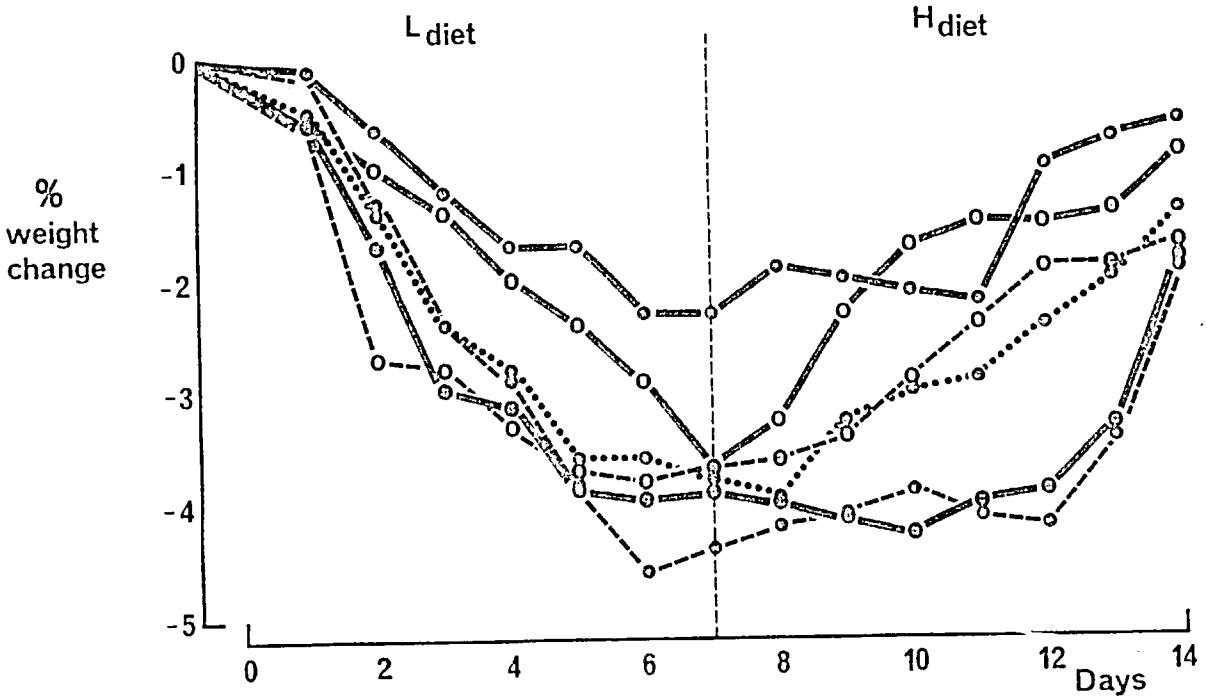


Figure 7.6

Weight changes during low-Na^+ low-carbohydrate (L_{diet}) and low-Na^+ high-carbohydrate (H_{diet}) Potassium intake was sustained at 56 mmol/day

Low-Na^+ high-carbohydrate diet in volunteers

During the second week, urinary Na^+ levels were not more than 5 mmol/day (Fig 7.4), compatible with the continued low Na^+ intake. Again there was no significant change in mean plasma Na^+ and K^+ concentrations during this period (paired t-test; $t = 0.13$; $p > 0.10$) (Appendix 7.2).

A change to a high carbohydrate intake produced in all volunteers a rise of RER towards unity, the maximum value on day 14 being 0.97 ± 0.04 (Fig 7.5).

TABLE 7.2

Weight, Water and Nitrogen data in 6 volunteers given a sustained potassium intake, and 2 volunteers (A & B) for whom potassium was restricted. Nitrogen balance derived from daily input and urinary urea excretion

		Weight (kg)			TBW (litres)			Cumulative N balance (g)	
Subject	Day	0	7	14	0	7	14	7	14
1		66.0	63.1	64.8	39.5	37.1	38.4	-15.1	35.8
2		77.2	73.4	75.3	41.6	39.3	40.6	-15.4	17.5
3		68.3	66.1	67.5	44.3	41.9	43.0	-24.9	12.7
4		58.8	56.6	58.2	38.2	36.2	37.4	-32.6	16.5
5		57.9	55.7	57.1	36.6	34.3	35.4	-16.5	20.0
6		50.7	48.0	49.8	28.3	25.7	27.1	-15.5	23.5
A		62.2	58.8	56.9	33.2	30.9	30.6*	-16.7	15.2
B		73.5	71.3	70.6	43.8	41.7	41.2	-17.5	16.3

* Day 11

In the 6 volunteers who received a sustained K^+ intake, a gradual weight gain of 1.63 $\pm$ 0.21 kg (2.75 $\pm$ 0.55 per cent) was achieved by day 14 (Fig 7.6; Table 7.2). This weight gain was associated with an increased in TBW of 1.23 $\pm$ 0.12 litres (3.57

± 0.97 per cent). A strong linear relationship was demonstrated between changes in TBW and body weight (Fig 7.7) the equation of the regression line being:

$$\Delta TBW = 0.67 \Delta Weight + 0.33; \quad p < 0.005$$

Of the 2 volunteers who were deprived of K^+ during high carbohydrate feeding, only one completed the full second week of the diet. In the other, the experiment was terminated on day 11 because of subjective feelings of ill health accompanied by a severe fall in plasma K^+. She continued to lose weight in the 4 days of the second week and the other subject failed to gain weight (Fig 7.8). Their RERs rose to a final range 0.89 - 1.03. Their TBW measurements remained unchanged between the end of the first and second week (Table 7.2).

Malnourished patients on parenteral feeding

Fig 7.9 shows the results of clinical studies in 2 patients with total dysphagia. As a consequence of an absent oral intake both patients presented with maximal renal Na^+ conservation, with Na^+ excretion of no more than 10 mmol/day. Water replacement in the form of intravenous 5% dextrose generated weight gains of 1.20 kg over the next 3 days. With high carbohydrate (20% dextrose) infusion, against a background of zero Na^+ input, a further gain in weight of 2.20 kg was observed over the next 5 days. The latter weight gain was associated with an increase in TBW of 1.60 litres and a return

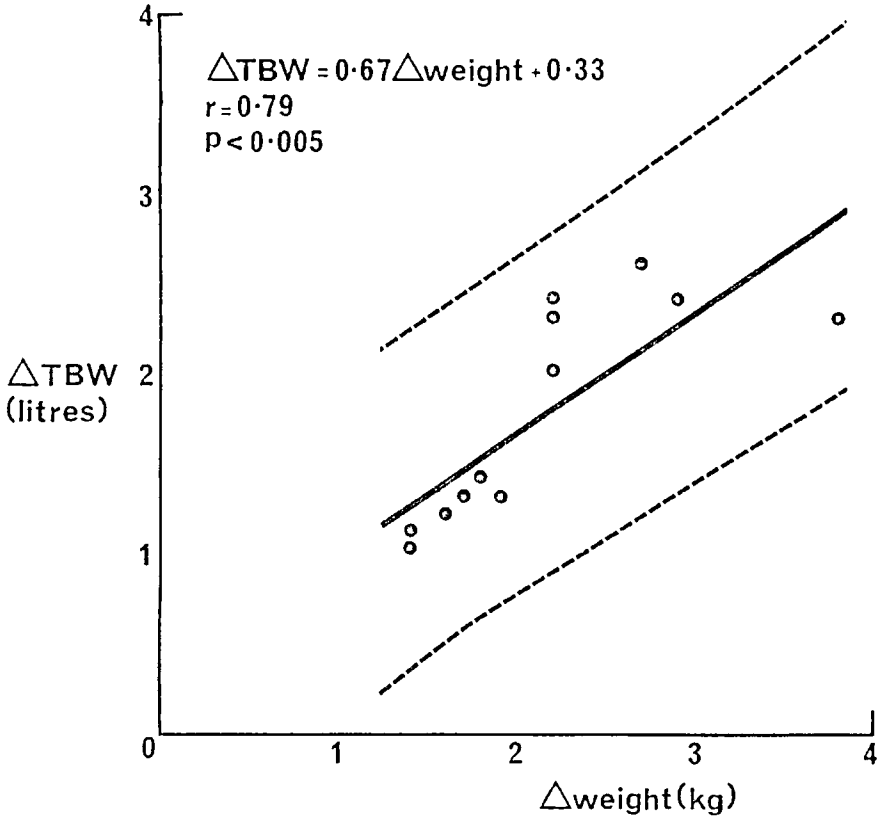


Figure 7.7

Regression plot of the relationship between changes in TBW and body weights during the test diets in 6 volunteers who received a sustained K^+ intake. The dotted lines define the 95 per cent tolerance limits

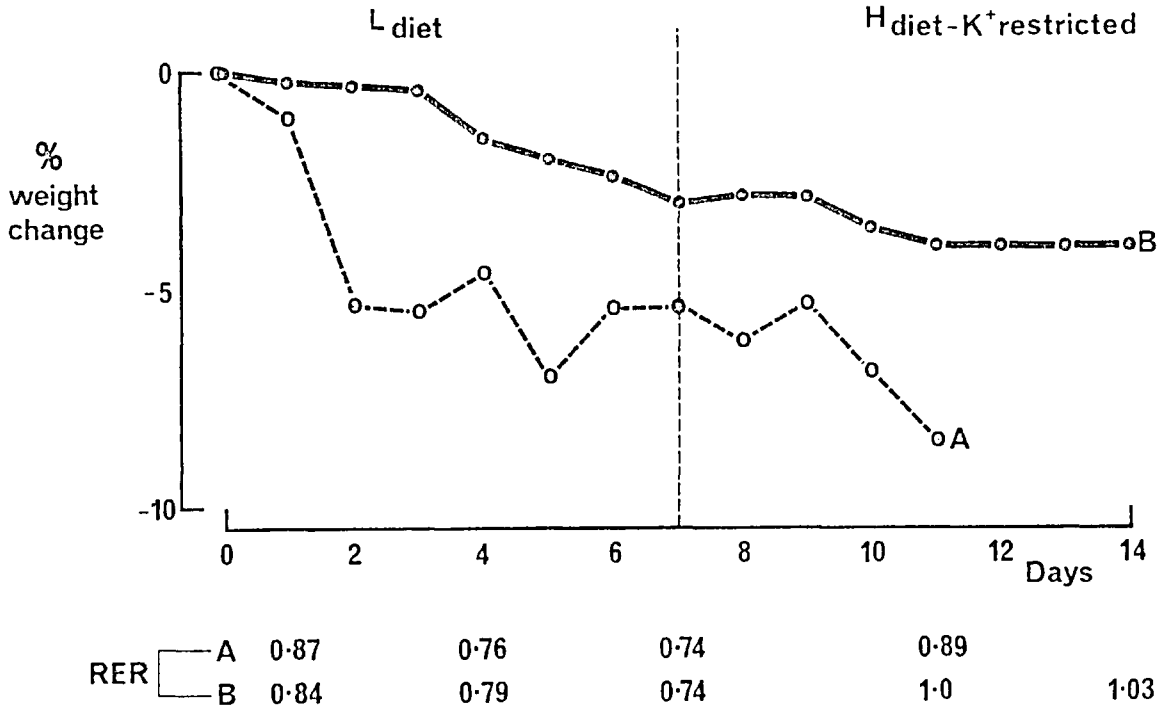
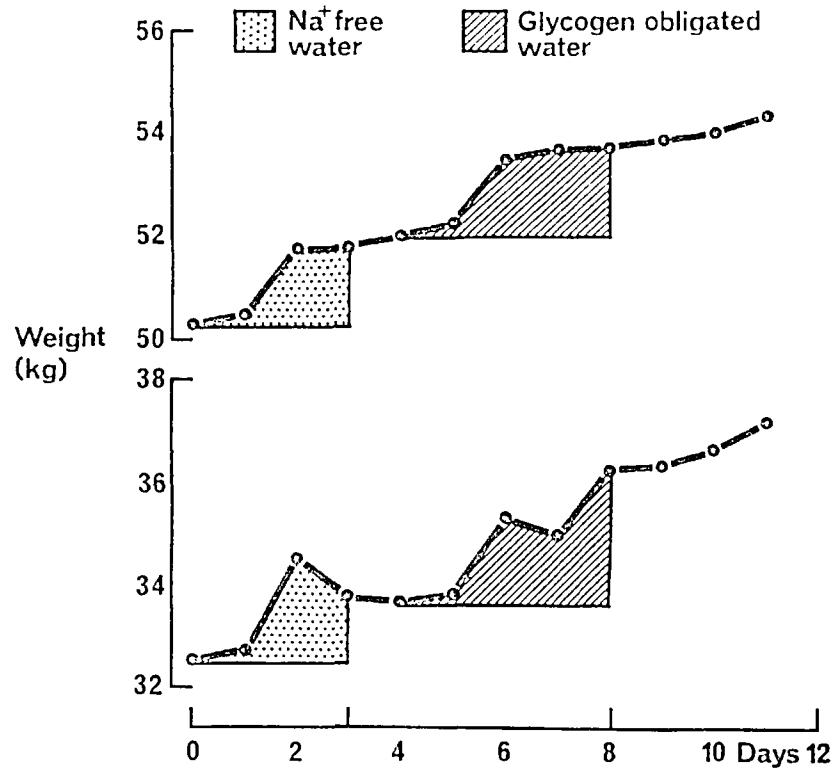


Figure 7.8.

Weight and RER changes in 2 volunteers for whom K^+ was restricted to 5 mmol/day during low-Na^+ high-carbohydrate (H_{diet}) feeding



IVT	5% Dext.		20% Dext.		Dext. + AA's	
	L diet		H diet			
MJ	1·67		6·70		8·37	
Na^+ input	0		0		77 mmol	
K^+ input	60		60		60 / day	
RER	0·72		0·97		1·03	
	0·72		0·92		1·06	
TBW	31·4			34·3		34·7
(litres)	22·5			25·2		25·8

Figure 7.9

Weight charts of 2 patients with total dysphagia during parenteral feeding

(IVT - Intravenous therapy; AAs - amino acids)

of RER towards unity; the weight gain was maintained while the patients continued to receive dextrose and amino acids (Fig 7.9).

Estimation of Glycogen Obligated Water

'Solid' gain can be calculated from the difference between weight gain and TBW gain. This was 0.40 ± 0.11 kg (Table 7.3). There are three possible components: protein; accumulation of faecal residue; and glycogen. As to the first, the nitrogen balance data on all subjects, assuming a ratio of 3 g of water for each gram of protein (Drenick, 1980) shows an average of 0.21 kg gain in the 6 subjects after a similar loss in the first week (Table 7.2). As to the second, stool weight was not measured and there is no data which will answer the question of how much of either positive or negative weight changes can be attributed to faecal accumulation in, or loss from, the colon in circumstances such as these. Stool frequency was less in the first 7 days but was constant thereafter. Even if the weight of faeces in the colon doubles, changes in the body weight as a consequence could not exceed 600 g. Thus it can be confidently stated that the majority of the weight changes observed were the consequence of changes in total body water and glycogen storage, with 1 g of glycogen obligating 3.21 ± 0.57 g water (Table 7.3).

TABLE 7.3

Individual Glycogen Storage

Subject	Weight gain (kg)	TBW gain (litres)	Glycogen storage (g)	Glycogen-obligated-water(g) (per g glycogen)
1	1.7	1.3	400	3.25
2	1.9	1.3	600	2.17
3	1.4	1.1	300	3.67
4	1.6	1.2	400	3.00
5	1.4	1.1	300	3.67
6	1.8	1.4	400	3.50
Patient				
1	2.2	1.7	500	3.40
2	2.0	1.5	500	3.00

7.6 Discussion

Carbohydrates constitute the primary source of energy in most parenteral feeding regimens. In that glycogen storage obligates water, glycogen repletion with such regimens might be expected to increase body water and weight. The physiological model used in this study of isoenergetic high-carbohydrate feeding against a stable background of minimal Na^+ intake allows distinction of the weight gain that is consequent upon such glycogen storage from that which might be the result of changes in body Na^+.

The provision of a virtually Na^+-free and carbohydrate restricted diet resulted in initial weight loss in the normal volunteers which reflects two things: gradual decrease in the volume of ECF in turn the consequence of the change in dietary Na^+ (Strauss et al, 1958); and depletion of glycogen stores. Na^+ conservation in this model is slow, probably because the diet used was low in carbohydrate (Gamble, 1946; Bloom, 1962; North et al, 1974). Na^+ balance is achieved at the lower level of intake when the reduction of body Na^+ and ECF volume is sufficient to limit the excretion of Na^+ to match the lower level of intake. The observation that the plasma Na^+ concentrations showed no significant changes indicates an

isotonic loss of ECF volume during the initial period of Na+ restriction. In the subjects the loss of ECF can be calculated from the 24 h Na^+ excretion and concomitant plasma Na^+ concentration (Table 7.4). Over the first week, this ranged from 0.90 - 1.70 litres with a mean of 1.32 $\pm$ 0.31. By difference between these figures and the measured reduction in TBW a 'pure water loss' is obtained and was 1.02 $\pm$ 0.39 litres. In the second week, when gain of ECF was prevented by continuing to feed a low Na^+ diet, an average gain of TBW of 1.23 $\pm$ 0.12 litres was found. There is no significant difference between these figures ($t = 1.37$; $p > 0.10$) and this permits the inference that water loss and gain reflects a common process.

TABLE 7.4

Water and Na^+ balances at the end of the first week in 6 volunteers

Subject	Cumulative Na^+ balance (mmol)	Plasma Na^+ conc (mmol/l)	ECF (litres)	'Pure water loss' (litres)
1	-164.9	146.0	-1.1	-1.3
2	-232.9	138.0	-1.7	-0.6
3	-218.8	141.6	-1.6	-0.8
4	-199.6	139.0	-1.4	-0.6
5	-115.7	136.0	-0.9	-1.4
6	-163.8	142.4	-1.2	-1.4

The low RER values reached in the first week imply predominant fat metabolism with the inevitable minimum protein contribution for gluconeogenesis. Though a direct inference that glycogen stores are maximally depleted cannot be made, all the information available (Olsson and Saltin, 1970; Bergstrom and Hultman, 1972; Jette et al, 1978) makes this probable. Refeeding with carbohydrate returns the RER towards unity and increases body water. The equality between loss and gain of water as distinct from Na^+ and water leads to the conclusion that the common process is depletion and repletion of glycogen

stores. In this process water is obligated to the storage carbohydrate. From these observations the volume of water that is obligated to intracellular glycogen storage is found to be 3.21 $\pm$ 0.57 g of water per gram of glycogen stored. Others have found similar figures in animal studies (Puckett and Wiley, 1932; Fenn and Haege, 1940) and in liver and muscle biopsies from humans (Bergstrom and Hultman, 1972). Weight does not return to the pre-experimental level because of the maintained low ECF volume.

The preliminary observations on the 2 K^+-deprived subjects suggest that glycogen-water storage is K^+ dependent in this model. Much evidence has been accumulated that K^+ is intimately linked to carbohydrate metabolism (Fenn, 1939; Gardner et al, 1950; Mortimore, 1961; Hue et al, 1975). The finding that their RER approached unity during the second week indicates that glucose can still be catabolised despite the inability to store glycogen (Askanazi et al, 1980). This observation has subsequently been confirmed in a larger study (Johnson, Kapadia and Dudley, 1982).

The studies in 2 patients with total oesophageal obstruction show that parenteral feeding with high-energy glucose-based solutions produces a similar amount of water retention because of glycogen storage. Their initial weight gain whilst being fed Na^+-free water can be ascribed to total body rehydration. Further weight gain durng high-carbohydrate infusion was associated with increase in total body water and RER values of carbohydrate utilisation.

These results, far from suggesting that the surgical patient on total parenteral nutrition is over-hydrated, support the view that there is a return to normality in two respects: first, cellular hydration as glycogen is stored in cells such as liver and muscle; and second, if Na^+ is given, a change in extracellular hydration towards the midpoint of Na^+ homeostasis - the latter representing 1.0 - 1.6 litres of extracellular water. These changes are physiological and potentially important if the rehabilitated patient is to undergo surgery because they imply a readily available source of energy and a normal extracellular volume.

7.7 Summary

Early weight gain by starving patients managed with total parenteral nutrition has been regarded as spurious - that is, merely an increase in body water . An experiment has been designed to produce a mimic of the starved state, in which glycogen stores are depleted and Na^+ intake is very low. The subjects were then repleted using a Na^+-free, high-carbohydrate intake. All subjects who received K^+ gained weight and switched to a respiratory exchange ratio which suggested mainly carbohydrate oxidation. From changes in weight and total body water, the weight gain was calculated to be the consequence of glycogen storage, with 1 g of glycogen obligating 3.21 $\pm$ 0.57 g water. Two patients with total dysphagia showed a similar pattern. Two subjects who did not receive K^+ showed a rise in respiratory exchange ratio, but failed to store glycogen.

Early weight gain in patients who receive high-carbohydrate feeding after starvation is a normal phenomenon and represents a return to a more hydrated state consequent upon glycogen repletion.

C H A P T E R 8

A HYPOTHETICAL MODEL THAT INTERLINKS WATER AND SODIUM MOVEMENTS WITH THAT OF GLYCOGEN STORAGE

8.1 INTRODUCTION

It is tempting to equate hyponatraemia with Na^+ depletion, but the usual cause is the result of an excessive amount of water in the body, in turn caused by failure of renal excretion, often abetted by continued ingestion or administration of fluids (Dudley et al., 1954; Moore, 1962). Indeed, this dilutional hyponatraemia may arise in patients who have an overall increase in body Na^+.

Because the serum Na^+ level is clearly correlated with serum osmolality (see Chapter 3) and since most body fluids are isotonic, the serum Na^+ level represents the degree of dilution or concentration of body fluids produced by disease. This assumes that significant changes in the non-osmotic, bound fraction of body Na^+ do not occur. Intracellular Na^+ binding is of uncertain extent both in normal and pathological situations (Swales, 1975), although it is freely invoked as a cause of fluid and electrolyte anomalies. Changes in bone Na^+ content (bone accounts for by far the greatest binding of Na^+ in non-osmotic form) have been implicated as an explanation of anomalous Na^+ balances, but in one clinical study this remained unchanged in a variety of diseases (Pellegrino and Farber, 1960). Furthermore, in a classic study by Edelman et al. (1958), there was no evidence

for sufficient osmotic inactivation of exchangeable Na^+ (Na_e) to produce significant changes in serum Na^+ concentration.

Thus, the determinants of the serum Na^+ are (see Chapters 3 and 4):

(i) the total quantity of metabolically active Na^+ (Na_e);

(ii) the total quantity of metabolically active K^+ (K_e) which is almost equal to total body K^+;

(iii) total body water (TBW);

(iv) factors other than Na^+ and K^+ which may, in certain clinical situations, change the ratio between ICF and ECF water. The intracellular release of non-ionic molecules which obligate the presence of water may lead to the development of hyponatraemia associated with osmolal gaps (Chapter 4).

A low serum Na^+ concentration is a common feature of severe systemic illness, whatever its cause. The concept of a "sick cell syndrome" has been loosely applied, generally with the explicit or implicit suggestion that hyponatraemia can be attributed to migration of Na^+ into the ICF as a consequence of a disturbance of membrane transport. Flear (1970) and Flear et al. (1980) adduced isotope dilutional evidence that Na^+ moves into the cells and increased solute is generated within the cells which then leaks out into the ECF. The relevance of such a

disturbance in the development of hyponatraemia in the clinical situation is doubtful. Leaf (1962) has pointed out that such intracellular Na^+ migration also demands that the Na^+ be osmotically inactivated, since otherwise water would move into the cells and the serum Na^+ would remain unchanged.

8.2 Glucose-postassium-insulin ('GKI') Therapy and Hyponatraemia

The management of hyponatraemia usually resolves itself into the management of the underlying condition. In the majority of cases, the causal disease represents a much greater threat than the Na^+ disturbance. The use of hypertonic saline is almost always contraindicated (Swales, 1975) since in most cases encountered clinically, Na^+ is already present in excess. Theoretically, water restriction and K^+ loading should help to correct a low serum Na^+ concentration. The former practice is regularly employed, while in ordinary circumstances the latter may be a dangerous manoeuvre.

While studying the effects of insulin on nitrogen metabolism, Hinton et al. (1971; 1973) noted striking effects of this hormone on electrolyte levels. Using a regimen of glucose infusion (600 g daily), potassium (100-300 mmol), and insulin (200-600 units daily), they demonstrated a rise in serum Na^+ concentration in patients with severe burn injuries who had marked hyponatraemia. This 'GKI' regimen also resulted in a diuresis and natriuresis. The successful use of GKI therapy has since been recorded by others (Weisul et al., 1975) and experimental studies have also demonstrated its salutary effects in endotoxic shock (Manny et al., 1978).

8.3 Hypothesis

As water is ubiquitous in the composition of body cell mass, apart from its lack in storage fat, a hypothetical model of body composition can thus be represented, as in Figure 8.1.

A good deal of clinical and experimental evidence exists that glycogen storage in the cell obligates water. That water is bound to liver glycogen during a high carbohydrate diet has been known for some time (Pavy, 1860; Bridge and Bridges, 1932). In animal studies, biochemical analyses of liver slices have demonstrated that the deposition of 1 g of glycogen is associated with 1-3 g of water (Puckett and Wiley, 1932; Fenn and Haege, 1940). Similar figures have been obtained in human muscle and liver specimens by needle biopsy techniques under conditions of starvation and re-feeding with carbohydrates (Olsson and Saltin, 1970; Bergstrom and Hultman, 1972; Nilsson and Hultman, 1973). The experimental model in Chapter 7 in volunteers and patients demonstrates that during carbohydrate replenishment an absolute increase in total body water (TBW) occurs which accounts for the observed weight gain that is independent of changes in body Na^+. The volume of water that is obligated to intracellular glycogen storage is calculated to be 3.21 $\pm$ 0.57 g of water per gram of glycogen stored.

As a corollary to the observation that substrate storage

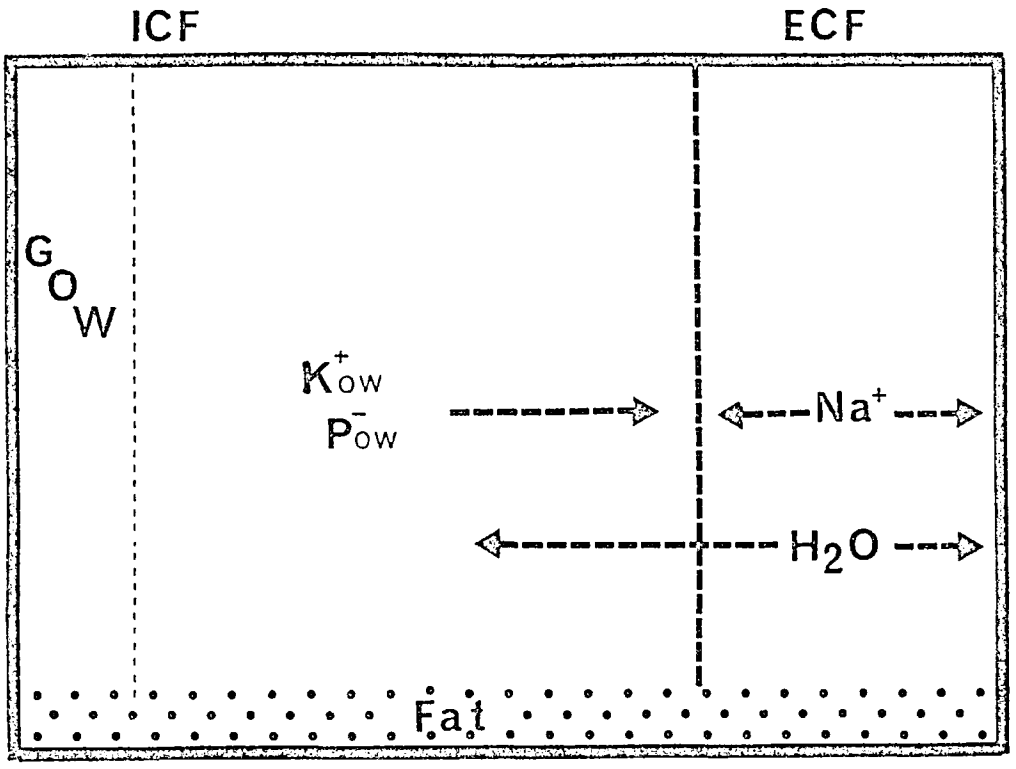


Figure 8.1

Hypothetical model of body composition
Water is obligated to glycogen
(Glycogen-Obligated-Water),
K^+ and proteins in the intracellular phase

obligates water, it has been well documented that during starvation intracellular water is liberated from many tissues as a result of consumption of glycogen and body protein stores (Moore, 1958; 1959; Gump and Kinney, 1968; Drenick, 1980).

8.4 A Rationale of 'GKI' Therapy, Based on the Glycogen Obligated Water Model

The classical sequence of events following severe injury is said to be characterised by the following: rapid lysis of body protein; fat oxidation quickly achieves a maximal rate; substrate utilisation is in favour of the immediate production of energy from carbohydrate; Na^+ and water conservation is immediate and prolonged (Moore et al., 1975). In such circumstances, the body stores of glycogen will be exhausted within a matter of hours.

The net effect of GKI therapy is promotion of intracellular glucose storage. The provision of glucose alone does not necessarily equate with glycogen storage, as ample evidence exists that this process is dependent upon the availability of K^+ (Fenn, 1939; Gardner et al., 1950; Mortimer, 1961; Hue et al., 1975). The peripheral uptake of glucose by cells is associated with a shift of K^+ from the ECF into cells, and many enzymes required for glycolysis and oxidative phosphorylation are K^+ dependent (White et al., 1964). Furthermore, K^+ deficiency is often seen in the clinical states of protein-calorie malnutrition (Alleyne et al., 1970; Mann et al., 1975) and it has been documented that K^+ depletion inhibits the secretion of insulin by pancreatic islet cells (Anderson et al., 1969; Mann et

al., 1975).

The hypothetical model in Figure 8.1 would explain the rise in serum Na^+ concentration with GKI therapy as a direct consequence of glycogen storage and its obligation of water into the cells.

Repletion of body glycogen (450 g) will potentially trap 1350 ml of body water in the intracellular compartment. This amount of compartmental shift of water would reduce extracellular volume by about nine to 10 per cent, and raise serum Na^+ concentration by 12 to 14 mmol/litre. The greatest change in serum Na^+ concentration in Hinton's burn patients (1973) following GKI therapy was 10 to 12 mmol/litre. Figure 8.2 shows the data of two patients with severe hyponatraemia treated with 'GK' regimen. The rise in serum Na^+ concentration during therapy was 12 mmol/litre. More importantly, respiratory exchange ratio measurements rose from 0.77 before therapy to 0.95 following the GKI regimen. The inference is that glycogen stores have been replenished and during the process water is obligated intracellularly and a concomitant rise in serum Na^+ observed.

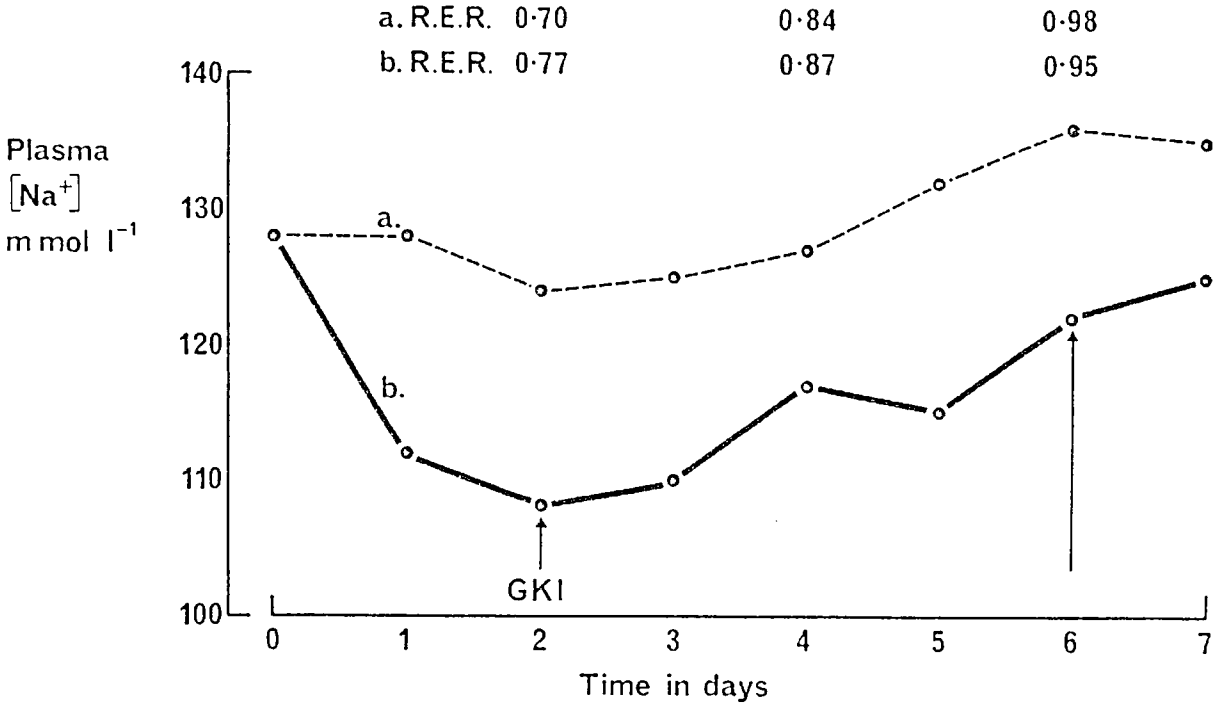


Figure 8.2

Changes in s-Na^+ and RER during 'GK' therapy in 2 patients with severe hyponatramia (see Appendix 8.1 for patients' details

8.5 Post-traumatic Energy Perturbations and Hyponatraemia

Using the same hypothetical model of body composition (Fig. 8.1) the immediate consequence of glycogen mobilisation to supply energy is that water obligated to glycogen is also being mobilised to enter the total body water (Fig. 8.3). Its excretion is opposed by antidiuresis (Dudley et al., 1954) and the serum Na^+ concentration will fall. In the post-traumatic state, hyponatraemia is often further exaggerated by misguided fluid therapy in the form of excessive water being given. In protracted stress and injury, glycogen mobilisation is limited and the next sequence of events is increased cellular breakdown of protein with its attendant release, and extracellular migration of intra cellular K^+. The net effect is further shrinkage of cellular volume.

In osmoregulatory terms, if we accept that we have put cell volume as the controlled variable at the centre of a feedback system (Morgan and Thomas, 1979) - and this is teleologically attractive - it is then not inconceivable that osmoreceptors in the brain partake in the cell volume shrinkage consequent upon glycogen depletion. Stimulation of antidiuretic hormone (ADH) release will be enhanced by such osmoreceptor shrinkage with its attendant reduction in renal water excretion and fall in serum Na^+ concentration.

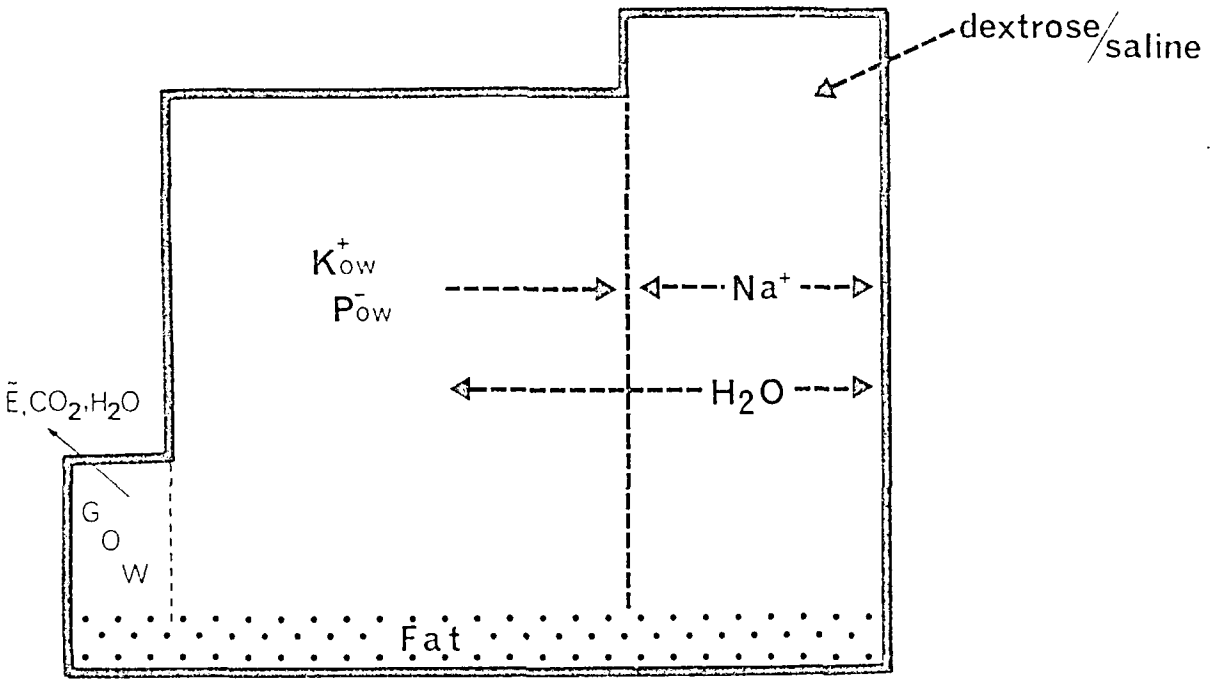


Figure 8.3

Post-traumatic hyponatraemia: glycogen stores are mobilised for energy ($\tilde{E}$) and total body water rises. Intravenous dextrous-saline will further exaggerate extracellular hypotonicity

The post-traumatic release of ADH has also been found to have a direct bearing on liver carbohydrate metabolism. In experimental studies, ADH not only can stimulate the breakdown of glycogen in the liver, but inhibits net glycogen accumulation in starved rats, in vivo or in the perfused liver (Hems and Whitton, 1973). ADH may thus contribute to the accelerated release of hepatic glucose during severe trauma. More importantly, the action of ADH may mobilise the water that is stored in conjunction with glycogen, that can amount to two to four times the weight of glycogen (Fenn, 1939; Mortimer, 1961; Herrera and Freinkel, (1968).

8.6 Discussion

The rationale behind the therapeutic advantage of 'GKI' over simply the provision of glucose or other substrates for energy metabolism has not been fully explained. Hinton et al. (1973) have postulated that their data on burn injuries would suggest that insulin may have caused Na^+ and Cl^- to pass from the ICF to the ECF space and would fit with the observation of Flear (1970) that severe injury may be associated with a failure of cell membrane function, allowing excess Na^+ to pass into the cells. It may also be that the intracellular K^+ load results in the osmotic movement of water into the cells, perhaps with Na^+/K^+ exchange also contributing. The tubular load of Na^+ would then rise and produce a natriuresis (Swales, 1975).

Clinical and experimental evidence suggests that glucose homeostasis is associated in the ill and injured patient with the phenomenon of 'sick cell hyponatraemia', which may be associated with extracellular osmolal gaps (see Chapter 4). Furthermore, the provision of extra substrate - glucose - and large doses of insulin and K^+ are capable of overriding the block to glucose uptake by the cell and thus producing improvement in organ function and correction of extracellular hypotonicity. The hypothetical model presented here can explain this. The dynamics of glycogen storage can cause sufficient body fluid shifts between cellular compartments to account for marked changes in serum Na^+

levels. In sick hyponatraemic patients, excess water in the ECF space (its excretion being opposed by ADH) can be translocated by promoting the storage of carbohydrate in the cell. Indeed, the nutritional status of the patient may help to determine water and electrolyte flux. It is unnecessary to postulate that insulin promotes Na^+ shift into the ECF space, for which there is no evidence.

8.7 Summary

A hypothesis is proposed that the dynamics of glycogen storage can cause sufficient body fluid shifts between cellular compartments to account for marked changes in serum Na^+ levels. The successful reversal of 'non-dilutional' hyponatraemia with glucose, potassium and insulin therapy can be rationally explained by extracellular to intracellular compartmental fluid shift consequent upon glycogen storage. Disturbance of membrane function need not be directly implicated in such hyponatraemic states. Conversely, mobilisation of glycogen obligated water in the post-traumatic state may be an important underlying factor in contributing to dilutional hyponatraemia as its excretion is opposed by antidiuresis.

P A R T I V

EFFECTS OF WATER AND SODIUM INFUSION WITH RESPECT TO INTESTINAL SURGERY

C H A P T E R 9

THIRD SPACE SEQUESTRATION AT THE SITE OF RABBIT SMALL BOWEL ANASTOMOSIS

9.1 INTRODUCTION

As indicated in Section 1.4 of the historical review, the early 1920s witnessed the intravenous infusion being slowly added into medical practice, but it was not until the '50s that clear evidence was produced that intravenous therapy causes an increasing positive cumulative balance both of Na^+ and water during and after surgery.

During this early period of inquiry into the physiology of Na^+ and water metabolism in the post-operative phase, the evidence from various studies of renal haemodynamics appeared to show insufficient changes to account for the post-operative Na^+ and water retention. Carl Moyer (1950) concluded at this time that the renal functional changes "cannot be ascribed to alterations in renal blood flow, to a deficit of water, to deficits of Na^+ or Cl^-, to blood loss, or to the action of the anaesthetic agent. The only apparent possible causes for them are distributional shifts of the body fluids and the afferent stimuli arising in the operative area".

That sequestration of fluid could occur in and about traumatised tissues had been commented upon by Lewis in 1927, and this he ascribed to increased capillary permeability. The studies of Blalock in the 1930s (Blalock, 1930; 1931; 1934; Beard and Blalock, 1931) had shown that, following trauma, there was sequestration of fluid in and about traumatised tissues, in the interstitial fluid of the wall and in the lumen of the bowel, following manipulation during gastrointestinal tract surgery, and in serous cavities following thoracic and abdominal surgery. Animal experiments have also confirmed these findings (Ricca et al., 1945; Fox and Baer, 1947; Schilling et al., 1953).

Further, and more recent, support of fluid sequestration came from the studies of Flear et al. (1969), who carried out muscle biopsies in patients undergoing major vascular operations, and found that by the end of the operation muscle cells had gained water, Na^+ and Cl^- ions, and lost K^+; the significance of these changes depends on the extent to which muscles away from the operation site are involved.

9.2 The Water Content of Healing Incisions

Since the early descriptions by Celsus of the inflammatory response to tissue injury, it has been widely observed that oedema to some degree is a normal feature of wound healing (Adamsons et al., 1967). However, it has also been suggested that excessive wound oedema may be deleterious as it is a feature of wounds in animals made malnourished (Thompson et al., 1938; Irvin and Hunt, 1974).

Many reports have appeared in the surgical literature describing attempts to enhance healing by preventing or decreasing wound oedema. Calnan and his associates injected chymotrypsin in rats to reduce oedema in the hind legs produced by the injection of egg albumin (Calnan et al., 1963). When he compared the weight of hind limbs, he found less oedema in the treated group, although measurements of water concentration were not carried out. Clinically, he found this drug ineffective.

Hypoproteinaemia is known to cause generalised tissue oedema and impaired wound healing. However, it has not been proved that the impaired healing is the result of oedema, although this is generally conceded. Irvin and Hunt (1974) noted anastomotic oedema occurred during colon healing in animals starved for seven weeks; the collagen content of anastomoses in these animals was

significantly lower than the value in control animals.

Adamsons et al. (1967) in a study of abdominal wounds in guinea pigs reported that a normal wound maintains a signficantly elevated water content during the first fifteen post-operative days, with insignificant daily variation. The water content returns slowly to normal by the forty-fifth post-operative day.

9.3 Objective

Intestinal surgery is usually associated with the parenteral administration of Na^+ and water, sometimes in amounts considerably in excess of excretory capacity.

Though many elegant studies of wound swelling have been done in relation to general body tissues, the intestinal anastomotic wound, a common feature of abdominal surgery, has received little attention. Furthermore, quantitative assessments of the amount of oedema and studies on the change of water content of intestinal anastomoses have been few in number (Shields and Dudley, 1971; Irvin and Hunt, 1974).

The data presented in Chapter 3 of this thesis have shown that in patients given a conventional fluid regimen there is extracellular fluid dilution in the post-traumatic period that is more prolonged than had previously been thought. Currently, there is no doubt that fluid sequestration can occur and major surgery or extensive trauma produces large areas of damaged tissue into which ECF may leak. However, though attempts should be made to replace these losses by the peri-operative fluid regimen, studies are lacking on the effects of administration of intravenous water and Na^+ (oftimes with excessive enthusiasm) on the water content of an area of 'deliberate' damage, such as an intestinal anastomosis.

The objective of this present study was:

To Elucidate the Influence of Water and Na^+ Infusion Comparable to That Used in Common Intra- and Post-operative Fluid Regimens on the Pattern of Development and Regression of Water Content in an Area of a Standard Bowel Anastomosis.

9.4 Materials and Methods

The model chosen was a single-layer end-to-end anastomosis of adult rabbit small bowel. The rabbits were New Zealand White strain of both sexes, weighing on average 2.5 kg.

With full aseptic precautions and under intravenous pentobarbitone anaesthesia, the peritoneal cavity was entered via a mid-line incision. The small bowel was divided 10 and 20 cm proximal to the origin of the appendix mesentery. Interrupted 7/0 silk sutures on an atraumatic round-bodied needle were then used to reunite the ends of the seromuscular layers without inversion. Bleeding was diminished by ligature of the terminal mesenteric vessel on either side of the anastomosis with 7/0 silk, and stay sutures of the same material reduced the handling.

The animals were randomly allocated to one of two groups:

Group 1: did not receive intravenous therapy;

Group 2: intravenous infusion of Hartmann's solution was begun at the induction of anaesthesia (Fig. 9.1). During the operative procedure, the rate of infusion was 5 ml/kg/h and the volume of infusion ($\bar{x}$ 18.8 ml) was calculated to correspond to a one-litre over-expansion of extracellular volume in a 65 kg man (total body water in the rabbit: 668-743 ml/kg). Subsequent intravenous infusion was continued to 48 hours post-operatively and the volume was calculated to correspond to the total blood volume of the rabbit (Kaplan and Timmons, 1979):

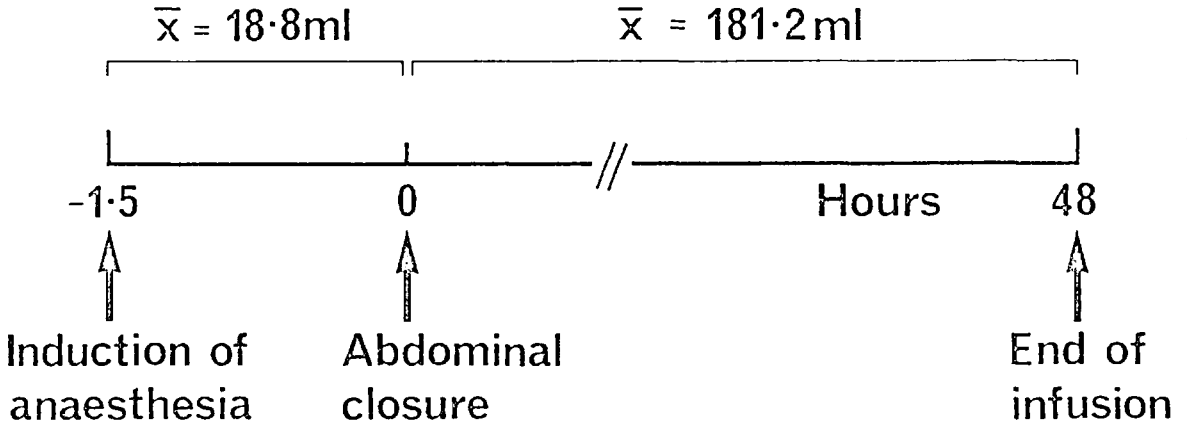


Figure 9.1

Duration and volume of intravenous infusion in Group 2

57.7-70 ml/kg. Translated to clinical practice, this amounts to 3 l of crystalloid infusion per 24 hours.

Peri-operative urine output was monitored by per urethral catheterisation using a fine polyethlene tubing.

Five animals were studied in each group at 0 (defined as abdominal closure - Fig. 9.1) and 6 hours, and daily for five days, making a total of 70 in all. In addition, five animals were used to provide control tissue.

After each operation, the abdominal wound was closed in one layer with interrupted nylon sutures and whilst awaiting the study period each animal was returned to its cage with provision of food and water.

In each animal, two tissue groups were examined (Fig. 9.2):

Tissue group A - bowel containing an anastomosis;

Tissue group B - bowel from 5 cm above the proximal anastomosis, from midway between the anastomoses, and from 5 cm below the distal anastomosis.

Estimation of water content:

After killing a test animal with an overdose of pento-barbitone, five pieces of small bowel, each 2 cm long, were taken. The choice of length of bowel was not arbitrary: there was usually slight bruising for 1 cm on either side of an anastomosis; a greater length would have introduced too much

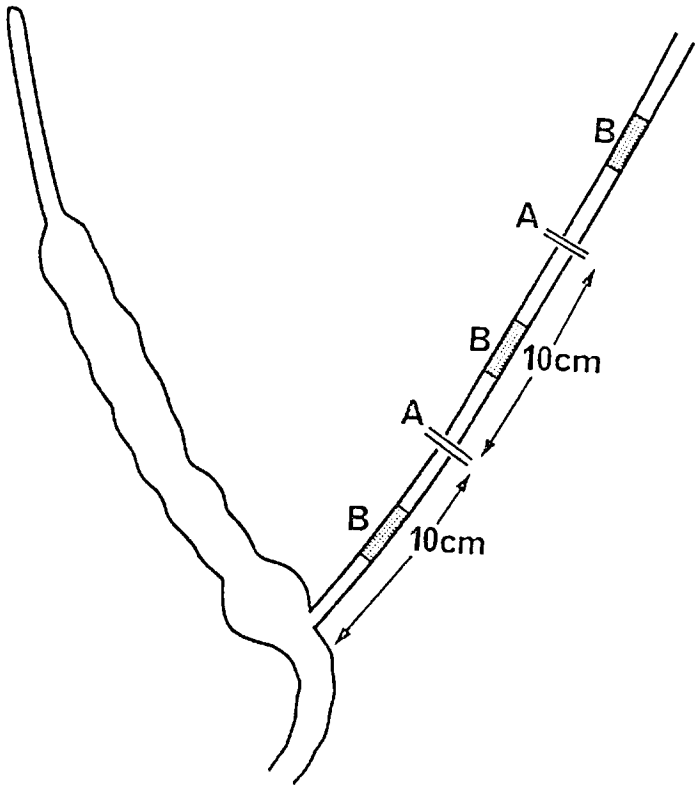


Figure 9.2

Tissue groups examined in each animal:
(A) Bowel containing an anastomosis;
(B) Bowel from 5 cms above the proximal anastomoses, from midway between the anastomoses, and from 5 cms below the distal anastomosis

untraumatised bowel, whilst a lesser amount could have given undue importance to the weight of the coagulum adhering to the anastomosis.

Two of the pieces contained an anastomosis (Tissue group A). The other pieces came from above, between, and below the anastomoses (Tissue group B). Thus, there were 10 samples of Tissue group A and 15 samples of Tissue group B in each sub-group determined by time.

Each piece of bowel was individually washed in Ringer's solution, gently mopped with absorbent paper tissue, then placed in a covered crucible and weighed immediately on a pharmacological balance. After dessication at 80°C overnight, when no further weight loss could be demonstrated, it was re-weighed.

Water content was expressed as the ratio of the fresh, or wet, weight of a sample to its dry weight - the wet/dry ratio. Ten samples of small bowel were taken from each animal in the control group, making 50 in all.

Removal of suture material before weighing and drying would have resulted in a delay and disturbance of the anastomotic site, and was therefore not done. Independent determinations of the weights of suture material used showed it to be approximately 1 mg, or about one per cent of the dry weight in Tissue group A.

Statistical methods and calculations:

The Mann-Whitney U Test was used to assess the significance of change in water content of the tissue sub-groups of A and B

with respect to the control, and the difference in water content between the two major groups of animals, 1 and 2.

The average change in water content of the tissues examined with respect to the normal control was converted to a percentage above or below normal by means of the following formula (Shields and Dudley, 1971):

$$\frac{\text{Mean wet/dry ratio of test tissue}}{\text{Mean wet/dry ratio of control tissue}} \times 100 - 100 =$$

% weight change from normal due to water

Water content of rectus and lungs:

In an attempt to seek further evidence for fluid redistribution in all body compartments during the peri-operative period, all animals sacrificed on Day 1 had both lungs and rectus muscle samples taken for estimation of water content. A 1 cm^2 sample of rectus muscle was taken from either side of the abdominal wound well away from the site of trauma. Water content was expressed as the ratio of the wet weight to its dry weight as in the estimation of gut water content.

9.5 Results

All the animals survived operation and seemed healthy afterwards. Antibiotics were not used. Daily oral water consumption averaged 260 ml in Group 1 and 265 ml in Group 2.

Examination after death showed few adhesions to the suture lines and no evidence of sepsis, leakage or obstruction. Within the lumen of the anastomotic specimens, blood clot was found to be adherent to the suture line; these became leached out within 24 hours to form a line of white coagulum, which gradually separated thereafter.

Urine output:

Though the mean urine volume in Group 2 ($\bar{x}$ 2.60 ml/h) was greater than that of Group 1 ($\bar{x}$ 2.46 ml/h), there was no significant difference in urine volume for the first 18 hours post-operatively (Mann-Whitney U: $U = 113.5$; $z = 1.53$). During this period, urine volume did not exceed 0.05 ml/min (see Appendix 9.1).

Bowel tissue water content:

Table 9.1 shows the mean and range of the wet/dry ratios of the Tissue groups A and B,and of the two groups of animals, 1 and 2.

By using the formula given above, the mean ratios are converted to percentage changes in water content and these values

TABLE 9.1

Mean and Range of Wet/Dry Ratios of Tissue Groups Studied*

Tissue Group	[1]		0	6h	Day 1	Day 2	Day 3	Day 4	Day 5
A:		$\bar{x}$	5.48	5.34	5.39	5.48	5.55	5.56	5.39
Anastomosed bowel		Range	5.41 - 5.55	5.28 - 5.41	5.23 - 5.54	5.41 - 5.56	5.44 - 5.65	5.49 - 5.62	5.47 - 5.71
B:		$\bar{x}$	5.50	5.40	5.41	5.51	5.45	5.19	5.12
Unanastomosed bowel		Range	5.41 - 5.48	5.34 - 5.45	5.31 - 5.50	5.43 - 5.60	5.34 - 5.54	5.11 - 5.28	5.03 - 5.21
	[2]								
A:		$\bar{x}$	6.00	5.60	5.68	5.65	5.81	5.82	5.84
Anastomosed bowel		Range	5.95 - 6.05	5.56 - 5.63	5.56 - 5.80	5.59 - 5.72	5.72 - 5.90	5.77 - 5.86	5.70 - 5.99
B:		$\bar{x}$	5.90	5.69	5.65	5.67	5.57	5.28	5.26
Unanastomosed bowel		Range	5.84 - 5.97	5.56 - 5.82	5.55 - 5.75	5.66 - 5.68	5.41 - 5.74	5.21 - 5.36	5.21 - 5.32

Control: $\bar{x}$ 5.09 Range: 4.20 - 5.98

*Each value used for the range of ratios represents the mean value obtained from more than one segment of bowel.

are displayed graphically in Figures 9.3 and 9.4 (Appendix 9.1). The percentage weight change above normal due to water in the group of animals not given intravenous infusion (1) showed a five to 10 per cent increase of tissue weight, both at the anastomotic site and at 5 cm away from anastomosed bowel over the first three days following surgery (Fig. 9.3). This was significant at the 1 per cent level (Mann-Whitney U). Thereafter, increased water content persisted at the anastomoses, but resolved in normal gut.

In Group 2, the animals receiving Na^+ and water infusion during the peri-operative period, a further five per cent increase in tissue weight over Group 1 was demonstrated ($p < 0.01$), persistent at the anastomotic site over five days, though resolving elsewhere after three days (Fig. 9.4).

Lungs and recti water content:

Table 9.2 shows the wet/dry ratios of lungs and rectus samples taken from the two major groups, 1 and 2, on Day 1. Although the average water content of both lungs and recti were higher in Group 2, there was no significant difference when compared to Group 1 (Mann-Whitney U:
Lungs: $U = 53$, $z = 0.23$: Recti: $U = 59$, $z = 0.68$).

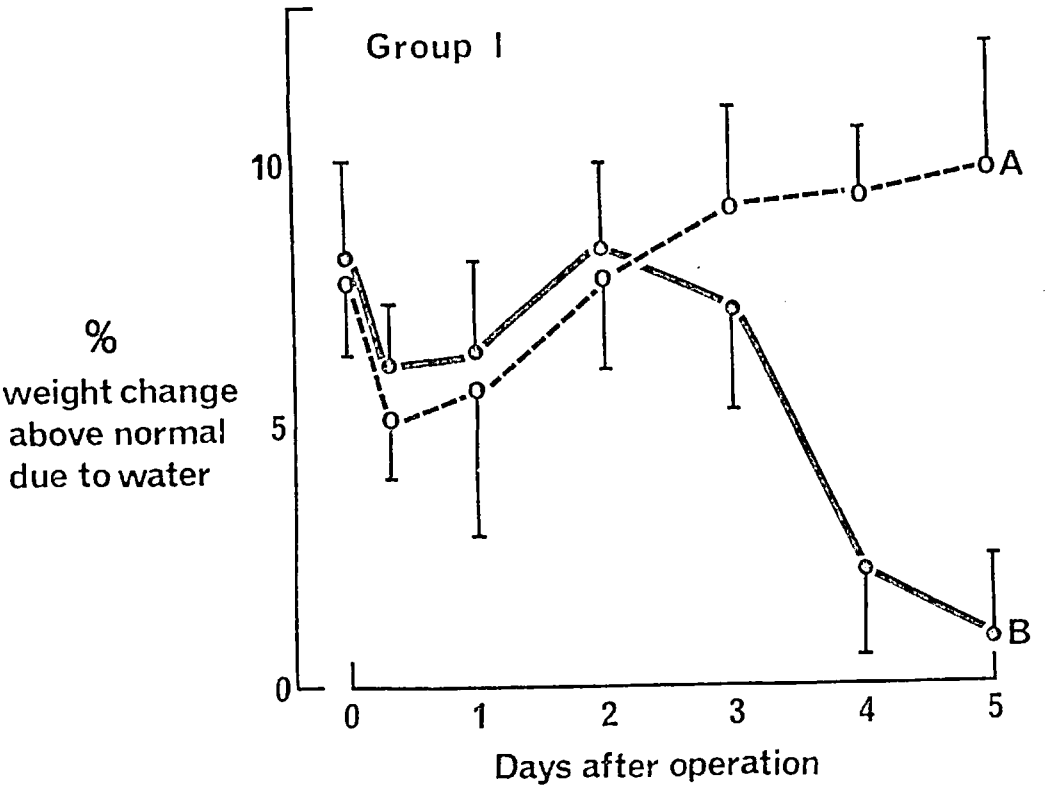


Figure 9.3

Percentage changes ($\bar{x}$ + SD) in water content in Group 1 not given intravenous infusion over five post operative days

A - anastomotic site;
B - bowel away from anastomotic site

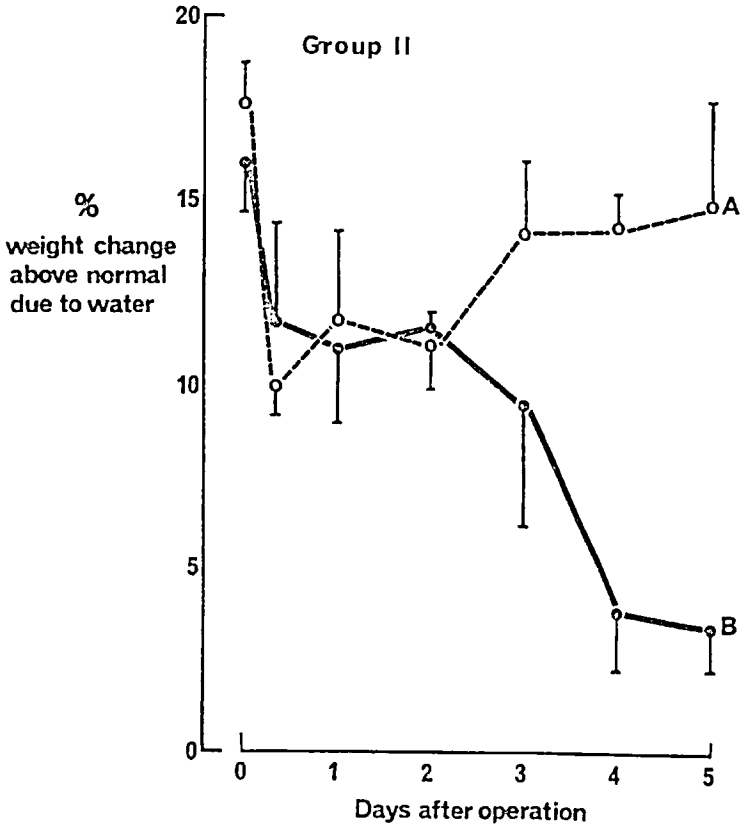


Figure 9.4

Percentage changes ($\bar{x}$ + SD) in water content in Group 2 given Na^+ and water infusion on Days 0 and 1.

A - anastomotic site;

B - bowel away from anastomotic site

TABLE 9.2

Wet/Dry ratios of Rectus Samples and Lungs on Day 1

	RECTUS		LUNGS	
	i.v. (Group 2)	no i.v. (Group 1)	i.v. (Group 2)	no i.v. (Group 1)
	1.84	3.41	1.05	3.73
	1.15	1.35	1.52	6.18
	1.21	1.04	2.60	1.08
	2.52	1.06	3.61	1.12
	2.23	1.42	2.24	1.07
	3.37	2.22	5.88	1.09
	1.39	3.05	4.24	4.34
	2.47	2.15	1.64	4.74
	3.13	2.17	1.82	2.36
	1.57	1.46	4.67	2.15
$\bar{x}$	2.09	1.93	2.93	2.79

9.6 Discussion

Major surgery is usually associated with parenteral water and Na^+ administration at a time when renal excretory capacity is reduced and water in excess of need must therefore be retained (LeQuesne and Lewis, 1953; Dudley et al., 1954). This consideration apart, the major factors which condition peri-operative fluid replacement are: the need to maintain cardiac output, and thus oxygen delivery to tissue; the volume of 'anatomical third space', that is, acute inaflammation such as peritonitis and the oedema of extensive tissue trauma (Baxter, 1974); and the possibility of a 'non-anatomical' third space with reduction in effective extracellular volume (Shires et al., 1961). Based on these considerations, current trends in surgical practice have been to administer larger volumes of water and Na^+ intra- and post-operatively than can be shown to have been lost to the exterior (Roth et al., 1969).

The possible deleterious effect of oedema in a healing wound has interested several investigators in the past (Thompson et al., 1938; Findlay and Howes, 1950; Adamsons et al., 1967). However, there is minimal data on the pattern of development and regression of water content at a suture line in the gastro-intestinal tract - a constant wound for the gastrointestinal surgeon. Moreover, of greater clinical significance is the lack

of information regarding the influence of water and Na^+ infusion on this pattern. Weech and Ling (1931) made reference on the effect of large amounts of sodium chloride intravenously intensifying tissue oedema, but the duration of this effect was not precisely mentioned.

Increases in the water content of a wound represent the sum of two independent, but simultaneous, processes: local wound oedema occasioned by injury and the healing process, and systemic changes in water metabolism occasioned by major stress (Adamsons et al., 1967). The observations in this study indicate that the water content at an anastomosis is increased compared to normal bowel and unanastomosed bowel up to five days following surgery, even if parenteral fluids are not given.

However, the water content is not different compared to bowel adjacent to an anastomosis up to three days. Thus, change in water content after three days may be looked upon as changes in wound water resulting from injury and wound repair. Studies by Adamsons et al. (1967) have identified this moiety of 'wound water excess' in abdominal wounds to be constant for about 15 days before receding slowly to normal 45 days post-operatively. It is putatively associated with the intense cellular activity phase of wound healing.

Of more clinical significance is the observation in this study that modest extracellular volume expansion in the form of Na^+ and water infusion in the peri-operative period produces a

further five per cent increase in wound water over the group which did not receive intravenous therapy. The average volume load during the peri-operative period was 200 ml; (total blood volume in the rabbit being about 57.7-70 ml/kg). This effect from volume expansion follows the same time course as wound water excess and is thus persistent at the anastomotic site over at least five days. This moiety of wound water may be truly termed 'wound oedema' - abnormal retention of water in tissues which normally contain less. In that there was no difference in water content in tissue samples away from the site of direct trauma (lungs and recti) between Groups 1 and 2, intravenous therapy has effectively exaggerated an anatomical third space in the region of the anastomosis.

Furthermore, the small overall changes in other tissues suggest that after a laparotomy most of any 'excess' Na^+ and water infused is sequestered in the gut, though decreased after four to five days. Total animal weight was not measured and no attempt was made to partition body fluid compartments in these experiments. The results (Table 9.2) show a wide individual variation and clearly, further exploration of this problem would be of importance for the management of patients after major abdominal surgery.

The tide of peri-operative fluid and electrolyte loading in the early years after Shires' original work (1961) may have now receded, but the water mark remains at a level still well above

that of the post-Coller days (Coller et al., 1936) and vastly in excess of restrictive regimens practised with success by Wilkinson (1956). Apart from the obvious hazard of cardiac failure in the elderly, consideration must be given to the potential local deleterious effects on the wound of the administered fluid load. The deleterious effects of excessive infusions of saline solution on tissue oxygen transport have been well documented (Mangalore and Hunt, 1972; Hueghan et al., 1972). The present experiment has demonstrated oedema at a gastrointestinal suture line from extracellular volume expansion which is persistent. In anastomoses of already critical size, it is conceivable that extracellular volume expansion may well contribute to acute, if temporary, occlusion superimposed upon factors such as tissue inverson and clot formation. These experiments are limited to small bowel anastomoses and further work will be required to elucidate the effects of extracellular volume expansion on the more critical large bowel anastomoses and on wound healing.

In that there is little or no objective evidence to support the view that large volume replacement with crystalloid is necessary or desirable in routine major surgery, the observations in this study reinforce the call for 'moderation' made by Moore and Shires in 1967 (Editorial: Ann. Surg. 1967).

9.7 Summary

Intestinal surgery is usually associated with the parenteral administration of Na^+ and water, sometimes in amounts considerably in excess of excretory capacity. The effects of this on the water content of the gut at and 5 cm from a single-layer end-to-end anastomosis in the rabbit have been studied. Water content was measured by desiccation.

One group of animals (1) did not receive intravenous therapy. The other (2) received 5 ml/kg/h of Hartmann's solution during the operative period and thereafter to a total volume of 200 ml by 48 hours. In Group 1 there was a five to 10 per cent increase of tissue weight, both at the anastomotic site and at 5 cm ($p < 0.01$, Mann Whitney U test) on the first three days. Thereafter water content at the anastomosis persisted, but resolved in normal gut. In Group 2 a further five per cent increase in weight over Group 1 occurred ($p < 0.01$), persistent at the anastomotic site over five days, though resolving elsewhere after two days.

Extracellular fluid volume expansion exaggerates an anatomical third space present in the region of an anastomosis. At the suture line, oedema so induced is persistent and could be deleterious.

P A R T V

GENERAL COMMENTS AND CONCLUSIONS

C H A P T E R 1 0

SIGNIFICANCE OF THE RESULTS AND RECOMMENDATIONS FOR FUTURE WORK

10.1 INTRODUCTION

This chapter presents an overview of the results from the various studies in this thesis. The limitations of some of the techniques used to explore the problem will be discussed with recommendations of possible directions that future work should follow.

Part II: The initial objective of the study was to delineate normal and abnormal serum sodium concentration in relation to surgical trauma, with particular reference to their role in clinical decision-making. A review of the literature in 1979, when the work for this thesis was commenced, revealed that little was known about the magnitude and significance of fall in sodium concentration after injury, its statistical limits and the decision (if any) that could be made on the basis of observed change. Furthermore, no data existed for serum sodium concentration that was standardised for water and electrolyte administration.

The water dilution studies by Dudley et al. (1954) have yielded results which were unpredicted and which, if they were confirmed, have significance for the interpretation of serum sodium concentration in post-operative patients where water excretion is limited by the non-osmotic secretion of antidiuretic

hormone. Thus it was necessary to re-study the effects of a large oral water load in normal man. This present study (Chapter 2) has validated that water loading did in fact cause the expected dilution. The previous conflicting report could be the result of: (i) erratic rates of exchange of a large water load in the gastrointestinal tract; (ii) not allowing for possible changes in non-ionic components of the extracellular fluid, and therefore in total osmolality; (iii) the use of Pitressin as the antidiuretic agent; Desmopressin (DDAVP), used in the current study, has antidiuretic activity two to 10 times greater than that of a standard pituitary extract (Pitressin) and has much less pressor activity. Although deuterium oxide was used by the previous study to estimate total body water, the accuracy should be comparable with those of tritiated water used in this study.

Armed with the information that a large water load dilutes body compartments proportionally in normal man, the next phase of the work was to set up a prospective clinical study (Chapter 3) to determine if the serum sodium concentration after surgical injury follows dilutional trends. It could be argued that the data on serum sodium concentration could be obtained by retrospective analysis but in order that the data be standardised for water and electrolyte administration, a prospective investigation was deemed mandatory. Furthermore, osmolality, total exchangeable sodium and total body water were necessary to interpret the data, and these

are non-standard measurements in clinical practice.

The results in Chapter 3 established the range of change in serum sodium concentration following surgical operation (for the first time) using a conventional fluid regimen. No evidence of other factors than dilution was obtained for uncomplicated patients. It is of interest to note that the changes reported here were much more prolonged than had previously been thought. The reasons for this remain to be established. If the cause of the prolonged dilution is the result of persistent antidiuretic hormone (ADH) activity, it cannot easily be overcome.

Though analysis of the serum sodium data was the main pillar of this study, knowledge of body composition provides a more quantitative appraisal of fluid-electrolyte derangements. More detailed investigations by isotope dilution of 14 patients allowed the calculation of the relationship between serum sodium concentration and the sum of body electrolytes divided by total body water, a measure of tonicity. This provided independent evidence that the changes were dilutional. Furthermore, post-operative dilutional hyponatraemia is at times thought to result from the combined effects of water retention and potassium loss in the urine; by defining the relationship between Na_e, K_e and TBW corrected for external balance changes, the possibility of any

large potassium shifts have been accounted for.

It should be mentioned at this point that the K_e values have been calculated from the formula of Edelman and Moore (Moore et al., 1956; Edelman et al., 1958). The prime reason for not measuring K_e was that it was not felt justified to expose the subjects to further isotope studies in addition to Na_e and TBW measurements. Having measured Na_e and TBW, the indirect measurement of K_e could be obtained from the following relationship:

$$K_e = R \times TBW - Na_e$$

where R is the ratio of the sodium plus potassium content divided by the water content of a whole blood sample. The validity of this technique has been established experimentally in both man and the experimental animal by simultaneously determining K_e indirectly and by a direct measurement (Shizgal 1977).

In the case of balance measurements over the study period, there was no difficulty in measuring the concentration of sodium and potassium in urinary samples because this involved an accurate flame photometer reading. However, it must be accepted that accurate 24hour urine collections are notoriously difficult to make, although close and personal supervision by one Research Fellow (the author) of input and output charts helped to reduce any errors. A further limitation is the assessment of accurate

water balance. There are inevitable errors incurred in estimating water losses via skin and lungs (insensible loss) and the small fraction of metabolic water has not been determined in this group of uncomplicated patients. Other routes of extra-renal loss were not a major concern. No patient included in the study had any significant degree of vomiting and it is our practice not to institute naso-gastric suction post-operatively. Very few had a bowel action during the study period. Sweating was minimal in these patients.

The observation that lesser changes were seen in the patients given a more restricted fluid regimen provided the final evidence of dilutional hyponatraemia. In that they were subjected to the same magnitude of surgery and their clinical course unremarkable indicates that conventional fluid regimens are almost certainly too liberal. Current trends in surgical practice are still to administer large volumes of water and sodium intra- and post-operatively (Roth et al. 1969).

The serum sodium data for six days on 50 uncomplicated patients have been analysed by parametric statistical methods. This was permissible after a test for skewness based on the third moment of the mean, although a priori evidence exists that serum sodium values in man conform to a normal distribution (Wotton et

al., 1951; Fawcett and Wynn, 1956). In order to have a clinical yardstick against which the post-operative serum sodium can be judged, the serum sodium data in the 50 uncomplicated patients were further analysed with 'population statistics'. Ninety-five per cent tolerance limits with 95% confidence probability were constructed by using the mean and standard deviation at each epoch for normally distributed data. The importance of these limits is that faced with any other single value from an unknown population, we can say with a given degree of conviction that it is not drawn from the population we have been studying. Thus, if the single value of unknown provenance was to be outside 95% tolerance limits drawn with a confidence probability of 0.95, the chances of it having been taken from the population under study are low ($p < 0.05$).

Though only limited use can be made of serum sodium concentration in the control of electrolyte therapy, a knowledge of the tolerance limits for a given regimen (Fig. 3.2) should permit more precise prediction of non-dilutional abnormalities and is essential to accurate interpretation. The clinical utility of this approach was demonstrated in Chapter 4 of the thesis.

Reference to a standard 'bedside' chart derived from the population of uncomplicated patients has enabled identification of any additional changes that may occur in patients who were ill before surgery (weight loss, sepsis) and who had a complicated post-operative course. In the course of this study seven such critically ill patients were found to have departures from the tolerance range of serum sodium concentration, and when their data were compared with the 'normal', osmolal gaps were identified. In that the presence of an osmolal gap was found in the sick hyponatraemic patient and was absent when the underlying illness was treated, this suggests that the identification of osmolal gaps might serve as a prognostic index for this group of patients. However, further work will be necessary to enable more precise interpretation of data derived from this group of patients. Firstly, there is no data on ADH levels and on volume and composition of urine for such surgical patients and they are often incorrectly styled as 'inappropriate ADH secretors' on quite inadequate evidence. Secondly, it will be necessary to establish the nature of any non-ionic 'middle sized' molecules in the serum of such patients - these have been postulated but never confirmed.

Though the possibility of decline in the sodium gradient across the cell membrane has been accepted on the basis of the observation of post-traumatic hyponatraemia, direct measurements of such sodium flux have not been made previously in patients undergoing standard medium severity single trauma, using a constant anaesthetic and fluid administration regimen. Using in vitro studies of erythrocytes and measuring total sodium fluxes, the results in Chapter 5 showed no change in sodium flux across the membrane after elective surgery and in critically ill and malnourished surgical patients with unequivocal hyponatraemia.

It has become a central dogma about 'sick cell syndrome' with hyponatraemia that it is caused primarily by the sick cells! For this dogma the results of this study have been unable to find direct support. The potential source of error in calculating intracellular sodium concentration has been overcome by (i) washing the erythrocytes in a solution containing intracellular amounts of sodium, and thus avoiding possible extracellular contamination; (ii) using an isotonic wash medium for the cells. The alternative explanation of hyponatraemia in the sick and malnourished patients is that the sodium pump acts as a background phenomenon and is changed by intracellular solutes; changes in extracellular concentration, particularly in the serum sodium concentration, are the consequences of changes in the

intracellular solutes rather than changes in the sodium pump per se.

One undoubted problem which has emerged during the course of this study is the clinical observation that the sick and hyponatraemic surgical patient is also energy substrate deficient. The inference here is that the appropriate provision of total parenteral nutrition might benefit cellular function and reverse extracellular-intracellular derangements. Further work will be required to ascertain if there is a block to glycolytic energy supply in the red cell and to relate energy utilisation, water content of the cell and extracellular osmolality and sodium concentration. This may throw further light on the management of these difficult patients.

The explanation of the results presented so far has established that if a standard fluid and electrolyte regimen is administered to the patient after injury, dilution of body water takes place that is, unlike the normal response to a hypotonic load, which is the excretion of excess, the post-surgical patient retains water. This is a precise confirmation of the long-held interpretation of Le Quesne and Lewis (1953) and Dudley et al. (1954) that non-osmotic secretion of antidiuretic hormone (ADH) takes place after injury. Evidence from bioassay and radioimmunoassay suggests that this is so, but closer

examination of the available data does not prove conclusively that the evidence for ADH is 'watertight'. Plasma ADH levels generally show a marked elevation for several hours during the day of operation and return to near pre-operative values during the second day (Haas and Glick, 1978; Cochrane et al., 1981).

If the dilutional changes demonstrated in this study - which persist for longer than has been previously thought - are the consequence of ADH activity, they cannot easily be overcome and this is an argument for more restricted regimens than are currently practised. A study of urine volume and concentration after injury in the same circumstances of a single surgical insult, using a constant anaesthetic and fluid administration regimen (Chapter 6) showed that at least for the first 18 hours after injury, the concentration of urine was not that normally seen with maximum ADH activity. Either the detailed pattern of ADH release after injury differs from that conceived, or the kidney is, because of other factors, unable to respond. The matter is of some importance to day-to-day management of surgical patients, as both urine volume and concentration are widely used to 'monitor' the adequacy of the circulation and fluid and electrolyte replacement, as well as to reassure the clinician that the kidney is not threatened by failure.

Furthermore, renal failure is still a not uncommon event after injury (Leading Article, Br. Med. J., 1980) and its prevention is still very much based on pragmatism - the use of diuretics such as mannitol and frusemide. A better understanding of the immediate peri-operative events in renal function may well help to rationalise preventive management for renal insufficiency.

There is therefore an urgent need to make a detailed study of ADH concentration in the blood of patients undergoing moderate and major surgery at the same time as studying the volume and concentration of urine under the influence of a standard fluid load. It can be argued that radioimmunoassays are already available for ADH analysis. As indicated, studies up till now have not proved conclusively the temporal relatonship of ADH secretion and the renal response under standard surgical injury. Furthermore, many technical and interpretative problems remain with radioimmunoassays of ADH (Thomas and Lee, 1976). The rapid half-life (ranging from six to nine minutes in humans) and extensive distribution of ADH limit the ability to infer very much about moment-to-moment secretion rates from a single plasma sample, particularly after acute stimulation. The ADH (or more specifically AVP, arginine vasopressin) molecule is small, and of limited antigeneicity, which poses problems concerned with non-specific interference and the disparity between biological and

immunological activity. Different values have been obtained by radioimmunoassays of the same plasma samples (Thomas and Lee, 1976).

The recent availability of High Performance Liquid Chromatographic (HPLC) techniques has opened up new horizons in analytical chemistry. Though good sensitivity can be obtained with radioimmunoassays, they often lack specificity. HPLC does away with the need for specific antibodies and, in general, its limitations of detection allow quantitation down to much lower levels in plasma samples (Knox, 1977).

During the latter part of this work, attempts have been made in the Surgical Unit Laboratory to measure plasma ADH levels by HPLC techniques. Experience has been gained from measuring plasma amino acid levels with this method and sensitivity down to femtomoles achieved. By labelling the N-terminal group of the ADH molecule with fluorescamine, detection could only be achieved at the picomole level. The main limitation of analysis by HPLC lies in the detection system and much more research is needed for its use in plasma ADH analyses.

Part III: Reference has already been made in Part I of this thesis that the injured patient is exposed to the twin problems of starvation and the catabolic response to injury. The recent increasing use of nutritional supportive therapy (particularly via the parenteral route) has brought into focus the inter-relationships of energy-substrate turnover with water and sodium balance.

Patients who receive nutritional support nearly always show a rapid initial gain in weight which has been largely attributed to increase in body water (Hill et al., 1978; Yeung et al., 1979; Macfie et al., 1981). The studies on normal volunteers (Chapter 7) were aimed at distinguishing between short term weight changes caused by increase in sodium and water content and those which may be associated with the hydration of storage carbohydrate (glycogen). These studies and results from two totally dysphagic patients suggest that the early weight gain during nutritional rehabilitation is the consequence of the obligation of water to glycogen and a return to the mid-point of sodium homeostasis. Weight gains of two to three kilograms are a normal phenomenon and do not imply over-hydration.

The purpose of these investigations was to throw some light on the acute weight changes seen in clinical practice during the early period of nutritional support. In that measurements of body glycogen were not attempted and the techniques used were balance studies and space measurements, it is only permissible to make indirect inferences about the meaning of the changes. However, both in volunteers and in patients it was possible to distinguish the weight changes that were associated with the movement in and out of the body - on the one hand of sodium and water, and on the other of water during changes in respiratory exchange ratios. In doing so, the studies have neglected possible changes in faecal water losses and the wholly unexplored theoretical possibility that dietary and electrolyte manipulation of this kind may affect the metabolism of colonic bacteria so affecting body weight. However, in that the intra-colonic faecal bulk rarely is in excess of one kilogram, it seems unlikely that more than a small amount of the acute weight changes could be accounted for by this unproven mechanism.

Future studies of this kind could incorporate the use of needle biopsy techniques to obtain specimens of liver and muscle in severely malnourished surgical patients before and after nutritional rehabilitation.

The results showed that if body sodium content is held at a low level, then an increase in carbohydrate intake resulted in a rise in body weight and total body water. This was associated with the rise of respiratory exchange ratios towards unity. If it is assumed that the greater part of the water is obligated to glycogen, then 3.21 $\pm$ 0.57 g of water is obligated to each gram of glycogen stored - figures similar to those from animal experiments (Puckett and Wiley, 1932; Fenn and Haege, 1940) and assays of liver and muscle biopsies in man (Bergstrom and Hultman, 1972). The two patients studied confirmed the results in volunteers and indicate that in the clinical setting, acute weight changes are the consequence of (a) a return to the mid-point of water homeostasis (correction of acute water lack), (b) storage of carbohydrate, and (c) if sodium is given, a similar move towards the mid-point of sodium homeostasis. All these changes are 'physiological'. They represent a more diluted body state than that seen in starvation, which frequently precedes nutritional treatment in the surgical patient.

The human model used in Chapter 7 to study glycogen repletion has established that water gain can be separated from sodium and water gain. The results in Part II of this thesis have found no evidence of other factors than dilution to account for the change in serum sodium concentration following injury. As it

is unnecessary to postulate intracellular sodium binding as a cause of sodium and water anomalies in the clinical situation of hyponatraemia (Swales, 1975) the model of glycogen-obligated-water would seem to explain best the problem of hyponatraemia and the possible source of 'pure water' which might dilute the extracellular phase, so producing hyponatraemia. The hypothesis is that water obligated to glycogen - the storage carbohydrate of liver and muscle - is mobilised in the post-injury phase and its excretion opposed by antidiuresis. Hyponatraemia is often further exaggerated by misguided fluid therapy in the form of excessive water being given. The corollary of this is that in the 'keto-adapted', glycogen depleted and water-overloaded patient, water can be translocated from the extracellular space by promoting the storage of carbohydrate. The preliminary results of two patients (Chapter 8) with marked hyponatraemia treated with glucose and potassium infusion suggest that this can be achieved. The rise in serum sodium concentration was accompanied by the rise in respiratory exchange ratios towards unity. The observations in Chapter 7 on the two potassium deprived volunteers demonstrated that glycogen-water storage is potassium dependent in this model and it has also long been known that glycogen obligates water and potassium (Fenn, 1939; Gardner et al., 1950; Mortimer, 1961; Hue et al., 1975). Potassium depletion per se inhibits the secretion of insulin by pancreatic islet cells (Anderson et al., 1969; Mann et al., 1975) and in the two patients studied in Chapter 8,

exogenous insulin was not required to be given to promote glucose and potassium entry into the intracellular phase.

Thus, the hypothetical model in Chapter 8 has provided a more rational explanation of the success of 'GKI' regimen in treatment of acute disorders of sodium and water imbalance.

Further work will be necessary to underpin the hypothesis. Again, measurements of plasma ADH levels by more precise analytical methods will be needed. A study of surgical patients with the use of high carbohydrate load could be fruitfully pursued with the particular aim of seeing if the release of glycogen obligated water from the cell could be prevented in the 'keto-adapted' state that normally accompanies surgery. Studies of glycogen synthetase activity (such as in white cells) would further yield information regarding the complex relationship between substrate turnover, ADH, and fluid and electrolyte balance. In experimental studies in animals, ADH stimulates the breakdown of glycogen and inhibits net glycogen accumulation (Hems and Whitton, 1973). Furthermore, little evidence exists in the literature of how the glycogen molecule is hydrated and whether the water associated with it in the cell is in full physical equilibrium, or whether it is sequestered by weak hydrogen bonding. Finally, although a threshold level of potassium administration appears necessary for glycogen storage, it is not

known whether this is because of obligation of potassium to the glycogen-water complex, or whether it is merely a triggering effect on an enzymatic process such as that of glycogen synthetase. These studies will not only make a contribution to further understanding of the dynamics of body composition, but will help design better methods of nutritional rehabilitation.

Part IV: The final work in this thesis (Chapter 9) has examined the effects of parenteral water and sodium infusion with respect to intestinal surgery in the rabbit small bowel. Though the presence of an 'anatomical third space' following injury has been known since the 1930s, it was in 1961 that Shires et al. popularised the suggestion that part of the extracellular fluid shifts into a space where it is 'non-functional'. As a result of these studies, he suggested that the extracellular fluid deficit should be replaced by massive infusions of sodium and water. Later work has cast doubt on the validity of Shires' conclusions and it has since been amply demonstrated that massive infusions of sodium and water invariably lead to sodium and fluid overload which persists for several days. Furthermore, the work of Cochrane (1978) has clearly shown that the amount of sodium administered is a major determinant of the amount retained in the post-operative period. He further suggested that instead of the sequestered fluid being a fixed volume, it increases in direct relationship to the volume of sodium and water infused. Thus, when very large sodium and water intakes are given during the post-operative period, frank oedema is produced.

Apart from the studies of Shields and Dudley (1971) on oedema at the site of small bowel anastomoses, there is no data on the pattern of development and regression of water content at a suture line in the gastrointestinal tract, under the influence of sodium and water infusion. The results in Chapter 9 of this thesis have demonstrated that even modest extracellular volume expansion (an amount calculated to correspond to a one-litre over-expansion in a 65 kg man) in the form of sodium and water infusion in the peri-operative period produced a further increase in anastomotic wound water over the group of animals which did not receive intravenous therapy. Intravenous therapy has effectively exaggerated an anatomical third space in the region of the anastomosis, the effect of which is persistent.

These results have once again confirmed the deleterious effects of sodium and water loading in the peri-operative period and that given in sufficient quantity they are likely to be harmful. They also lend further support to the observations in Part II of this thesis that 'conventional' fluid regimens are almost certainly too liberal. Further moderation is called for, perhaps towards the restrictive regimens practised with success by Wilkinson (1956).

As is often the case, a study of this kind raises as many questions as it answers. Attention should be turned to the cause of the prolonged water retention at the wound, and its possible effects on wound healing. A useful line of investigation that could be pursued is the study of collagen turnover at the gastrointestinal wound and its relationship to water content. In abdominal wounds, this late phase of local water retention is putatively associated with the intense cellular activity phase of wound healing, and it is conceivable that collagen synthesis might obligate water along with it.

In conclusion, the objectives of the study have been achieved. The work in this thesis has provided the author much more precise knowledge of how to interpret electrolyte concentrations (particularly sodium) in the surgical patient. Also, it has served to emphasise that careful attention to sodium and water balance, glucose metabolism and transcellular shifts can differentiate the causes, and hence delineate the management of many of the metabolic complications associated with the modern treatment of the surgical patient.

CLAIMS TO ORIGINALITY OF THIS THESIS AS A CONTRIBUTION TO THE SCIENCE AND PRACTICE OF SURGERY

The work in this thesis was initiated when precise data was lacking about the magnitude and significance of change in serum sodium concentration in response to an operation of moderate severity managed on a standard fluid and electrolyte regimen.

For the first time, a confidence band for change in serum sodium concentration has been established which not only enables the prediction of whether observed sodium values in patients are 'normal' for that point in their post-operative course, but also demonstrates that changes are much more prolonged than was at first thought.

It has been demonstrated by the work in this thesis the utility of having to hand firm information on normals. The tolerance range for serum sodium concentration has contributed to clinical decision making and has enabled osmolal gaps (which have treatment implications) to be identified in sick surgical patients.

Evidence has been obtained by a study of urine volume and concentration after injury that at least for the first eighteen hours after injury, the concentration of urine is not that normally seen with maximum antidiuretic hormone activity. The temporal pattern of urinary volume, solute and electrolyte excretion established for standard severe trauma and shown to be largely an adaptive phenomenon, provides a yardstick for interpretation of these measurements in surgical patients.

The investigations of metabolic substrate and sodium and water movements have developed a physiological model to study glycogen repletion in volunteers and patients in such a way that water gain can be separated from sodium and water gain. This method has not been explored previously. The results have provided a physiological explanation of water gain associated with weight gain during the initial period of nutritional rehabilitation. Prior to this work, weight gain has been loosely ascribed to water retention with the implication that no advantage was gained from nutritional support.

The studies obtained from the above have generated a hypothetical model concerning sodium and water flux between extracellular and intracellular compartments. Based on these observations, the hypothesis has been tested in sick hyponatraemic patients -excess water in the extracellular space (its excretion

being opposed by ADH) can be translocated by promoting the storage of carbohydrate in the cell. This has proved a much more rational explanation of 'sick cell hyponatraemia' than previously invoked intracellular sodium inactivation for which the studies of total sodium flux in this thesis have found no support.

The observations on the water content of gut anastomoses under the influence of parenteral sodium and water has confirmed the possible deleterious effects of over-expansion of the extracellular phase. No previous work has documented the duration of gut water content with extracellular over-expansion.

In addition, the overall results of this work have led to a practice of more restrictive fluid regimens in our surgical patients. Finally, the findings in this thesis have pointed the direction that future work should take.

SUMMARY OF PUBLICATIONS AND PAPERS PRESENTED TO LEARNED SOCIETIES

1. The serum sodium concentration after surgical operation: precision permits predictions.
   Chan, S., Radcliffe, A., Johnson, A.
   Br. J. Surg. 1980; 67: 711-4
   (Paper presented for the Moynihan Prize at the Association of Surgeons of Great Britain and Ireland Meeting, Bournemouth, March, 1980)

2. The serum sodium concentration after medium severity surgical injury.
   Presented to the Metabolic Group Meeting, Dundee, 1979

3. Identification of osmolal gap in post-surgical hyponatraemia.
   Chan, S., Dudley, H.A.F., Johnson, A., Radcliffe, A.G.
   Br. J. Surg. 1980; 67: 363
   (Paper presented to the Surgical Research Society Meeting, Glasgow, January, 1980)

4. Erythrocyte intracellular sodium and transmembrane flux in surgical patients.
Radcliffe, A.G., Johnson, A., Chan, S., Dudley, H.A.F.
Br. J. Surg. 1980; 67: 362

5. Transcellular movement and intracellular concentration of sodium in erythrocytes after surgery and in seriously ill patients.
Radcliffe, A.G., Goode, A.W., Johnson, A., Chan, S., Dudley, H.A.F.
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6. Urinary volume, concentration and solute excretion in the post-operative phase: relationship to ADH.
Dudley, H.A.F., Radcliffe, A.G., Chan, S.
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7. Urinary solute and electrolyte excretion in the peri-operative period.
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10. Glycogen Obligated Water: What weight is water?
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13. Endocrine aspects of water and sodium metabolism.
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15. Water electrolyte movement during starvation and following re-feeding with glucose.
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18. The use of diuretics in standard severe surgical trauma - an anaesthetic Pavlovian reflex.
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APPENDICES

APPENDIX 2.1

Calculation of theoretical dilution level of serum sodium

The concept of cells as 'perfect osmometers' applied to the interpretation of the osmolality disorders of body fluids (Wynn, 1978).

Assuming that the cells of the body behave as ideal osmotic systems, that is, ideal dilute solutions encased in a semi-permeable membrane offering no resistance to change of volume, osmotic adjustments would take place by the movement of water across the cell membrane until the osmotic pressure was the same on the two sides of the membrane. It is then possible to derive an osmotic equation which relates changes in plasma osmolality to changes in total body water and changes in the amount of osmotically active solutes in the body (Wynn and Houghton, 1957). Thus

$$Osm_1 \times TBW_1 + \Delta Osm = Osm_2 \times TBW_2$$

where Osm_1 and Osm_2 are the initial and final plasma osmolality (mOsm/kg). TBW_1 and TBW_2 are the initial and final total body water (litre) and ΔOsm is the change in the number of osmotically active solutes in the body (mOsm). Plasma osmolality is closely mirrored by plasma Na^+ because Na^+ salts normally represent about 95 per cent of the effective osmotically active solutes of plasma. Since the associated anions are mostly Cl^- and HCO_3^- which are univalent, plasma osmolality equals $2(Na^+)$ as a close approximation or can be calculated as $2(Na^+ + K^+)$ + urea + glucose where the concentrations of Na^+, K^+, urea and glucose are expressed in mmols per litre. By similar reasoning ΔOsm can be taken as equal approximately to twice the external balance of

$$(Na^+ + K^+).$$

Therefore, the osmotic equation can be written thus:

$$Na^+_1 \times TBW_1 + \Delta(Na^+ + K^+) = Na^+_2 \times TBW_2$$

or,

$$Na^+_1 \times TBW_1 + (Osm_2TBW_2 - Osm_1TBW_1) = Na^+_2 \times TBW_2$$

$$Na^+_2 = \frac{(Na^+_1)(TBW_1) + (Osm_2TBW_2 - Osm_1TBW_1)}{TBW_2}$$

This equation describes a predictable relationship between the plasma Na^+ and changes in total body water and the number of osmotically active solutes in the body.

TABLE A2.11

Theoretical dilution level of serum Na^+ at equilibration for the six healthy volunteers studied (Chapter 2)

Subject	Na^+_1 (mmol/l)	TBW_1 (l)	TBW_2 (l)	Osm_1 (mOsm/kg)	Osm_2 (mOsm/kg)	Na^+_2 (mmol/l)
STFC	136.2	35.5	37.3	292.0	279.0	130.7
AR	142.4	49.3	51.8	302.1	290.0	138.0
PE	135.2	40.2	42.2	290.5	277.1	129.2
NMR	140.0	43.3	45.5	298.1	283.7	133.2
AG	137.5	36.3	38.1	294.5	282.9	133.3
CN	139.4	42.4	44.5	298.3	284.6	133.2

TABLE A2.12

Free water excretion (C_{H_2O}) in the six healthy volunteers studied

$$C_{H_2O} = V_u - \frac{(U_{osm})(V_u)}{P_{osm}} \text{ ml/min}$$

where: V_u = urine volume (ml/min)

U_{osm}, P_{osm} = urine and plasma osmolalities (mOsm/kg)

Subject:	U_{osm}	V_u	P_{osm}	C_{H_2O}
STFC	900	0.61	278.8	-1.4
AR	985	0.26	288.9	-0.6
PE	864	0.14	287.8	-0.3
NMR	1125	0.08	281.6	-0.2
AG	780	0.90	282.9	-1.6
CN	810	0.42	292.2	-0.7

APPENDIX 2.2

Measurement of Total Body Water by tritiated water

The method used was that of Vaughan and Boling (1961) with minor modifications. Tritium-labelled water (^3H_2O) was obtained from the Radiochemical Centre, Amersham. Measurements were performed in collaboration with Mr S A J Suddle in the Department of Clinical Physics, St Mary's Hospital, London W2.

Method:

Before intravenous injection of a weighed quantity containing 50μCi (1.85 MBq) ^3H_2O in a 2 ml Plastipak syringe, a blood sample (10 ml) was taken for background radioactivity of plasma and another blood sample (10 ml) taken 3.5 hours later when the tracer substance was equilibrated in body water. No fluid was allowed during this period.

The tritium activity of duplicate samples was counted in a liquid scintillation counting system after vacuum distillation (Fig A2.21). The scintillation solution was toluene based. Samples were counted for 10^4 counts which gave $\pm$ 1 per cent variation of the measured radioactivity.

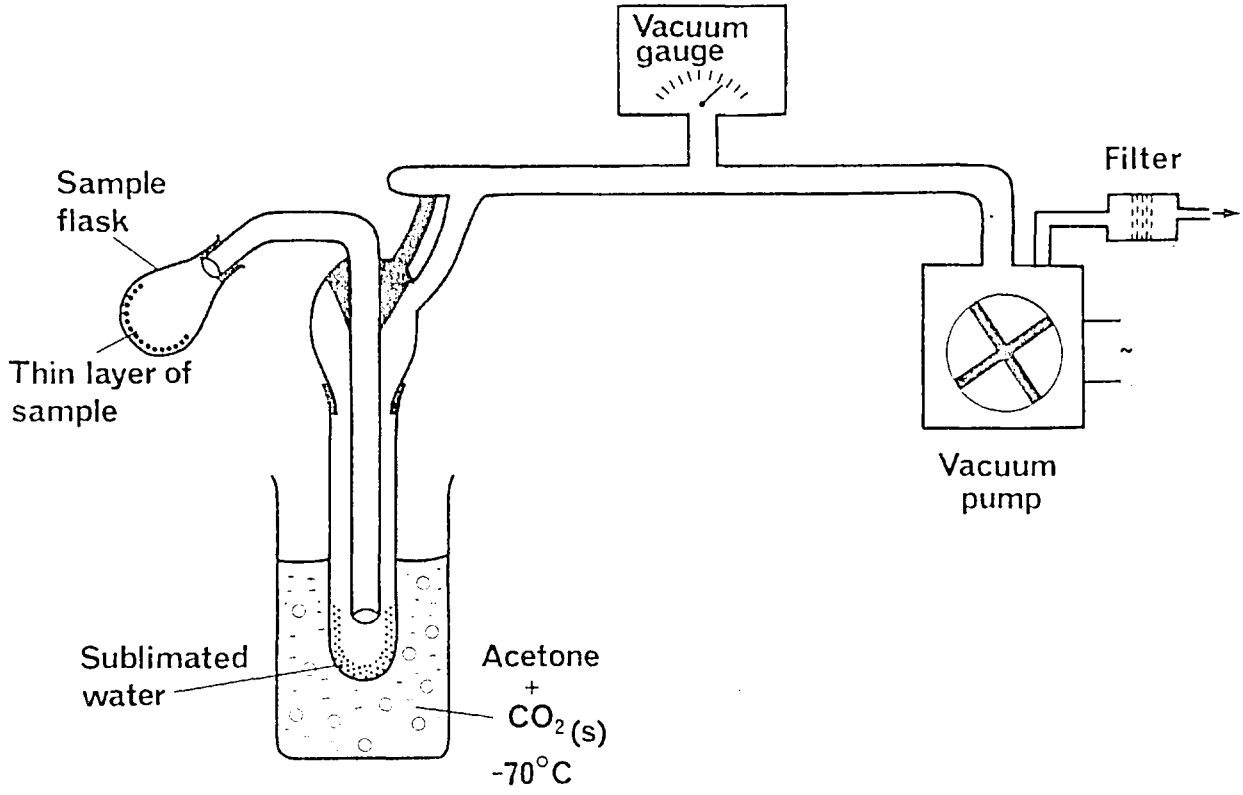


Figure A2.21

Schematic diagram of water sublimation system

Pure water was sublimated from 5 ml plasma specimens for liquid scintillation counting. The chief objectives of sublimating water from plasma specimen are:

(1) the water thus obtained is in a purified state, free from all chemical and radioactive contaminations other than the principal isotope under investigation, that is, $^{3}H_{2}0$;

(2) water obtained under such conditions can directly be made comparable with the standard solution made by diluting $^{3}H_{2}0$ in distilled water.

Liquid scintillation counting was carried out by mixing 1 ml of sublimated water with 10 ml Toluene-based liquid scintillator. Standard samples were also prepared in exactly the same way. The physical and chemical constituents of the samples including standard, so prepared, were the same for all practical purposes and when counted in a liquid scintillation spectrometer were statistically free from any correction factor.

During all the investigations, the channel ratios of the specimens and the standards were observed, and were found to be of the same order of magnitude.

This method has been used in the Department of Clinical Physics for 7 years. The accuracy for TBW with this method is within $\pm$ 2 per cent.

Sample calculation: Subject: PH Weight: 53 kg Height: 150 cms

Stock solution specific activity: 50μCi/ml

Dose weight: 3.4007 - 2.3365 = 1.0642 g

Standard weight: 3.9970 - 3.5610 = 0.4360 g ..... diluted to 1 litre

Liquid Scintillating Counting Data:

Sample	Time (min)	Counts: A	Counts: B	SCR	Counts/min	Counts - Background
Std (i)	1.445	6667	10000	0.667	6920.4	6908.05
Std (ii)	1.446	6648	10000	0.665	6917.7	
Pre - ^3H_2O:	10.000	2846	4327	0.658	432.7	
Post - ^3H_2O: (i)	9.186	6652	10000	0.665	1088.6	637.25
(ii)	9.512	6667	10000	0.667	1051.3	
Background:	10.000	68	110	0.618	11.0	

$$TBW = \frac{6908.05}{637.25} \times \frac{1.0642}{0.4360} = 26.5 \text{ litres}$$

The isotope ^3H_2O is rapidly distributed throughout the body and comes in equilibration approximately 3 - 4 hours in normal subjects although the equilibrium time is considerably longer in oedematous, ascitic or obese patients.

Plasma or urine samples may be employed for the dilution measurement after equilibration has been reached. If a urine sample is employed, it is essential that the subject has voided twice before the sample is taken. If this procedure is not rigorously followed, there is risk of obtaining a sample which does not reflect the true equilibration sample.

In this study we have relied on a venous sample which can be obtained at a precise time interval and also is freed from any technical uncertainties. Provided there is no fluid intake during the equilibration period of the tracer, it is not necessary to apply an excretion correction since any loss of tritium will be accompanied by a corresponding loss of water and therefore, the specific activity of the body water remains unchanged.

APPENDIX 3.1

Flame photometry for sodium and potassium in serum and urine

All measurements of Na^+ and K^+ in serum and urine were performed using a Corning 450 Flame Photometer (Corning Medical, Corning Limited, Essex, England) housed in the Surgical Unit Laboratory.

Principles of flame photometry: The alkali metals, when raised to a sufficiently high temperature, will absorb energy from the source of heat and be raised to an excited state in their atomic form. As these individual atoms 'cool' they will fall back to their original unexcited state and re-emit their absorbed energy by way of radiation at specific wavelengths, some of which are in the visible region. Therefore, if a mixture of the alkali metals, Na^+, K^+ and Li^+ in solution, are aspirated into a propane-air flame in an aerosol form they will, after excitation by the flame, emit a number of discrete frequencies which may be isolated by optical filters and individually allowed to fall on suitable photo-multipliers to be converted into electrical signals (Fig A3.11).

Lithium (Li^+) is added to all samples, as a reference element, to overcome the effects of random fluctuations due to variations in flame temperature, aspiration rate and various chemical interferences. The unknown Na^+ and K^+ signals are ratioed against the Li^+ signal to ensure that a steady readout is obtained.

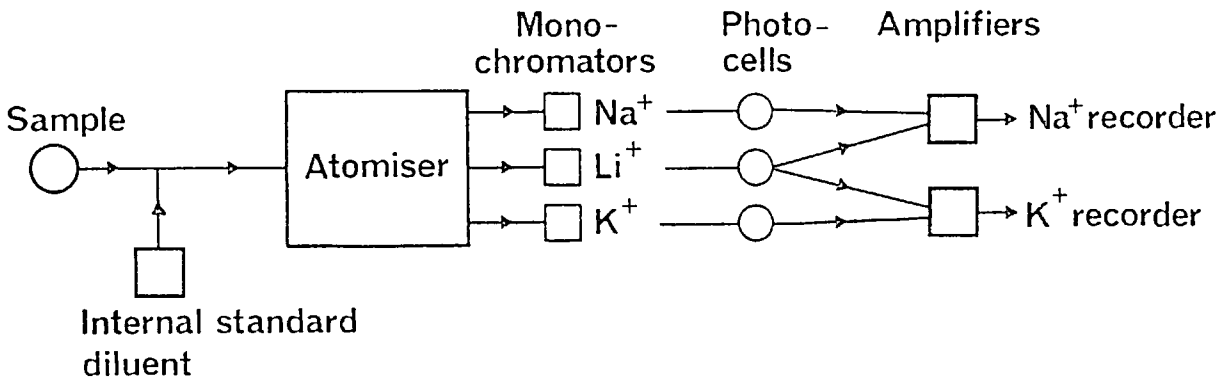


Figure A3.11

Emission flame photometer (schematic)

Reproducibility and sources of error: The most critical component in a flame photometer is the burner and its associated nebulizer. It is important that the flame is steady and has a constant thermal output and care should be taken to avoid obstruction in either the nebulizer or burner. Therefore gas flows should be monitored at all times.

After a one hour warm-up period, reproducibility over a 10-minute period with readings taken every 30 seconds, from a bulk sample, will be as shown in the following table:

Mode:	Range (mmol/l)	Sample (mmol/l)	Coeff.Variation %
S - Na^+	0.0 - 180.0	140.0	0.4
S - K^+	0.00 - 10.00	5.00	0.8
U - K^+	0.0 - 100.0	40.0	0.8
Li^+	0.00 - 5.00	2.50	0.6

Serum Na^+ and K^+ determinations: For serum Na^+ and K^+ analyses, 5 ml of venous blood was drawn (at a standard time of day) into a plain collecting glass tube (L.I.P.: z/10) and allowed to stand at room temperature until it clotted spontaneously. The specimen was then centrifuged (M.S.E.) for 5 min at 2000 r.p.m. After centrifugation, the serum was drawn off by a pipet with suction bulb into 5 ml stoppered tubes and stored at 4°C until the study on that particular patient was complete so that all samples from one patient could be analysed together. Analyses were normally performed on a weekly basis in the

Surgical Unit Laboratory.

For plasma Na^+ and K^+ analyses, the procedure was as above except that blood was drawn into a 5ml tube anticoagulated with crystalline Li-Heparin (Diotech : LH/5).

A one hour warm up period for the flame photometer was allowed. A bulk supply of LiCl solution at a concentration of 15 mmol/l was made up for use to dilute standards and samples in the ratio 100:1. This was achieved by weighing out 0.636 g LiCl (Oertling weighing balance) and dissolved in one litre deionized water - the molecular weight of LiCl being 42.4. For internal standard setting, a solution of 15 mmol/l LiCl was aspirated for 15 minutes to allow the flame and the operating temperature of the burner to stabilize.

Aqueous standards supplied by Corning-EEL containing 140 mmol/l of Na^+ and 5 mmol/l of K^+ and a deionised water blank were used to calibrate the flame photometer. In order to achieve a 100:1 dilution, 50µl of the standard solution was drawn off by a pipet (smi-micro/pettor) into 5 ml of LiCl solution.

Similarly all samples of serum and plasma were diluted in the ratio of 100:1 (5 ml of LiCl solution to 50µl sample). Calibration checks were performed after every 10 sample determinations. Replicate determinations of serum Na^+ and K^+ showed less than 1% error. The serum Na^+ values determined by the photometer compared well with those of daily

determinations by the hospital chemical pathology laboratory. The difference between the lower 95% tolerance limits for the two determinations was less than 0.44 mmol/l (mean), see Table A3.11.

Since serum normally has a water content of 92 per cent, the sodium concentration expressed more rigorously per litre of serum water is some 8 per cent higher. In none of the patients studied was there evidence of abnormally raised lipid-protein fraction of blood so that the correction factor for serum sodium is small.

TABLE A3.11

Details of serum Na^+ values of photometer determinations compared with those of hospital pathology laboratory (50 patients)

Day		0	1	2	3	4	5	6
Mean	A	139.96	134.16	133.57	135.15	136.27	137.35	138.74
	B	139.96	134.28	133.80	135.24	136.68	137.56	138.98
S.D.	A	2.21	2.74	2.91	3.38	3.23	3.38	3.02
	B	2.39	2.55	2.70	3.15	3.29	3.34	3.19
k_7S.D.	A	5.26	6.52	6.93	8.04	7.69	8.04	7.19
	B	5.69	6.07	6.42	7.49	7.83	7.95	7.59
Upper 95% tolerance limits	A	145.22	140.68	140.50	143.19	143.96	145.39	145.93
	B	145.65	140.35	140.22	142.73	144.51	145.51	146.57
Lower 95% tolerance limits	A	134.70	127.64	126.64	127.11	128.58	129.31	131.55
	B	134.27	128.21	127.38	127.75	128.85	129.61	131.39
Difference between lower 95% tolerance limits		0.43	0.57	0.73	0.64	0.26	0.30	0.17

A : Surgical Unit Flame Photometry

B : Hospital Chemical Pathology Laboratory Analyses

Urinary Na^+ and K^+ determinations : the volume of the 24-hourly urine collections was measured in a glass burette to the nearest millilitre and, after thorough mixing, a 5 ml sample was taken for measurement of Na^+ and K^+ concentrations. All such samples from a patient were kept frozen until the study on that patient was complete so that they could all be analysed at the same time. Analyses were normally performed on a weekly basis in the Surgical Unit Laboratory.

All samples were then thawed together, mixed thoroughly and centrifuged (M.S.E.) for 5 minutes at 2000 r.p.m. 50µl samples were then used for determinations of Na^+ and K^+ concentrations using the Corning 450 Flame Photometer. The procedure used was the same as that used for serum electrolyte determinations except that aqueous standards supplied by Corning-EEL containing 80 mmol/l of Na^+ and 40 mmol/l of K^+ were used to calibrate the flame photometer. Replicate samples were measured from each patient and the mean of the results taken.

APPENDIX 3.2

Osmometry

An Advanced Osmometer, Model 3L (Advanced Instruments, Inc.Mass.) housed in the Surgical Unit Laboratory, was used for all the measurements of serum, plasma and urine osmolality. In that the samples used for osmometry were also subjected to flame photometer determinatins of Na^+ and K^+, the procedure for collection and treatment of serum, plasma and urine was as outlined in Appendix 3.1.

Principles of osmometry: (Bevan, 1978): When a solute is dissolved in a solvent some of the physical properties of the latter change. The solvent properties change because the presence of solute enforces a more stable order on its molecules. Boiling point and osmotic pressure increase and freezing point and vapour pressure decrease. These are known as colligative properties because they are both common to the addition of any solute and interrelated and mathematically interconvertible.

An addition of 1 osmol of solute to 1 kg of water :
(a) increases boiling point by 0.52°C ;
(b) decreases freezing point by 1.858°C ;
(c) increases osmotic pressure by 2267 kPa ;
(d) decreases vapour pressure by 0.04 kPa ;

The extent of the changes is called osmolality and is directly related to the concentration of free particles in a solution so that for solute dissolved in water it is given by :

$$\text{Osmolality} = \phi nC = \text{osmol/kg } H_2O$$

where - Ø is the osmotic coefficient,
n is the number of particles dissolved in 1 kg H_2O
C is the concentration of solute in mol/kg H_2O

The osmotic coefficient describes the slight differences observed in the osmotic behaviour of complex or non-ideal solutions. In clinical practice the use of milliosmole unit enables the concentrations of body fluids to be expressed in whole numbers.

If a molecule dissociates in solution into two or three particles the osmolality is doubled or tripled respectively. Osmolality is measured in terms of mosmol/kg H_2O whereas osmolarity refers to the concentration per litre of solution. Any difference between the two is due mainly to the change of solvent volume with temperature. However, the limited temperature range and low solute concentrations found in clinical practice make the distinction between osmolality and osmolarity more of linguistic than practical importance.

Freezing-point (cryoscopic) osmometers: When an ideal solvent is cooled below its freezing point a cooling curve can be plotted. Initially the temperature falls at a rate proportional to the difference between the solvent temperature and its environment (Newton's law of cooling). When freezing point is reached a temperature plateau forms until all the solvent has been converted to the solid phase and then cooling recommences.

In practice all liquids tend to cool below their freezing point in a liquid state (a phenomenon known as supercooling) and the cooling curve has the appearance shown in Figure A3.21.

Cooling is continued below the freezing point until crystallization of the liquid occurs on an additional impetus from seed-crystallization or vibration. The temperature then rises due to latent heat of crystallization to form a plateau until the solvent is solid.

Operation: The range extender switch was adjusted to select the proper range for the sample being tested: 0-1000 mOsm/kg or 1000-2000 mOsm/kg. The instrument was calibrated by using 'Calibration Standards' Standards' of 100 mOsm/kg and 500 mOsm/kg (Advanced Instruments Inc., Mass.).

0.20 ml of serum or plasma were pipetted into special glass vessels (3L-A824) provided with the instrument and supercooled to several degrees below its freezing point. Freezing was then induced in the sample by briefly activating the vibrator and the freezing point plateau recorded by the thermistor within the glass vessel. The readout knob was adjusted as the Galvanometer spotlight moved to the right. The readout knob showed the final value when the spotlight stopped, then reversed direction. For urinary osmolality, 2ml samples were pipetted into special glass vessels provided and the above steps carried out as outlined. Replicate serum sample determinations showed that the coefficient of variation of the method to be 0.62% or repeatability of $\pm$ 1 mOsm/kg.

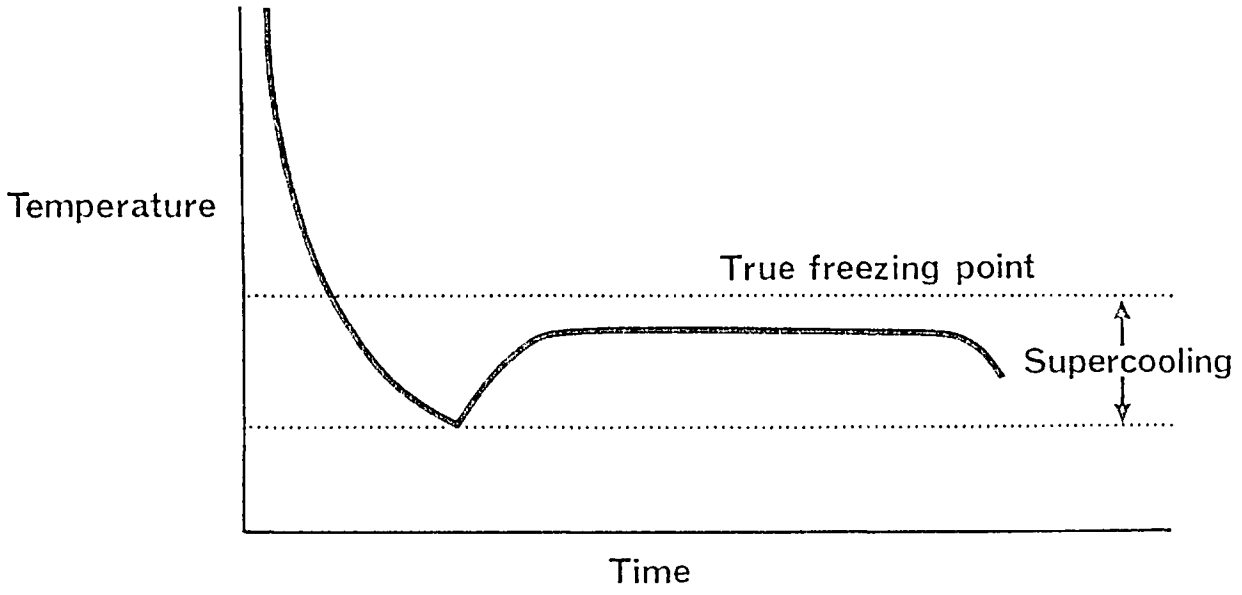


Figure A3.21

The supercooling effect in actual solutions

TABLE A3.21

Replicate serum sample determinations of osmolality (mOsm/kg)

Sample	A	B	$\bar{x}$
1	280.9	280.3	280.6
2	283.5	283.9	283.7
3	280.7	280.3	280.5
4	279.6	279.4	279.5
5	280.3	281.1	280.7
6	284.2	283.2	283.7
7	280.1	279.1	279.6
8	282.5	281.5	282.0
9	279.3	278.7	279.0
10	279.0	279.6	279.3
11	279.6	280.2	279.9
12	279.3	279.9	279.6
13	278.6	278.4	278.5
14	279.7	279.9	279.8
15	280.0	280.8	280.4
16	283.5	284.3	283.9
17	279.1	280.1	279.6
18	278.9	279.3	279.1
19	282.7	281.7	282.2
20	283.4	284.0	283.7
21	279.6	280.0	279.8
22	279.5	279.9	279.7

Calculated Osmolality:

A theoretical 'calculated osmolality' value of 310 mOsm/kg serum can be obtained by adding the molar concentrations in mmol/l - and thus the osmolar concentrations - of the individual solutes (electrolytes, urea, glucose, and so on) in serum.

$$\text{Calc - Osm} = 2(Na^+ + K^+) + \text{urea} + \text{glucose}$$

This value is close to but greater than the measured or observed osmolality (285 $\pm$ 5mOsm/kg) mainly because NaCl is only 93 per cent dissociated in serum.

Occasionally, the measured or observed osmolality (Obs-Osm) is higher than the calculated osmolality (Calc-Osm) in non-lipaemic serum and may be abnormally high. This discrepancy between Obs-Osm and Calc-Osm - 'osmolal gaps' indicates the presence of other osmotically active particles not accounted for by the above equation of Calc-Osm (see Appendix 4.1).

APPENDIX 3.3

Isotope measurement of Na_e

Measurement of body Na^+ content may be accomplished by radioisotope dilution. The method used was that of Forbes and Perley (1951) with modificiations. Radioactive sodium (^{24}Na, half-life 15 hours) was obtained from The Radiochemical Centre, Amersham. Measurements were performed in collaboration with Mr S A J Suddle in the Department of Clinical Physics, St Mary's Hospital, London W2.

There is a sizeable pool of rapidly exchangeable sodium and a slowly exchangeable or probably non-exchangeable pool of sodium in the bone. Since bone contains 35 to 40 per cent of total body sodium, exchangeable sodium (Na_e) is significantly less than total body quantity. The procedure employed was to introduce a known amount of radioactive sodium into the body, allow it to become distributed through the body tissues, and then determine the serum sodium specific activity. If allowance is made for excretion of radioactive sodium during the equilibration period, the total amount of sodium in equilibration with radioactive sodium can then be calculated. This method makes no distinction between extracellular and intracellular sodium.

Following the injection of a tracer dose of radioactive sodium, there is rapid disappearance of the tracer from the blood followed in 3 to 4 hours by a slower disappearance phase (Figure A3.31). Rapid disappearance of radioactive sodium from the blood during the first 30 - 40 minutes following injection is representative of a rapidly exchangeable fraction of body sodium which is primarily extracellular. After

24 hours, there is usually little further exchange. Tissue distribution studes by Forbes and Perley (1951) have shown that muscle, skin, kidney and liver equilibrate rapidly with radioactive sodium within 20 to 60 minutes. Bone and brain, however are not completely equilibrated at 18 hours, although approximately 45 per cent of bone sodium will exchange with radioactive sodium during this period. Thus total exchangeable sodium (Na_e) represents about 70 per cent of total body sodium.

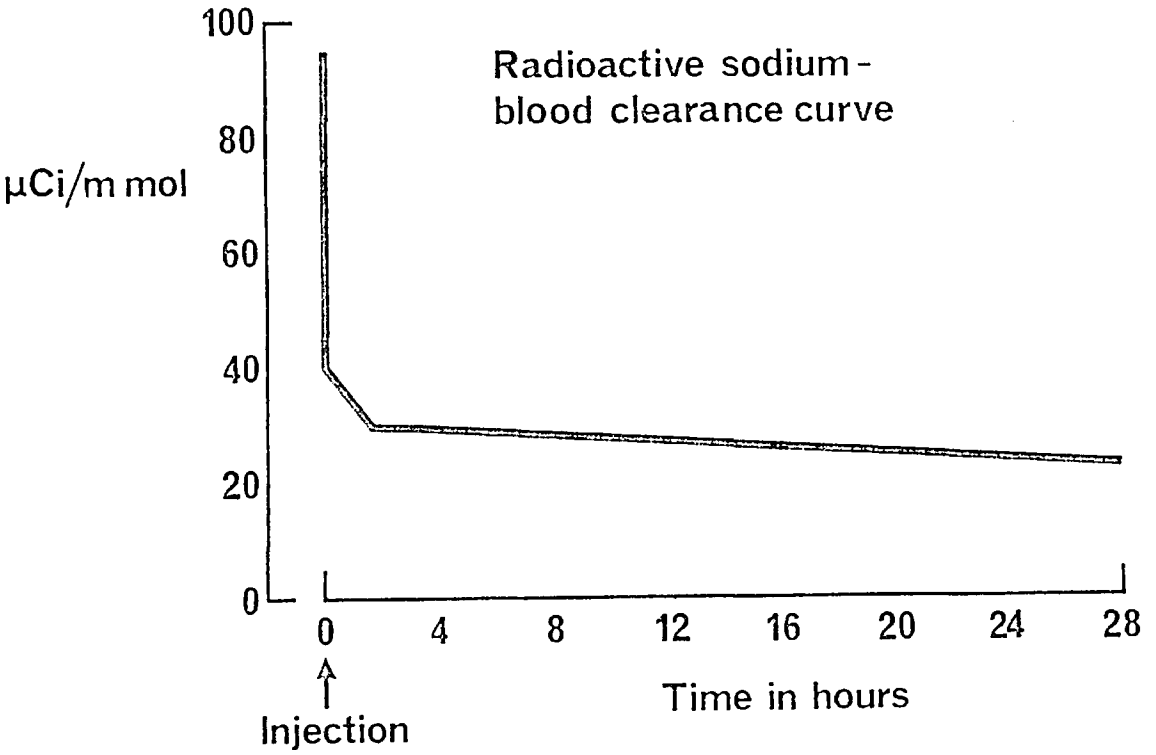


Figure A3.31

Radioactive sodium, blood disappearance curve

Method:

(Thursday) -

1 At 12.45 pm, 10 ml of venous blood was taken into lithium heparin tubes.
2 At 1.00 pm, a weighed quantity containing 20 μCi ^{24}Na was given intravenously by the Research Fellow.
3 A 24-hour urine save was begun at the same time.
4 The patient was kept nil by mouth from midnight on Thursday until 2.00 pm on Friday.

(Friday) -

1 At 12 mid-day, 15 ml of venous blood was taken into lithium heparin tubes.
2 At 1.00 pm, the 24-hour urine save was completed, volume measured and an aliquot kept with a note of the volume and the patient's body weight and height.
3 At 1.00 pm, 15 ml of venous blood was taken into lithium heparin tubes.
4 At 2.00 pm, 15 ml of venous blood was taken into lithium heparin tubes.

The stock solution of ^{24}NaCl solution was diluted with normal saline to contain 1.85 kBq/ml (5μCi/ml). Four ml of this solution was drawn gavimetrically into a syringe and given intravenously to the subject.

The counting standard was prepared by diluting the stock solution into a 1 litre flask with normal saline, a known amount of the stock solution to 1 litre.

Sample Calculation: Subject: PH Weight: 53 kgs Height 150 cms

Sample:	Time on (Hr):	Counts/t (sec):	Counts/sec/4ml:	Background: (Counts/sec)	Counts-Background:	$t_{\frac{1}{2}}$:	Decay Factor:	Counts: decay corrected
Background:		400/1000		0.40				
Plasma predose:		198/ 500		0.39				
Std (i):	1830	10k/128.3	77.942	0.40	77.542	1831	1.000	77.542
Std (ii):	1833	10k/128.0	78.125	0.40	77.725	1834	1.002	77.880
Std (iii):	1836	10k/128.5	77.821	0.40	77.421	1837	1.004	77.731
Pool urine:	1838	1k/679.3	1.472	0.40	1.072	1839	1.006	1.078
Plasma (1):	1849	1865/500	3.730	0.40	3.330	1855	1.019	3.393
Plasma (2):	1857	1575/500	3.150	0.40	2.750	1859	1.022	2.811
Plasma (3):	1905	1400/500	2.800	0.40	2.400	1909	1.029	2.470

Dose: 5.297 - 3.392 = 1.905 gm ≡ 30μCi

Std : 8.162 - 3.792 = 4.370 gm ..... diluted to 1 litre N-saline

Pool urine : 1700 ml

Plasma (1) Na^+ : 136 mmol/l

Plasma (2) Na^+ : 138 mmol/l

Plasma (3) Na^+ : 139 mmol/l

counts in : $\frac{77.718}{4} \times 10^3 \times \frac{1.905}{4.370}$ = 8470 c/s

counts out : $\frac{1.078}{4} \times 1700$ = 458 c/s

counts retained : 8470 - 458 = 8012 c/s

specific activity (1): $\frac{3.393}{4} \times \frac{10^3}{136}$ = 6.238

(2): $\frac{2.811}{4} \times \frac{10^3}{138}$ = 5.093

(3): $\frac{2.470}{4} \times \frac{10^3}{139}$ = 4.442

exchangeable Na^+ (1): $\frac{8012}{6.238}$ = 1284.39 mmol

(2): $\frac{8012}{5.093}$ = 1573.14 mmol

(3): $\frac{8012}{4.442}$ = 1803.70 mmol

mean exchangeable Na^+ = 1553.74 mmol

or, 29.32 mmol/kg body weight.

APPENDIX 3.4

Calculation of K_e and external balance changes

Serum Na^+ level reflects only the ratio of Na^+ to water in the ECF. This ratio is determined by total exchangeable Na^+ (Na_e), total body water (TBW), and the distribution of the latter between ECF and ICF compartments. The distribution of TBW is also dependent on total exchangeable potassium (K_e), the principal intracellular cation. Thus,

$$s - Na^+ = k. \frac{Na_e + K_e}{TBW}$$

where k is a constant, $s-Na^+$ equals the concentration of sodium per litre of plasma water, Na_e, K_e in millimoles and TBW in litres. Isotopic data from the study of body composition has confirmed this inter-relationship between Na_e, K_e and TBW (Moore et al, 1956; Edelman et al, 1958).

The sum of K_e and Na_ecalled 'total base' by Moore et al, (1963) has a very high correlation with TBW when each of the three variables are measured independently by isotope dilution techniques. Moore et al found the regression equation for this relationship to be :

$$Na_e \text{ (mmol)} + K_e \text{ (mmol)} = 163.19 \text{ TBW (l)} - 69$$
$$r = 0.99$$
$$p < 0.001$$

Unaffected by age groups or sex, this relationship permits close estimation of the third factor when any two are known. Furthermore, Shizgal et al, (1977) described a technique for the indirect measurement of K_e that involves neither the rapidly decaying radioisotopes of potassium nor a total body counter. K_e was calculated from:

$$K_e = R(TBW) - Na_e$$

where R is the ratio of the sodium plus potassium content divided by the water content in a sample of whole blood.

In 14 healthy patients (section 3.42) presenting for elective major abdominal surgery :

(1) Na_e was measured by the administration of 20μCi ^{24}Na intravenously ;

(2) TBW was determined by the intravenous administration of 100μCi of $^{3}H_2O$;

(3) K_e was then calculated from the formula of Edelman and Moore, validated by Shizgal, thus allowing preoperative quantitation of body composition.

(4) Daily balance measurements were used to revise sodium, potassium and water content so that a new value for $s\text{-}Na^+$ could be calculated for each day :

$$s\text{-}Na^+ = k \frac{(Na_e + Na_{BAL}) + (K_e + K_{BAL})}{TBW + \text{water balance}}$$

TABLE A3.41

Day 0:

Subject:	Na_e (mmol)	K_e (mmol)	TBW (l)	Na_{BAL} (mmol)	K_{BAL} (mmol)	H_2O_{BAL} (l)	measured s-Na^+ (mmol/l plasma water)	$\frac{Na_e + K_e}{TBW}_{BAL}$
1	2868	3542	39.7	-23	+45	-0.5	160	164
2	2559	3459	37.3	-55	+30	-0.3	159	162
3	2870	3621	40.2	+ 8	+22	+0.3	159	161
4	2550	3044	34.7	-48	-17	-1.0	160	164
5	2390	2730	31.8	+35	+ 9	+0.5	159	160
6	2760	3601	39.4	-21	-10	+0.4	155	159
7	2422	3400	36.1	+16	+39	+0.9	158	159
8	2600	3287	36.5	- 6	+29	+0.7	159	159
9	2500	3600	37.8	+20	- 6	+0.4	160	160
10	2613	3552	38.2	-14	+10	-0.2	160	162
11	2822	3555	39.5	+30	- 8	+0.5	160	160
12	2637	3055	35.3	-15	-20	-0.4	159	162
13	2530	3325	36.3	+10	+15	+0.7	156	159
14	2911	3646	40.6	+12	+22	+0.9	157	159

TABLE A3.42

Day 1:

Subject:	Cumulative Na-balance: (mmol)	Cumulative K-balance: (mmol)	Cumulative H_2O-balance: (l)	measured s-Na^+: (mmol/l plasma water)	$\frac{Na_e + K_e}{TBW}_{BAL}$
1	+ 9	- 72	+2.3	147	151
2	+ 18	-115	+2.4	150	149
3	+ 50	-102	+2.7	147	150
4	+ 27	- 98	+2.9	144	147
5	+126	- 34	+1.8	151	155
6	+ 63	-175	+3.4	142	146
7	+ 94	-127	+2.8	145	149
8	+145	- 42	+1.4	158	158
9	+133	- 82	+1.9	156	155
10	+109	- 54	+2.2	155	154
11	+138	- 46	+1.7	154	157
12	+ 88	- 37	+2.0	154	154
13	+110	- 99	+2.6	149	151
14	+ 24	- 86	+2.7	148	150

TABLE A3.43

Day 2:

Subject:	Cumulative Na-balance: (mmol)	Cumulative K-balance: (mmol)	Cumulative H_2O-balance: (l)	measured s-Na^+: (mmol/l plasma water)	$\frac{Na_e + K_e}{TBW}_{BAL}$
1	+ 21	-146	+3.6	147	145
2	+138	-155	+3.0	146	149
3	+ 63	-175	+4.7	143	142
4	+ 49	-138	+3.5	147	144
5	+168	- 72	+2.1	153	154
6	+174	-181	+3.5	144	148
7	+102	-137	+3.3	146	147
8	+151	-149	+3.0	156	149
9	+144	-180	+4.0	147	145
10	+140	- 86	+3.8	146	148
11	+168	- 55	+2.4	156	155
12	+189	- 60	+2.3	154	155
13	+216	-107	+2.7	152	153
14	+ 88	-101	+3.0	148	150

TABLE A3.44

Day 3:

Subject:	Cumulative Na-balance: (mmol)	Cumulative K-balance: (mmol)	Cumulative H_2O-balance: (l)	measured s-Na^+: (mmol/l plasma water)	$\frac{Na_e + K_e}{TBW}_{BAL}$
1	+219	+ 26	+3.8	151	153
2	+ 60	-162	+3.5	144	145
3	+108	- 29	+4.2	146	148
4	+ 72	- 60	+3.7	147	146
5	+175	-122	+2.9	147	149
6	+154	- 65	+3.6	149	150
7	+208	- 11	+3.5	148	152
8	+163	-145	+3.4	147	148
9	+321	+ 79	+3.3	157	158
10	+156	-202	+4.0	147	145
11	+170	-200	+3.1	147	149
12	+285	- 17	+3.4	152	154
13	+297	- 15	+3.8	152	153
14	+266	- 34	+3.2	150	155

TABLE A3.45

Day 4:

Subject:	Cumulative Na-balance:	Cumulative K-balance:	Cumulative H_2O-balance:	measured s-Na^+:	$\frac{Na_e + K_e}{TBW}_{BAL}$
	(mmol)	(mmol)	(l)	(mmol/l plasma water)	
1	+ 80	+ 50	+3.6	153	151
2	+ 40	-134	+3.0	149	147
3	+ 40	+ 11	+4.0	148	148
4	+ 60	+ 24	+2.9	149	151
5	+125	+ 37	+2.5	152	154
6	+ 48	+ 9	+3.1	149	151
7	+ 34	+ 12	+3.2	150	149
8	+ 43	-138	+3.5	147	145
9	+129	+ 80	+2.8	157	155
10	+196	+120	+2.9	159	158
11	+126	- 9	+3.0	152	153
12	+141	+ 50	+3.1	153	153
13	+199	+101	+3.3	153	155
14	+ 30	+ 8	+3.4	151	150

TABLE A3.46

Day 5:

Subject:	Cumulative Na-balance: (mmol)	Cumulative K-balance: (mmol)	Cumulative H_2O-balance: (l)	measured s-Na^+: (mmol/l plasma water)	$\frac{Na_e + K_e}{TBW}_{BAL}$
1	+164	+123	+3.0	153	157
2	+101	+109	+2.8	152	155
3	+ 50	+ 19	+3.7	151	149
4	+ 78	+ 82	+3.5	150	151
5	+ 67	+ 56	+2.2	152	154
6	+ 65	+ 25	+3.0	149	152
7	+103	+ 86	+3.0	151	154
8	+135	+107	+3.3	151	154
9	+ 91	+100	+3.1	158	154
10	+ 74	+ 38	+3.2	150	152
11	+155	+122	+2.4	158	159
12	+182	+153	+2.8	158	158
13	+135	+ 74	+2.9	155	155
14	+105	+ 66	+3.0	154	154

TABLE A3.47

Day 6:

Subject:	Cumulative Na-balance: (mmol)	Cumulative K-balance: (mmol)	Cumulative H_2O-balance: (l)	measured s-Na^+: (mmol/l plasma water)	$\frac{Na_e + K_e}{TBW}_{BAL}$
1	+150	+104	+2.8	156	157
2	+182	+148	+2.8	157	158
3	+100	+ 44	+4.3	151	149
4	+125	+ 87	+3.4	150	152
5	+ 62	+ 63	+2.3	152	154
6	+ 62	+ 39	+4.5	150	147
7	+197	+124	+2.9	155	158
8	+178	+121	+2.7	155	158
9	+166	+ 89	+2.6	154	157
10	+ 82	+ 72	+3.1	152	153
11	+ 95	+ 33	+3.1	156	153
12	+103	+ 79	+2.5	156	155
13	+ 93	+ 31	+2.8	153	153
14	+ 76	+ 27	+3.1	153	152

TABLE A3.48

Regression relationship between $s\text{-}Na^+$ (mmol/l plasma water) and $\frac{Na_e + K_e}{TBW}$ corrected for daily balance over 6 post-operative days (mmol/l) in 14 subjects

$s\text{-}Na^+$:	$\frac{Na_e + K_e}{TBW}$:	$s\text{-}Na^+$:	$\frac{Na_e + K_e}{TBW}$:	$s\text{-}Na^+$:	$\frac{Na_e + K_e}{TBW}$:	$s\text{-}Na^+$:	$\frac{Na_e + K_e}{TBW}$:	$s\text{-}Na^+$:	$\frac{Na_e + K_e}{TBW}$
160	164	160	164	158	159	160	162	156	159
147	151	144	147	145	149	155	154	149	151
147	145	147	144	146	147	146	148	152	153
151	153	147	146	148	152	147	145	152	153
153	151	149	151	150	149	159	158	153	155
153	157	150	151	151	154	150	152	155	155
156	157	150	152	155	158	152	153	155	153
159	162	159	160	159	159	160	160	157	159
150	149	151	155	158	158	154	157	148	150
146	149	153	154	156	149	156	155	148	150
144	145	147	149	147	148	147	149	150	155
149	147	152	154	147	145	152	153	151	150
152	155	152	154	151	154	158	159	154	154
157	158	152	154	155	158	156	153	153	152
159	161	155	159	160	160	159	162		
147	150	142	146	156	155	154	154		
143	142	144	148	147	145	154	155		
146	148	149	150	157	158	152	154		
148	148	149	151	157	155	153	153		
151	149	149	152	158	154	158	158		
151	149	150	147	154	157	156	155		

$$s\text{-}Na^+ = 0.85 \left(\frac{Na_e + K_e}{TBW} \right)_{BAL} + 22.11$$

$r = 0.88$
$t = 19.74$
$p < 0.001$

TABLE A3.49

Ninety-five per cent tolerance limits with ninety-five per cent confidence probability for the for the regression relationship between $s\text{-}Na^+$ (mmol/l plasma water) and $\frac{Na_e + K_e}{TBW}$ (mmol/l)

$\frac{Na_e + K_e}{TBW}$	$s\text{-}Na^+$: Upper limits:	Lower limits:
140	151	132
142	152	134
143	153	135
145	154	137
147	156	138
148	157	139
150	158	141
152	160	142
153	161	143
155	163	145
157	164	146
158	165	147
160	167	149
162	169	150
164	170	152

Calculation of tolerance limits :

$$yo \pm t_{n-2}\sqrt{\left[\frac{(Sy)^2(n-1)(1-r)^2}{(n-2)}\right]\left[1 + \frac{1}{n} + \frac{(x_o - \bar{x})^2}{(S_x)^2(n-1)}\right]}$$

(Documenta Geigy, 1970)

APPENDIX 3.5

Determination of normality of distribution for serum sodium data

When parametric terminology is used there is an underlying assumption that the frequency distribution of the population being studied conforms exactly to the normal distribution. The entire population cannot usually be examined, so that the decision about the form of the frequency distribution must be taken on a basis of the sample or samples available.

Though a priori evidence exists that serum sodium values in man conform to a normal distribution (Wotton et al, 1951; Fawcett and Wynn, 1956) the s-Na^+ data for six days on 50 uncomplicated patients have been tested for skewness based on the third moment of the mean. This test measures skewness by examining the asymmetry of deviations of the sample values from their mean. This was accomplished by summing the cubes of the deviations from the mean, thus preserving the sign. The sum of cubes equals or is very close to zero if the sample is normally distributed. The test statistic is γ_1 which is equal to ...

$$\frac{m_3}{m_2\sqrt{m_2}}$$

where m_3 is the average cubed deviation and m_2 is the variance (Snedecor and Cochran, 1967).

The s-Na^+ data for six days on 50 uncomplicated patients were found to be normally distributed for all patients at all times studied. It was thus permissible to construct ninety-five per cent tolerance limits with ninety-five per cent confidence probability by using the mean and standard deviation at each epoch for normally distributed data (Documenta

Geigy, 1970) where upper and lower tolerance limits are given by $\bar{x} \pm SD.k_7$. For sample size ...

$$n = 50,\ k_7 = 2.379.$$

Similar analyses were applied to the data for serum osmolality and serum potassium on the 50 uncomplicated patients.

TABLE A3.51

Serum Sodium Data for 6 days on 50 uncomplicated patients

Subject: Day	0	1	2	3	4	5	6
1	138.8	132.0	133.7	131.9	129.0	131.9	135.3
2	141.1	135.9	135.2	137.5	136.2	139.3	138.4
3	141.0	133.4	131.3	133.8	131.3	134.9	137.1
4	135.3	132.1	131.4	132.1	130.2	130.2	134.3
5	140.2	137.7	134.5	133.3	135.5	133.4	135.2
6	138.5	135.6	136.0	137.8	138.5	138.5	139.0
7	142.0	132.3	134.0	138.6	145.0	145.0	146.0
8	139.7	132.2	135.8	135.8	137.9	138.0	138.0
9	143.3	137.0	131.3	137.0	137.0	144.2	143.8
10	140.2	130.0	131.1	134.0	132.2	134.6	134.7
11	139.0	134.0	136.4	135.3	135.1	138.3	143.0
12	137.5	135.1	137.6	138.7	139.1	140.2	139.3
13	141.3	133.2	134.0	136.1	137.9	139.0	143.0
14	137.0	127.7	127.9	137.6	139.4	140.7	142.1
15	141.0	136.4	139.2	140.2	140.5	142.0	142.3
16	143.4	136.4	134.6	136.2	137.8	137.5	140.9
17	140.0	139.6	127.7	133.8	133.6	135.3	136.0
18	142.0	136.6	129.0	135.2	133.9	133.0	136.8
19	140.3	134.8	133.0	136.2	134.9	136.3	135.1
20	139.8	134.0	133.4	136.0	137.0	135.9	136.0
21	135.3	131.4	126.5	130.9	131.6	127.8	134.6
22	140.2	133.6	134.2	137.7	134.0	134.4	136.8
23	138.4	135.0	131.2	133.2	135.5	137.8	139.0
24	142.9	131.6	134.6	134.9	136.6	135.4	137.7
25	139.0	138.1	134.0	136.4	135.0	138.3	145.2
26	143.1	138.2	131.5	135.4	134.6	134.3	137.4
27	138.6	132.7	135.4	139.0	135.7	135.5	137.0
28	140.4	132.3	133.8	136.0	136.2	139.0	138.5
29	140.0	134.8	136.0	136.0	136.3	136.6	137.5
30	139.0	135.5	133.1	134.0	138.1	137.4	137.6

Subject: Day:	0	1	2	3	4	5	6
31	140.3	134.8	136.5	139.2	138.8	139.1	140.2
32	135.5	129.2	131.6	129.7	131.8	134.9	134.9
33	142.1	131.4	135.3	135.8	140.6	143.1	141.5
34	143.3	138.1	139.6	137.0	139.8	139.0	138.7
35	141.8	135.3	134.6	123.4	134.0	137.4	140.8
36	139.5	132.4	134.8	135.6	140.1	137.3	137.3
37	137.3	136.0	135.2	138.0	137.7	139.0	138.1
38	141.0	134.6	134.2	136.0	136.2	137.7	138.5
39	136.4	131.4	129.2	124.6	128.0	131.6	135.9
40	138.0	131.3	128.4	131.5	134.7	136.5	136.5
41	140.3	136.6	133.8	133.1	138.2	138.3	139.2
42	140.2	135.6	137.1	137.3	139.4	140.3	139.1
43	137.3	129.0	128.8	135.6	137.9	137.5	138.0
44	141.8	136.0	136.3	138.4	138.2	140.3	142.0
45	140.3	136.1	134.3	135.0	135.4	136.0	136.6
46	142.7	130.1	132.3	137.4	137.0	137.3	138.0
47	143.0	135.7	136.1	138.5	140.6	141.2	143.4
48	141.9	136.2	136.0	138.6	138.8	142.0	141.0
49	135.8	130.8	132.1	129.2	133.7	135.0	135.0
50	141.1	138.2	134.7	133.1	137.0	139.2	144.7
$\bar{x}$	139.96	134.16	133.57	135.15	136.27	137.35	138.74
m_2	4.77	7.37	8.31	11.22	10.25	11.20	8.96
m_3	- 4.62	-5.50	-11.37	-56.40	-9.43	-10.11	16.69
γ_1	- 0.44	-0.27	-0.47	-1.50	-0.29	-0.27	0.62
SD	2.21	2.74	2.91	3.38	3.23	3.38	3.02
$\bar{x} + K_7$ SD	145.22	140.68	140.49	143.19	143.95	145.39	145.92
$\bar{x} - K_7$ SD	134.70	127.64	126.65	127.11	128.59	129.31	131.56
t		15.86	15.78	10.44	8.65	6.04	3.05
p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.005
df		49	49	49	49	49	49

TABLE A3.52

Serum Osmolality Data for 6 days on 50 uncomplicated patients

Subject: Day:	0	1	2	3	4	5	6
1	276.4	265.8	269.5	265.2	259.0	260.8	268.2
2	280.6	275.8	271.6	271.9	273.1	279.5	277.9
3	283.7	264.9	261.8	264.5	260.8	265.9	274.3
4	276.6	262.2	261.7	263.1	260.4	259.6	269.9
5	280.5	271.3	266.9	264.8	267.7	267.3	275.8
6	279.5	270.5	271.9	275.3	274.9	275.2	279.1
7	280.7	261.6	262.9	268.5	283.0	284.3	287.0
8	283.7	267.2	273.8	272.2	275.3	274.6	276.5
9	289.9	276.8	267.6	269.9	273.9	289.5	287.2
10	286.6	266.8	271.3	270.0	268.1	270.3	275.2
11	276.6	264.2	269.3	266.2	265.8	272.0	279.9
12	275.8	272.1	272.3	273.6	277.5	278.8	276.7
13	282.2	263.6	264.2	270.6	275.5	277.8	285.3
14	279.6	259.8	260.0	268.9	279.3	285.3	287.6
15	282.0	271.6	272.7	273.2	277.5	280.6	281.3
16	287.9	273.7	271.4	273.3	278.4	277.6	283.7
17	279.0	274.1	258.8	266.0	268.1	271.6	272.8
18	285.5	270.7	260.2	269.4	266.9	266.0	274.7
19	279.3	271.5	264.9	267.6	265.3	273.0	271.4
20	279.9	269.1	267.5	269.8	273.6	272.4	275.9
21	269.9	262.2	259.2	260.9	261.5	258.9	270.1
22	279.6	264.8	265.3	272.6	269.8	268.8	274.4
23	276.1	267.2	260.5	263.1	267.6	272.8	276.3
24	290.7	265.2	266.7	268.4	271.7	269.9	276.3
25	276.3	272.7	269.1	270.7	269.3	275.7	285.1
26	286.6	273.5	261.4	269.8	268.5	267.9	276.1
27	276.6	260.6	264.0	270.6	268.2	267.2	275.5
28	278.5	260.1	263.4	269.9	271.1	275.1	277.8
29	279.8	268.1	268.9	268.8	269.2	270.1	277.9
30	278.1	272.5	265.3	265.3	272.6	271.9	277.6

Subject:	Day:	0	1	2	3	4	5	6
31		280.4	265.2	269.4	277.0	275.8	276.7	281.1
32		272.2	260.0	261.1	259.8	261.2	267.6	272.6
33		285.0	261.0	264.8	267.8	276.6	282.2	284.8
34		286.9	272.1	274.3	271.7	274.4	275.0	276.2
35		283.9	267.1	264.6	248.8	264.7	271.6	281.8
36		286.1	264.0	266.3	269.3	277.8	274.4	275.5
37		276.3	268.8	265.9	271.8	270.3	273.0	274.0
38		279.6	266.4	265.5	269.7	270.0	272.6	276.3
39		279.1	263.8	259.4	249.9	254.3	260.5	273.0
40		282.2	260.6	258.1	261.1	267.2	270.9	271.4
41		285.8	271.7	268.9	266.5	274.1	275.4	278.6
42		283.7	265.8	270.3	271.0	276.7	279.9	277.7
43		279.8	257.0	258.4	271.7	274.4	275.3	277.9
44		285.2	268.7	269.3	271.3	271.5	275.4	277.8
45		290.1	270.2	267.8	270.6	271.9	273.1	277.9
46		286.9	262.7	263.7	270.9	271.5	270.8	278.0
47		284.6	269.1	268.8	270.9	275.7	277.2	281.7
48		286.3	269.9	270.2	274.5	276.7	282.4	281.7
49		279.7	261.2	263.3	259.8	264.6	267.8	269.9
50		288.9	272.3	265.4	263.2	270.1	274.7	287.9
$\bar{x}$		281.62	267.16	265.99	268.03	270.66	273.15	277.67
m_2		21.45	22.94	18.97	29.93	34.10	40.45	23.22
m_3		- 4.74	- 5.14	- 4.46	-258.58	-102.38	- 7.42	44.12
γ_1		- 0.05	- 0.05	- 0.05	- 1.58	- 0.51	- 0.03	0.39
SD		4.68	4.84	4.40	5.53	5.90	6.42	4.87
$\bar{x} + K_7$ SD		292.75	277.82	276.46	281.19	284.70	288.42	289.26
$\bar{x} - K_7$ SD		270.49	256.50	255.52	254.87	256.62	257.88	288.08
t		18.35	20.38	15.05	13.07	9.37	5.33	
p		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	
df		49	49	49	49	49	49	

Regression analysis of serum osmolality
on serum sodium data on 50 uncomplicated patients

$r^2 = 0.84$
$r = 0.92$
$a = 18.74$
$b = 1.86$
$t = 42.91$
$p < 0.001$

where the simple linear regression equation takes the form:

$$y = bx + a$$

TABLE A3.53

Serum Potassium Data for 6 days on 50 uncomplicated patients

Subject: Day:	0	1	2	3	4	5	6
1	4.4	4.3	4.7	4.5	3.5	3.3	3.2
2	4.0	4.2	4.2	3.7	3.9	3.8	4.0
3	4.2	4.0	4.0	3.4	3.4	3.2	3.4
4	3.9	4.6	5.1	4.2	4.9	4.3	4.2
5	4.4	4.0	4.1	4.5	4.5	4.4	4.8
6	4.8	4.2	4.2	3.7	3.6	3.5	4.5
7	4.2	3.7	3.5	3.2	3.6	3.6	3.9
8	4.8	4.8	5.4	4.8	3.5	4.0	3.3
9	4.0	4.2	4.0	3.6	3.7	4.0	3.9
10	3.8	3.7	3.7	4.6	4.3	4.7	4.2
11	3.1	3.9	3.4	3.2	3.6	3.6	3.1
12	4.0	4.2	3.5	3.7	3.5	3.7	4.1
13	3.6	3.9	4.4	4.2	3.9	4.0	4.2
14	4.0	3.9	3.7	3.4	3.8	4.4	3.9
15	4.3	4.1	3.6	3.3	3.9	4.0	4.6
16	4.2	4.9	5.1	4.3	3.8	4.9	4.1
17	3.6	3.5	3.9	3.3	3.5	2.7	3.3
18	4.0	4.3	4.5	4.4	4.0	4.2	4.1
19	3.5	4.4	3.7	3.4	4.0	4.3	4.4
20	3.7	3.8	3.4	3.6	4.0	4.1	4.2
21	3.7	3.3	3.9	4.0	4.2	4.7	4.6
22	3.5	4.2	4.7	4.7	4.7	4.3	4.8
23	3.9	4.4	4.1	4.0	4.1	4.6	4.3
24	3.7	4.0	3.5	4.1	4.3	4.0	3.9
25	3.7	3.7	3.9	4.3	4.2	4.6	4.0
26	3.5	3.6	3.9	4.3	4.4	3.6	3.6
27	4.0	3.3	3.3	3.4	4.2	4.2	4.5
28	4.5	3.8	4.2	4.3	4.6	4.1	4.8
29	4.1	3.8	4.1	4.6	3.8	4.2	4.9
30	4.6	3.6	4.2	4.4	3.2	4.0	4.1

Subject: Day:	0	1	2	3	4	5	6
31	4.4	3.5	3.9	4.6	4.2	4.0	4.3
32	3.6	4.2	5.0	4.7	4.5	4.0	4.0
33	4.0	5.0	4.0	4.0	3.8	3.9	4.0
34	4.6	4.3	4.1	4.1	4.6	4.2	4.2
35	4.0	3.5	3.9	4.2	4.2	3.9	4.0
36	4.3	3.6	4.5	4.4	4.0	3.5	3.7
37	4.1	3.5	3.6	3.3	3.4	2.9	3.3
38	3.6	3.9	3.9	3.4	3.7	4.1	3.9
39	3.9	4.2	4.2	4.7	4.6	4.4	4.0
40	4.5	4.3	4.6	4.6	3.6	3.4	3.5
41	4.1	4.3	4.3	3.8	4.0	3.9	4.1
42	4.3	4.1	4.1	3.5	3.5	3.3	3.5
43	4.0	4.7	5.0	4.3	5.0	4.4	4.3
44	4.5	4.2	4.2	3.9	3.7	3.6	3.9
45	3.8	3.8	4.1	4.0	4.2	4.0	4.5
46	4.5	4.9	3.4	3.9	3.7	3.5	4.0
47	4.4	4.4	3.7	3.0	3.5	3.8	3.9
48	4.5	4.1	4.2	4.6	4.6	4.5	4.9
49	4.9	4.3	4.3	3.8	3.7	3.6	4.6
50	4.3	3.8	3.6	3.3	3.7	3.7	4.0
$\bar{x}$	4.08	4.06	4.09	3.98	3.98	3.95	4.07
m_2	0.15	0.17	0.23	0.25	0.18	0.21	0.20
m_3	-0.0025	0.02	0.08	-0.02	0.04	-0.04	-0.01
γ_1	-0.04	0.30	0.68	-0.16	0.48	-0.39	-0.16
SD	0.39	0.41	0.49	0.50	0.43	0.46	0.45
$\bar{x} + K_7$ SD	5.01	5.04	5.26	5.17	5.00	5.04	5.14
$\bar{x} - K_7$ SD	3.15	3.08	2.92	2.79	2.96	2.86	3.00
t	0.32	-0.10	1.14	1.13	1.37	0.78	
p	NS	NS	NS	NS	NS	NS	
df	49	49	49	49	49	49	

TABLE A3.54

Serum Sodium Data for 6 days on 10 uncomplicated patients given a restrictive fluid regimen

Subject: Day:	0	1	2	3	4	5	6
1	143.3	132.7	135.4	138.3	138.8	137.9	140.3
2	142.1	132.5	135.3	138.7	137.9	139.2	141.5
3	135.3	137.2	140.1	137.6	137.2	138.1	138.1
4	145.3	129.8	143.6	135.5	136.2	143.3	142.7
5	145.0	142.1	136.3	136.7	136.9	137.3	139.0
6	136.8	135.0	138.2	138.3	139.4	139.1	139.8
7	143.3	141.5	136.7	136.5	130.9	136.5	141.2
8	138.5	137.2	138.1	136.5	136.7	137.0	137.9
9	139.6	134.5	137.1	128.9	135.5	138.0	139.2
10	139.4	138.0	135.1	131.6	140.0	138.4	139.3
$\bar{x}$	140.86	136.05	137.59	135.86	136.95	138.48	139.90
SD	3.45	3.93	2.62	3.18	2.56	1.90	1.53
t	2.82	2.35	3.49	2.51	2.16	1.13	
p	<0.05	<0.05	<0.05	<0.05	NS	NS	
df	9	9	9	9	9	9	
$\bar{D}$	4.81	3.27	5.00	3.91	2.38	0.96	
S_D	5.39	4.39	4.53	4.92	3.49	2.68	

APPENDIX 4.1

Calculation of data for patients with osmolal gaps

TABLE A4.11

Serum osmolality data - observed and calculated - for uncomplicated patients. Calculated osmolality = $2(Na^+ + K^+)$ + urea + glucose

s-Na^+ (mmol/l)	s-K^+ (mmol/l)	s-Urea (mmol/l)	s-Glu (mmol/l)	Obs-Osm (mOsm/kg)	Calc-Osm (mOsm/kg)
147.2	3.2	2.9	3.0	309.3	306.7
135.2	4.1	4.5	5.0	298.5	288.1
135.2	3.7	6.0	5.0	299.1	288.8
138.9	3.3	4.5	4.5	298.3	293.4
140.8	3.7	5.0	4.9	308.8	298.9
143.5	3.9	2.5	3.1	309.9	300.4
146.3	3.6	2.8	3.1	310.1	305.7
138.0	4.5	4.3	4.8	298.4	294.1
134.3	4.7	4.7	6.7	295.3	289.4
132.5	3.8	6.2	5.4	288.8	284.2
137.1	3.4	4.1	4.5	294.8	289.6
139.8	3.0	4.6	5.5	306.3	295.7
144.4	4.0	5.4	3.6	309.9	305.8
140.3	4.4	4.2	5.2	301.8	298.8
135.2	4.9	6.4	4.1	294.7	290.7
131.6	5.0	5.8	7.5	294.7	286.5
134.3	4.3	6.3	4.0	292.5	287.5
136.2	3.9	5.2	5.0	295.3	290.4
138.9	3.1	5.7	4.3	296.6	294.0
138.9	4.1	4.6	4.9	298.5	295.5
141.2	3.5	5.1	4.0	300.1	298.5
132.5	4.2	4.3	4.8	287.4	282.5
135.2	4.0	6.5	4.9	295.6	289.8
135.2	4.7	5.8	6.3	297.8	291.9
140.8	4.2	3.0	3.3	307.6	296.3

$s\text{-}Na^+$ (mmol/l)	$s\text{-}K^+$ (mmol/l)	s-Urea (mmol/l)	s-Glu (mmol/l)	Obs-Osm (mOsm/kg)	Calc-Osm (mOsm/kg)
137.1	3.3	7.2	4.9	296.8	292.9
138.0	3.8	4.3	4.7	298.8	292.6
138.0	4.2	5.4	5.9	298.7	295.7
146.3	3.0	2.5	3.4	308.8	304.5
138.9	4.4	4.7	5.3	299.4	296.6
140.8	4.0	4.0	3.8	302.6	297.4
135.2	4.9	3.9	4.0	295.3	288.1
139.8	3.5	4.1	4.6	306.7	295.3
139.8	3.7	3.7	4.0	305.7	294.7
139.8	4.0	2.9	3.9	298.3	294.4
142.6	3.1	3.9	4.0	302.9	299.3
127.0	3.0	3.5	4.0	269.8	267.5
130.5	3.5	3.0	4.2	279.2	275.2
137.1	4.3	4.0	5.1	296.1	291.9
137.1	4.5	4.0	4.3	301.4	291.5
137.1	3.9	3.8	4.7	299.6	290.5
138.0	4.0	4.0	4.2	297.6	292.2
141.4	3.8	3.4	4.1	309.9	297.9
131.4	3.0	3.0	3.8	288.8	275.6
134.3	4.9	3.5	4.0	289.9	285.9
136.2	4.1	3.7	3.9	299.9	288.2
138.0	4.6	2.8	3.2	298.0	291.2
138.9	3.3	4.7	4.9	298.8	294.0
142.6	3.0	4.8	5.8	308.7	301.8
143.3	4.2	2.8	4.0	308.9	301.8
141.4	3.5	4.1	4.4	308.1	298.3
140.5	4.4	5.2	4.1	306.6	299.1
135.2	3.6	2.9	4.0	288.8	284.5
135.2	4.0	4.4	4.0	289.8	286.8
138.9	3.8	2.7	4.3	296.4	292.4
140.7	4.5	4.8	4.8	302.0	300.0

s-Na^+ (mmol/l)	s-K^+ (mmol/l)	s-Urea (mmol/l)	s-Glu (mmol/l)	Obs-Osm (mOsm/kg)	Calc-Osm (mOsm/kg)
141.2	3.9	3.0	3.3	307.5	296.5
133.5	4.1	4.4	5.4	288.1	285.0
135.2	4.5	6.3	5.7	297.6	291.4
132.4	3.7	6.7	6.0	289.8	284.9
135.4	4.0	3.3	3.7	286.8	285.8
134.4	3.6	3.1	3.3	289.5	282.4
140.0	3.5	3.0	3.4	298.0	293.4
132.7	4.0	4.1	3.7	289.5	281.2
135.1	3.6	3.3	4.3	294.9	285.0
135.3	3.5	4.0	3.4	289.0	285.0
131.2	3.7	5.2	5.0	288.9	280.0
132.3	4.0	5.3	3.8	289.9	281.7
132.5	3.8	4.9	5.0	292.2	282.5
135.5	4.1	2.9	3.1	288.2	285.2
135.2	4.3	3.0	3.0	293.1	285.0
136.7	3.8	5.0	4.0	299.4	290.0
139.5	3.5	2.8	3.1	299.6	291.9
135.2	4.3	3.0	3.7	289.7	285.7
137.8	3.6	4.4	5.1	298.6	292.3
135.4	4.4	7.1	6.5	295.2	293.2
136.5	4.0	3.0	3.1	294.2	287.1
137.3	3.9	4.0	4.2	299.1	290.6
135.7	4.5	6.5	5.8	296.7	292.7
135.7	3.6	4.3	4.4	299.3	287.3
139.8	3.3	3.2	3.8	298.6	293.2
140.8	3.5	2.3	2.7	295.7	293.6
135.4	4.0	4.8	5.7	294.6	289.3
136.5	4.9	5.4	5.1	296.3	293.3
139.5	3.8	3.1	3.3	298.1	293.0
137.1	4.2	6.7	4.5	297.9	293.8
139.8	3.1	4.3	4.0	299.5	294.1

s-Na^+ (mmol/l)	s-K^+ (mmol/l)	s-Urea (mmol/l)	s-Glu (mmol/l)	Obs-Osm (mOsm/kg)	Calc-Osm (mOsm/kg)
139.8	3.6	3.4	4.1	298.6	294.3
140.8	3.5	3.2	2.9	305.9	294.7
137.3	4.3	5.5	3.8	299.8	292.5
138.6	4.0	5.0	3.3	299.5	293.5
140.4	3.9	4.3	4.3	309.3	297.2
136.2	3.3	4.5	5.4	294.2	288.9
136.2	4.7	4.8	4.7	297.1	291.2
138.0	4.1	5.3	4.1	299.6	293.6
138.9	4.6	3.1	4.0	298.1	294.1
141.7	3.0	3.1	3.8	299.5	296.3
137.8	4.2	2.9	3.5	299.3	290.4

Regression analysis of Obs-Osm on Calc-Osm data for uncomplicated patients

$r^2 = 0.82$

$r = 0.91$

$a = 15.11$

$b = 0.97$

$t = 21.14$

$p < 0.001$

where the simple linear regression equation takes the form -

$$y = bx + a$$

TABLE A4.12

Ninety-five percent tolerance limits with ninety-five per cent confidence probability for the regression relationship between Obs-Osm and Calc-Osm - uncomplicated patients

Calc-Osm: (mOsm/kg)	Obs-Osm: (mOsm/kg)	
	Upper limits	Lower Limits
268	290	259
270	292	261
275	297	266
280	301	270
285	306	275
290	310	280
295	314	284
300	319	289
305	324	294
308	326	297

Calculation of tolerance limits

$$yo \pm t_{n-2} \sqrt{\left[\frac{(Sy)^2(n-1)(1-r)^2}{(n-2)}\right]\left[1 + \frac{1}{n} + \frac{(x_o-\bar{x})^2}{(Sx)^2(n-1)}\right]}$$

(Documenta Geigy, 1970)

TABLE A4.13

Data for 7 critically ill surgical patients

Patient:	Post Op.Day:	s-Na^+ (mmol/l)	Osmolal Gap: (mOsm/kg)	Na_e (mmol)	K_e (mmol)	TBW (l)	Cumulative Na^+-Bal: (mmol)	Cumulative K^+-Bal: (mmol)	Cumulative H_2O-Bal: (l)	$\frac{Na_e + K_e}{TBW}$ Bal (mmol/l):
FC	8	124.2	26	2987.8	3079.2	37.6	+79	+23	+2.2	155.0
GW	5	125.6	27	2274.3	1883.3	25.9	+255	+68	+3.1	154.5
SBR	11	125.0	28	2924.9	3032.7	36.9	+283	+76	+3.3	157.1
RB	9	126.5	26	2499.3	2147.9	28.9	+102	+86	+1.9	157.0
FA	6	128.3	25	2927.7	2883.1	36.0	+68	+59	+1.6	157.9
HJ	12	127.4	27	2660.4	2300.1	30.8	+298	+152	+3.1	159.6
VP	7	129.9	26	3050.4	3086.7	38.0	+125	+103	+1.8	159.9

APPENDIX 5.1

Data and calculation for sodium influx and efflux and intracellular sodium concentration

TABLE A5.11

Plasma Na^+ levels in 9 healthy patients

Patient:		Plasma Na^+ (mmol/l)
1	(D)	135.2
2	(W)	130.7
3	(M)	132.2
4	(H)	135.3
5	(H)	132.2
6	(D)	128.0
7	(B)	132.3
8	(M)	136.0
9	(O)	130.2

Plasma Na^+ levels in 14 critically ill surgical patients

Patient:		Plasma Na^+ (mmol/l)
1	(M)	129.8
2	(H)	129.7
3	(D)	120.0
4	(H)	129.2
5	(C)	125.1
6	(D)	119.7
7	(P)	124.5
8	(H)	130.4
9	(H)	109.0
10	(M)	131.1
11	(C)	130.9
12	(T)	123.0
13	(A)	123.2
14	(L)	130.9

TABLE A5.12

Na^+ flux data and intracellular sodium concentration $(Na)_{ICF}$ in 9 healthy patients

Pre-operative:

Patient:	Influx: (mmol/l-cell/hr)	Efflux: (mmol/l-cell/hr)	$(Na)_{ICF}$: (mmol/l-cell)
1	3.45	3.40	9.6
2	3.57	3.20	11.0
3	1.87	2.10	7.5
4	2.25	2.20	5.4
5	2.86	1.90	7.1
6	4.00	3.80	8.5
7	3.00	3.20	8.1
8	3.40	3.30	7.2
9	2.90	3.00	9.0

$\bar{x} \pm$ SEM: 3.03 $\pm$ 0.24 2.90 $\pm$ 0.22 8.16 $\pm$ 0.54

Influx: Efflux: Wilcoxon Matched-Pairs Signed-Ranks Test:
T = 16; p : NS

Post-operative:

Patient:	Influx: (mmol/l-cell/hr)	Efflux: (mmol/l-cell/hr)	$(Na)_{ICF}$ (mmol/l-cell)
1	3.86	3.50	9.9
2	4.12	3.00	12.0
3	2.51	2.10	8.4
4	1.72	1.80	5.9
5	3.24	1.60	7.4
6	3.60	3.10	8.5
7	3.30	3.20	7.2
8	3.10	3.20	7.6
9	3.17	3.90	9.0

$\bar{x} \pm$ SEM: 3.18 $\pm$ 0.24 2.82 $\pm$ 0.28 8.43 $\pm$ 0.59

Influx: Efflux: Wilcoxon Matched-Pairs Signed-Ranks Test:
T = 13; p : NS

Wilcoxon Matched-Pairs Signed Ranks Test

Influx: Pre-operative, Post-operative T = 17, p : NS

Efflux: Pre-operative, Post-operative T = 8.5, p : NS

$(Na)_{ICF}$: Pre-operative, Post-operative T = 5.5, p : NS

TABLE A5.13

Na^+ flux data and intracellular sodium concentration Na^+_{ICF} in 14 critically ill patients

Patient:	Influx: (mmol/l-cell/hr)	Efflux: (mmol/l-cell/hr)	$(Na)_{ICF}$ (mmol/l-cell)
1	2.80	3.90	9.0
2	2.40	3.30	6.0
3	3.00	2.00	7.0
4	3.00	2.90	10.0
5	3.20	2.60	7.9
6	3.60	3.50	8.0
7	3.50	3.85	9.4
8	2.00	2.10	5.0
9	3.60	4.20	6.0
10	2.40	2.80	7.0
11	1.20	2.24	6.0
12	2.10	2.60	6.0
13	3.20	3.12	8.5
14	3.20	3.17	8.5
$\bar{x} \pm$ SEM:	2.80 ± 0.13	3.02 ± 0.18	7.45 ± 0.42

Influx: Efflux: Wilcoxon Matched-Pairs Signed-Ranks Test:

$T = 52$; p : NS

Mann Whitney U Test:

Influx: : Pre-operative healthy patients, critically ill patients
U = 71, Z = 0.5, p : NS

Efflux : Pre-operative healthy patients, critically ill patients
U = 59, Z = -0.25, p : NS

$(Na)_{ICF}$: Pre-operative healthy patients, critically ill patients
U = 79.5, Z = 1.04; p : NS

$(Na)_{ICF}$: Post-operative healthy patients, critically ill patients
U = 79.5, Z = 1.04, p : NS

Regression equation of Na^+ efflux against $(Na)_{ICF}$ -

Healthy patients:

$$\text{Efflux} = 0.22(Na)_{ICF} + 1.01 \; ; \quad r = 0.52, \; t = 2.41$$

Critically ill patients:

$$\text{Efflux} = 0.18(Na)_{ICF} + 1.68 \; ; \quad r = 0.40, \; t = 1.52, \; p : NS$$

APPENDIX 6.1

Data and calculation for urine volumes, solute and electrolyte excretion in patients and volunteers

TABLE A6.11

Data for patients (n = 7) : Mean ± SEM

Time: (hr)	U_{osm}: (mosm/kg)	C_{H_2O}: (ml/min)	$U_{Na}+$: (mmol/hr)	U_K+: (mmol/hr)	Oosm: (mOsm/hr)	V_u: (ml/hr)
1	434 ± 72.1	-0.5 ± 0.1	5.7 ± 1.2	2.4 ± 0.4	19.0 ± 3.3	85.7 ± 22.8
2	410 ± 71.1	-0.7 ± 0.2	6.7 ± 1.9	2.6 ± 0.7	24.3 ± 7.2	43.1 ± 11.8
3	434 ± 67.9	-0.6 ± 0.2	8.9 ± 3.3	1.7 ± 0.5	21.8 ± 7.7	82.1 ± 22.4
4	465 ± 46.0	-0.6 ± 0.2	8.4 ± 3.0	2.5 ± 0.5	21.9 ± 6.4	58.9 ± 19.1
5	448 ± 40.3	-0.7 ± 0.1	9.3 ± 2.6	3.4 ± 0.7	27.4 ± 6.6	72.1 ± 16.3
6	481 ± 38.7	-1.1 ± 0.2	16.5 ± 5.5	3.4 ± 0.5	45.9 ±11.0	79.4 ± 18.4
7	514 ± 29.3	-1.5 ± 0.5	10.4 ± 3.2	3.3 ± 0.6	39.1 ± 8.1	97.9 ± 29.5
8	547 ± 29.0	-1.2 ± 0.3	7.9 ± 2.5	3.7 ± 0.6	40.4 ± 4.3	85.3 ± 18.9
9	567 ± 27.7	-1.1 ± 0.2	6.6 ± 1.1	3.9 ± 0.3	32.3 ± 6.6	62.1 ± 10.1
10	588 ± 33.3	-1.2 ± 0.2	4.4 ± 0.8	3.9 ± 0.6	28.5 ± 4.4	50.0 ± 3.9
11	610 ± 37.3	-0.9 ± 0.1	4.6 ± 1.0	3.7 ± 0.6	23.6 ± 2.5	47.1 ± 5.3
12	621 ± 42.0	-1.0 ± 0.2	3.7 ± 0.5	3.2 ± 0.8	23.7 ± 4.8	38.1 ± 6.0
13	654 ± 40.0	-1.1 ± 0.2	3.2 ± 0.5	3.1 ± 0.7	31.0 ± 6.6	40.1 ± 6.1
14	668 ± 43.3	-1.1 ± 0.3	3.4 ± 0.7	3.0 ± 0.6	32.1 ± 3.6	36.1 ± 6.1
15	660 ± 49.5	-1.2 ± 0.2	3.1 ± 0.6	3.9 ± 0.8	37.4 ± 4.9	38.7 ± 1.7
16	642 ± 49.5	-1.2 ± 0.2	7.3 ± 1.5	3.6 ± 0.6	29.2 ± 5.2	49.3 ± 9.3

Time: (hr)	U_{osm}: (mosm/kg)	C_{H_2O}: (ml/min)	$U_{Na}+$: (mmol/hr)	U_K+: (mmol/hr)	Oosm: (mOsm/hr)	V_u: (ml/hr)
17	658 ± 53.3	-1.5 ± 0.2	6.1 ± 0.7	4.6 ± 0.7	33.8 ± 5.5	61.3 ± 9.6
18	629 ± 52.0	-1.1 ± 0.3	6.7 ± 1.6	3.2 ± 0.6	22.8 ± 3.5	64.9 ± 18.0
19	610 ± 63.7	-1.0 ± 0.3	5.1 ± 0.7	3.9 ± 0.8	32.5 ± 3.9	92.7 ± 35.5
20	622 ± 72.0	-0.6 ± 0.5	3.8 ± 1.1	3.5 ± 0.7	22.4 ± 4.1	125.7 ± 58.6
21	641 ± 70.7	-0.7 ± 0.3	2.6 ± 0.4	3.1 ± 0.5	24.8 ± 5.0	135.6 ± 78.2
22	635 ± 71.1	-0.7 ± 0.4	6.3 ± 1.6	3.4 ± 0.6	25.4 ± 3.9	94.9 ± 34.4
23	666 ± 69.0	-0.7 ± 0.2	4.1 ± 0.8	3.8 ± 0.4	36.0 ± 4.2	87.1 ± 34.0
24	609 ± 61.7	-1.3 ± 0.3	4.2 ± 1.8	4.2 ± 0.6	30.3 ± 8.7	49.0 ± 10.5
25	611 ± 88.3	-0.7 ± 0.2	3.9 ± 1.3	3.4 ± 0.3	32.7 ± 6.1	80.4 ± 46.1
26	520 ± 81.7	-0.1 ± 0.5	2.2 ± 0.3	3.5 ± 0.5	23.2 ± 2.5	56.6 ± 12.1
27	520 ± 99.7	+0.5 ± 1.0	3.5 ± 1.0	2.5 ± 0.5	25.0 ± 4.6	91.4 ± 28.6
28	532 ±100.3	+0.7 ± 1.3	1.9 ± 0.4	2.5 ± 0.3	20.2 ± 3.3	169.0 ±122.0
29	560 ±101.3	-0.1 ± 0.5	2.8 ± 1.2	2.2 ± 0.4	19.5 ± 3.5	125.0 ± 79.7
30	542 ± 87.7	-0.2 ± 0.5	1.7 ± 0.5	2.5 ± 0.5	18.4 ± 3.5	103.4 ± 44.7
31	530 ± 96.2	+0.5 ± 1.0	1.7 ± 0.6	3.1 ± 0.9	23.6 ± 3.1	65.0 ± 25.8
32	488 ± 93.3	+0.2 ± 0.7	1.5 ± 0.7	3.1 ± 0.8	28.5 ± 8.8	93.1 ± 59.3

Time: (hr)	U_{osm}: (mosm/kg)	C_{H_2O}: (ml/min)	$U_{Na}+$: (mmol/hr)	U_K+: (mmol/hr)	Oosm: (mOsm/hr)	V_u: (ml/hr)
33	481 ± 96.2	-0.1 ± 0.8	1.5 ± 0.4	2.8 ± 0.4	37.1 ± 8.5	110.4 ± 46.6
34	415 ± 92.3	-0.1 ± 0.3	2.9 ± 0.3	3.0 ± 0.5	25.8 ± 3.5	124.3 ± 44.0
35	408 ± 97.2	+1.2 ± 1.8	2.4 ± 1.2	2.5 ± 0.4	35.5 ± 7.8	90.7 ± 30.3
36	365 ±104.7	+0.5 ± 0.8	1.3 ± 0.4	2.4 ± 0.3	25.0 ± 9.3	84.3 ± 22.8
37	349 ± 93.3	-0.1 ± 0.3	0.7 ± 0.2	2.1 ± 0.4	38.5 ±11.2	86.9 ± 32.8
38	349 ± 89.5	+0.4 ± 0.6	1.9 ± 1.3	2.3 ± 0.3	21.6 ± 4.1	111.8 ± 49.3
39	387 ± 98.3	+0.6 ± 0.8	2.5 ± 1.4	2.3 ± 0.5	34.9 ± 7.5	122.3 ± 46.3
40	278 ± 88.4	+0.6 ± 0.4	1.5 ± 0.6	2.7 ± 0.5	28.3 ± 4.7	154.7 ± 36.1
41	335 ± 61.5	+0.1 ± 0.8	1.3 ± 0.6	2.2 ± 0.4	36.3 ± 8.5	126.7 ± 35.6
42	308 ± 79.2	-0.3 ± 0.5	2.3 ± 1.4	2.5 ± 0.8	23.3 ± 6.6	77.0 ± 22.8
43	338 ± 89.8	-0.4 ± 0.3	1.3 ± 0.6	3.2 ± 0.7	34.7 ± 8.2	76.3 ± 19.4
44	376 ±104.3	-0.7 ± 0.3	1.0 ± 0.3	3.1 ± 0.5	22.3 ± 5.9	70.0 ± 15.2
45	388 ±101.7	-0.8 ± 0.5	0.8 ± 0.1	2.6 ± 0.5	25.0 ± 4.8	34.2 ± 8.7
46	426 ±113.0	-0.6 ± 0.6	1.4 ± 0.4	2.7 ± 0.3	33.0 ± 5.4	40.2 ± 16.0
47	448 ±113.0	-1.1 ± 1.1	2.5 ± 1.6	2.7 ± 0.5	29.6 ± 8.2	72.5 ± 24.6
48	399 ±111.0	-0.3 ±,0.7	1.7 ± 1.2	1.5 ± 0.1	21.4 ± 4.7	49.0 ± 28.0

TABLE A6.12

Data for volunteers on 'Dextrose' (n = 6) : Mean ± SEM

Time: (hr)	U_{osm}: (mosm/kg)	C_{H_2O}: (ml/min)	U_{Na^+}: (mmol/hr)	U_{K^+}: (mmol/hr)	Oosm: (mOsm/hr)	V_u: (ml/hr)
1	765 ± 90.1	-1.3 ± 0.3	4.1 ± 1.2	3.6 ± 0.6	58.4 ±20.0	69.2 ± 22.7
2	755 ±109.8	-0.7 ± 0.3	3.5 ± 1.0	4.3 ± 1.1	27.2 ± 4.9	35.0 ± 8.0
3	749 ± 75.9	-0.9 ± 0.3	3.6 ± 1.9	4.0 ± 1.5	27.4 ± 8.8	31.0 ± 9.0
4	552 ±126.5	-0.3 ± 0.3	3.2 ± 1.6	4.0 ± 1.0	27.3 ± 5.7	47.8 ± 11.1
5	532 ±121.1	-0.3 ± 0.2	3.1 ± 1.2	2.8 ± 0.5	22.5 ± 3.5	72.7 ± 27.0
6	449 ± 96.9	-0.3 ± 0.3	2.9 ± 1.1	2.6 ± 0.5	22.6 ± 3.8	53.5 ± 11.0
7	538 ± 99.9	-0.3 ± 0.2	2.5 ± 0.8	2.0 ± 0.2	18.4 ± 3.0	46.0 ± 14.0
8	518 ±126.3	-0.1 ± 0.3	1.7 ± 0.7	1.4 ± 0.5	15.7 ± 2.6	75.5 ± 29.0
9	487 ±120.2	-0.1 ± 0.2	2.0 ± 1.0	1.5 ± 0.4	15.5 ± 3.7	58.7 ± 21.2
10	495 ± 77.1	-0.4 ± 0.1	1.6 ± 0.6	1.6 ± 0.3	17.5 ± 2.2	29.0 ± 8.3
11	393 ±134.9	+0.3 ± 0.4	1.7 ± 0.5	1.7 ± 0.7	18.7 ± 2.3	70.5 ± 22.8
12	355 ± 81.2	+0.1 ± 0.2	2.2 ± 0.8	1.6 ± 0.4	21.9 ± 4.9	71.7 ± 25.7
13	461 ± 97.5	-0.2 ± 0.1	1.3 ± 0.3	1.0 ± 0.2	13.1 ± 1.4	29.0 ± 9.9
14	475 ± 81.2	-0.2 ± 0.1	1.0 ± 0.3	0.9 ± 0.2	13.9 ± 1.5	39.3 ± 12.7
15	248 ± 61.7	+0.4 ± 0.3	1.2 ± 0.4	0.8 ± 0.2	19.0 ± 4.2	95.0 ± 20.5
16	200 ± 53.6	+0.6 ± 0.4	1.0 ± 0.3	0.8 ± 0.1	14.9 ± 3.4	88.7 ± 29.2

Time: (hr)	U_{osm}: (mosm/kg)	C_{H_2O}: (ml/min)	$U_{Na}+$: (mmol/hr)	U_K+: (mmol/hr)	Oosm: (mOsm/hr)	V_u: (ml/hr)
17	224 ± 46.4	+0.7 ± 0.4	1.6 ± 0.3	0.9 ± 0.2	21.9 ± 4.0	99.3 ± 24.3
18	272 ± 80.5	+0.3 ± 0.2	1.1 ± 0.2	0.7 ± 0.3	12.4 ± 2.6	82.2 ± 13.9
19	197 ± 35.4	+0.6 ± 0.3	0.9 ± 0.1	1.1 ± 0.6	15.2 ± 1.8	82.0 ± 15.4
20	236 ± 42.6	+0.3 ± 0.2	0.9 ± 0.2	1.1 ± 0.6	15.0 ± 3.6	69.8 ± 13.9
21	200 ± 40.9	+0.8 ± 0.4	1.0 ± 0.2	0.8 ± 0.2	16.0 ± 2.3	99.0 ± 19.3
22	165 ± 29.3	+0.8 ± 0.2	1.2 ± 0.6	0.8 ± 0.2	17.4 ± 4.9	118.0 ± 26.1
23	232 ± 43.1	+0.3 ± 0.3	1.3 ± 0.3	1.7 ± 0.5	18.6 ± 3.0	121.5 ± 21.0
24	377 ±100.1	+0.2 ± 0.4	1.2 ± 0.3	1.7 ± 0.4	16.7 ± 1.2	68.7 ± 26.5
25	438 ± 61.3	-0.2 ± 0.1	1.3 ± 0.6	1.8 ± 0.7	16.2 ± 4.8	31.8 ± 9.1
26	402 ± 60.0	-0.1 ± 0.1	2.2 ± 1.2	2.8 ± 1.1	18.9 ± 4.5	53.0 ± 15.7
27	296 ± 50.9	+0.2 ± 0.3	2.0 ± 0.9	2.2 ± 0.5	21.9 ± 4.3	78.3 ± 22.9
28	270 ± 84.3	+0.4 ± 0.2	1.1 ± 0.4	1.6 ± 0.3	15.3 ± 2.2	89.3 ± 24.1
29	381 ± 69.8	-0.1 ± 0.1	1.0 ± 0.6	1.6 ± 0.4	13.8 ± 2.4	49.5 ± 21.3
30	376 ± 75.5	-0.1 ± 0.3	0.8 ± 0.3	1.3 ± 0.2	14.4 ± 2.3	41.3 ± 10.1
31	432 ± 59.2	-0.2 ± 0.1	0.6 ± 0.2	1.0 ± 0.2	11.8 ± 1.5	21.7 ± 5.6
32	416 ±105.8	+0.1 ± 0.3	1.0 ± 0.3	1.3 ± 0.2	19.1 ± 3.7	48.3 ± 21.8

Time: (hr)	U_{osm}: (mosm/kg)	C_{H_2O}: (ml/min)	$U_{Na}+$: (mmol/hr)	U_K+: (mmol/hr)	Oosm: (mOsm/hr)	V_u: (ml/hr)
33	366 ±110.3	+0.4 ± 0.4	1.0 ± 0.2	1.3 ± 0.2	17.7 ± 2.5	68.2 ± 32.5
34	408 ± 95.5	+0.1 ± 0.2	0.8 ± 0.2	1.0 ± 0.2	14.2 ± 3.5	83.3 ± 30.0
35	485 ± 89.4	-0.4 ± 0.3	1.4 ± 0.6	2.3 ± 1.4	18.8 ± 6.4	35.0 ± 19.0
36	368 ± 91.4	+0.1 ± 0.2	1.3 ± 0.6	1.7 ± 0.9	18.8 ± 4.7	43.2 ± 12.5
37	459 ±102.4	-0.1 ± 0.2	2.7 ± 1.2	2.9 ± 1.3	19.4 ± 6.0	65.8 ± 18.1
38	407 ± 70.6	-0.1 ± 0.1	0.7 ± 0.3	1.4 ± 0.8	14.1 ± 3.1	37.8 ± 7.2
39	406 ± 98.4	+0.1 ± 0.2	1.6 ± 0.7	3.2 ± 1.6	15.4 ± 2.6	69.5 ± 21.2
40	265 ± 60.7	+0.3 ± 0.3	1.1 ± 0.6	0.8 ± 0.2	18.6 ± 4.0	58.2 ± 20.0
41	253 ± 54.2	+0.3 ± 0.2	1.2 ± 0.9	1.0 ± 0.6	17.3 ± 4.5	53.0 ± 16.0
42	306 ± 91.0	+0.5 ± 0.4	0.9 ± 0.6	0.7 ± 0.3	16.4 ± 3.1	81.0 ± 15.9
43	226 ± 35.3	+0.2 ± 0.1	0.5 ± 0.2	0.4 ± 0.1	11.1 ± 2.6	90.8 ± 31.2
44	218 ± 27.8	+0.4 ± 0.2	0.9 ± 0.5	0.6 ± 0.2	19.2 ± 3.3	60.2 ± 17.8
45	138 ± 15.0	+1.0 ± 0.3	0.6 ± 0.2	0.5 ± 0.1	12.7 ± 2.4	86.8 ± 16.0
46	226 ± 49.8	+0.6 ± 0.2	1.3 ± 0.2	0.8 ± 0.1	14.3 ± 1.5	99.2 ± 28.4
47	285 ± 97.6	+0.5 ± 0.3	1.0 ± 0.3	0.8 ± 0.2	14.8 ± 2.4	82.3 ± 22.7
48	261 ± 77.1	+0.3 ± 0.1	0.8 ± 0.3	0.5 ± 0.2	10.0 ± 2.2	58.3 ± 22.3

TABLE A6.13

Data for volunteers on 'Dextrose Saline' (n = 6) : Mean ± SEM

Time: (hr)	U_{osm}: (mosm/kg)	C_{H_2O}: (ml/min)	$U_{Na}+$: (mmol/hr)	U_K+: (mmol/hr)	Oosm: (mOsm/hr)	V_u: (ml/hr)
1	794 ± 27.2	-0.6 ± 0.5	3.7 ± 0.6	3.6 ± 0.7	30.4 ± 4.1	41.5 ± 8.2
2	769 ± 91.6	-1.6 ± 0.6	4.5 ± 1.5	4.1 ± 1.2	37.5 ±11.9	55.0 ± 17.3
3	713 ±113.7	-0.9 ± 0.4	4.0 ± 1.4	3.0 ± 0.4	29.7 ± 4.9	75.0 ± 28.2
4	717 ±109.3	-0.7 ± 0.2	4.9 ± 1.7	3.6 ± 0.8	27.6 ± 4.4	87.8 ± 44.7
5	726 ±118.5	-0.6 ± 0.4	4.3 ± 1.2	3.6 ± 0.8	27.9 ± 1.7	64.5 ± 25.8
6	667 ±121.5	-0.7 ± 0.2	4.3 ± 1.4	3.8 ± 0.8	29.6 ± 4.7	68.1 ± 22.2
7	665 ±121.0	-0.7 ± 0.3	5.3 ± 1.8	3.8 ± 0.8	29.3 ± 3.4	45.8 ± 10.3
8	640 ±115.2	-0.7 ± 0.6	5.2 ± 1.8	3.9 ± 0.8	41.3 ± 4.3	62.2 ± 22.9
9	692 ± 79.8	-0.9 ± 0.1	5.3 ± 1.4	3.7 ± 0.4	29.0 ± 2.4	79.2 ± 38.7
10	711 ±100.8	-1.1 ± 0.1	6.0 ± 1.4	4.5 ± 0.7	34.1 ± 3.7	58.8 ± 12.5
11	651 ±155.6	-0.6 ± 0.3	3.5 ± 0.8	3.1 ± 1.0	22.8 ± 3.4	41.8 ± 11.3
12	568 ±173.7	-0.4 ± 0.4	2.6 ± 0.7	2.3 ± 0.7	23.0 ± 4.4	66.5 ± 21.6
13	601 ±139.2	-0.5 ± 0.5	4.0 ± 1.2	2.7 ± 0.8	32.7 ± 4.2	54.0 ± 20.9
14	551 ± 79.4	-0.4 ± 0.1	3.7 ± 0.7	2.5 ± 1.2	25.0 ± 6.0	68.2 ± 10.5
15	588 ±118.1	-0.5 ± 0.2	4.0 ± 0.6	2.0 ± 0.6	24.1 ± 2.6	58.8 ± 17.4
16	479 ±129.0	+0.3 ± 0.4	3.5 ± 0.8	1.8 ± 0.4	24.2 ± 3.7	68.2 ± 27.4

Time: (hr)	U_{osm}: (mosm/kg)	C_{H_2O}: (ml/min)	U_{Na^+}: (mmol/hr)	U_{K^+}: (mmol/hr)	Oosm: (mOsm/hr)	V_u: (ml/hr)
17	445 ±150.0	+0.2 ± 0.4	3.9 ± 1.3	1.9 ± 0.6	21.8 ± 3.9	89.5 ± 36.5
18	456 ±133.3	+0.5 ± 0.9	4.1 ± 1.9	1.6 ± 0.3	27.2 ± 7.3	144.2 ± 78.8
19	460 ±121.8	+0.1 ± 0.5	4.2 ± 2.4	1.2 ± 0.2	23.2 ± 6.2	103.2 ± 47.8
20	511 ±121.8	-0.4 ± 0.2	3.2 ± 1.3	1.1 ± 0.3	21.9 ± 5.0	100.2 ± 35.3
21	419 ±110.2	+0.3 ± 0.7	2.5 ± 1.0	0.7 ± 0.3	24.8 ± 9.2	101.3 ± 60.5
22	431 ±113.2	+0.1 ± 0.3	3.6 ± 1.2	2.3 ± 1.3	24.8 ± 5.5	57.8 ± 12.4
23	508 ±108.8	-0.4 ± 0.3	5.5 ± 1.6	3.4 ± 1.2	30.3 ± 6.0	113.0 ± 43.8
24	494 ±133.7	-0.1 ± 0.3	4.8 ± 1.6	1.9 ± 0.6	25.7 ± 4.1	50.3 ± 13.2
25	556 ± 77.9	-0.6 ± 0.1	3.1 ± 1.0	1.9 ± 0.5	23.1 ± 2.7	57.5 ± 19.0
26	562 ± 86.8	-0.3 ± 0.2	4.1 ± 1.6	2.3 ± 0.7	27.1 ± 9.6	64.9 ± 26.4
27	617 ±111.9	-0.4 ± 0.2	3.2 ± 0.9	1.9 ± 0.3	19.4 ± 2.3	40.2 ± 13.1
28	648 ± 53.5	-0.8 ± 0.1	3.4 ± 1.6	2.1 ± 0.5	24.0 ± 4.8	59.8 ± 32.9
29	628 ± 80.4	+3.8 ± 4.3	3.0 ± 1.4	1.6 ± 0.3	20.2 ± 2.6	35.0 ± 4.9
30	644 ± 83.1	-0.6 ± 0.1	2.6 ± 0.9	1.7 ± 0.3	19.8 ± 2.0	18.3 ± 4.0
31	694 ± 71.2	-0.8 ± 0.1	2.9 ± 1.0	1.7 ± 0.3	22.4 ± 2.5	38.2 ± 9.0
32	631 ± 84.8	-0.6 ± 0.1	1.8 ± 0.6	1.3 ± 0.3	19.5 ± 3.1	46.2 ± 14.0

Time: (hr)	U_{osm}: (mosm/kg)	C_{H_2O}: (ml/min)	U_{Na^+}: (mmol/hr)	U_{K^+}: (mmol/hr)	Oosm: (mOsm/hr)	V_u: (ml/hr)
33	628 ± 79.1	-1.0 ± 0.3	3.3 ± 1.0	1.6 ± 0.3	33.1 ±12.9	35.5 ± 6.8
34	563 ±119.0	-0.5 ± 0.3	2.0 ± 0.6	1.2 ± 0.3	22.9 ± 5.2	90.0 ± 36.6
35	536 ±150.0	-0.1 ± 0.3	2.2 ± 0.7	0.9 ± 0.1	17.1 ± 2.0	39.0 ± 15.0
36	418 ±120.6	+0.2 ± 0.5	2.0 ± 0.6	0.9 ± 0.2	18.9 ± 2.3	42.0 ± 9.0
37	481 ±133.2	-0.2 ± 0.3	2.5 ± 0.6	2.6 ± 1.4	27.7 ± 6.2	42.3 ± 12.3
38	505 ±132.5	-0.2 ± 0.1	1.5 ± 0.4	2.2 ± 1.4	18.0 ± 3.2	100.0 ± 70.7
39	473 ±113.3	-0.3 ± 0.2	2.2 ± 0.6	0.9 ± 0.2	21.7 ± 3.8	44.5 ± 19.0
40	433 ±123.0	-0.1 ± 0.2	2.2 ± 0.8	0.9 ± 0.1	19.9 ± 3.1	71.3 ± 20.4
41	319 ± 87.2	+0.8 ± 0.3	3.4 ± 1.3	1.2 ± 0.2	27.8 ± 7.1	69.0 ± 25.4
42	205 ± 34.5	+0.6 ± 0.4	3.1 ± 0.6	1.5 ± 0.3	24.4 ± 1.8	105.7 ± 34.0
43	311 ± 18.7	+0.2 ± 0.1	2.4 ± 0.3	1.4 ± 0.2	19.0 ± 0.9	83.5 ± 44.5
44	383 ± 5.8	+0.1 ± 0.1	3.0 ± 0.7	1.3 ± 0.2	17.7 ± 0.6	85.2 ± 20.0
45	372 ± 14.4	+0.2 ± 0.1	3.8 ± 1.2	1.8 ± 0.5	15.8 ± 0.8	94.0 ± 32.0
46	251 ± 15.8	+0.3 ± 0.1	2.9 ± 0.6	1.6 ± 0.3	23.0 ± 1.1	95.0 ± 30.0
47	257 ± 12.6	+0.4 ± 0.1	3.1 ± 1.2	1.5 ± 0.3	19.1 ± 0.6	71.0 ± 32.0
48	332 ± 3.6	-0.1 ± 0.1	2.2 ± 0.1	2.2 ± 0.1	18.2 ± 0.3	64.8 ± 19.0

APPENDIX 7.1

Measurement of Respiratory Exchange Ratio

The Surgical Unit Laboratory has a paramagnetic oxygen (O_2) analyser and an infra-red carbon dioxide (CO_2) analyser which, when used in conjunction with a Douglas bag collecting system can be used for indirect calorimetry.

Indirect calorimetry represents a chemical method of determining the amount of energy released as heat from the subject rather than a physical method of measurement as in direct calorimetry. Energy can be calculated from the rate of elimination of the end products of fuel oxidation, and three types of end products are taken into account - CO_2, H_2O and nitrogen-containing compounds derived from protein. The small amount of H_2O produced is difficult to identify so that O_2 consumption represents a more convenient measurement which can be used in its place.

In the open circuit method of indirect calorimetry, the subject breathes through a valve system so arranged that it separates the inspired from the expired air which is collected and anlysed. Expired air is then compared with inspired or room air which has known concentration of O_2, CO_2 and N_2. The volume of expired air is measured by collecting it in a Douglas bag. These bags are constructed of rubber protected by canvas and have a capacity of 100 to 200 litres.

Gas analysis

Expired air must be analysed for O_2 and CO_2 after collection.

The partial pressure of O_2 in a sample can be determined by measuring its magnetic susceptibility, since O_2 is strongly paramagmetic.

Similarly, CO_2 analysers are based on selective absorption in the infra-red region of the spectrum. The degree of absorption is proportional to the CO_2 concentration. The advantage of these techniques lies in the fact that the gas mixture need not be separated physically and is not altered by analysis.

Respiratory Exchange Ratio (RER)

This is the ratio of volume of CO_2 produced divided by the volume of O_2 consumed during the same time period ($\dot{V}_{CO_2}/\dot{V}_{O_2}$). The quantity of O_2 required and the amount of CO_2 produced in the combustion of food depends on the chemical composition of the fuel. In carbohydrates, H_2 and O_2 are always present in the proportions necessary to form H_2O, and, on combustion, extramolecular O_2 is required only for the formation of CO_2. Under these circumstances, the RER will be 1.0. In the oxidation of fat, extramolecular O_2 is required for the oxidation of carbon as well as for hydrogen. For this reason, the RER will be less than unity. Food fats which are composed chiefly of the glycerides of palmitic, stearic and oleic acids, give RERs of approximately 0.71. It is more difficult to calculate the RER of protein combustion in the body. An amino acid mixture thought to be representative of the usual

dietary protein is used, and variations from this idealised protein are not well defined. Furthermore, combustion of protein or amino acids is incomplete. Based on the analysis of ingested protein and excreta, determinations have led to a figure of 0.802, (Gump et al, 1973).

Factors other than oxidative processes can affect the RER. Hyperventilation will increase CO_2 excretion and increase the RER. This may take place when expired air is collected from untrained subjects. The application of a mask or mouthpiece may lead to a period of hyperventilation; even a canopy which leaves the face free can induce temporary hyperventilation.

Procedure for RER

Prior to each analysis, the paramagnetic O_2 analyser (OA 272 Taylor Servomex Ltd) and the infra-red CO_2 analyser (17070 Godart-Statham Ltd) were calibrated using 100% N_2 (zero gas) and a gas mixture (5% CO_2, 17% O_2, 77% N_2) (BOC Ltd Gold Star grade).

Though we had used a rubber Douglas bag provided by the Department of Physiology for the studies in Chapters 7 and 8, we had changed to a 100 litre capacity PVC-Douglas bag (Ealing Biosciences, Watford, England) as it is known that the rate of diffusion of CO_2 is appreciable when samples are stored in rubber bags.

A light weight one-way breathing valve was used

for all experiments and tubings, connectors and nose-clip were provided by Ealing Biosciences. The gas meter was a Parkinson Cowan dry gas type.

The subjects were allowed a 10 minute equilibration period before collecting expired gases for 6 minutes.

(1) The Douglas bag was checked for leaks prior to use;
(2) The mouthpiece was sterilised with alcohol;
(3) The noseclip was placed firmly on the subject's nose and tested for leak by trying to blow air through the nose.
(4) The mouthpiece was fitted comfortably;
(5) The Douglas bag was completely emptied;
(6) The exit tube from the Douglas bag was connected to the three-way tap and the corrugated tube was connected from the mouthpiece to the three-way tap;
(7) The three-way tap was adjusted so that the subject's expired air was going to the outside.
(8) The subject was allowed a 10 minute equilibration period;
(9) The clamp to the exit tube was released, the stop-watch was started and the three-way tap adjusted so that all expired air was collected in the bag for 6 minutes;
(10) The neck of the bag was clamped off;
(11) The bag's contents were mixed by kneading it a few times on the floor;
(12) The three-way tap was connected to the inlet of

the gas meter;

(13) Gas volumes were reduced to Standard Temperature Pressure Dry (STPD) volumes using standard tables, (Documenta Geigy, 1970);

(14) Minute volumes were calculated using -

$$\dot{V} \text{ (litres/min) STPD} = \dot{V} \text{ air expired} \times \frac{\% \text{ gas expired}}{100} \times \text{STPD factor}$$

(15) $$\dot{V}_{CO_2} \text{ (litres/min)} = \frac{\dot{V} \text{ gas (litres/min)}}{100} \times \text{true } CO_2$$

$$\dot{V}_{O_2} \text{ (litres/min)} = \frac{\dot{V} \text{ gas (litres/min)}}{100} \times \text{true } O_2$$

The volume of inspired air usually does not have the same composition as that of expired air. Unless the RER is exactly 1.00, 'true' O_2 and CO_2 estimations are required. To facilitate computation, these values may be obtained from a normogram (Consolazio et al, 1963).

APPENDIX 7.2

Details of nitrogen-energy, fluid-electrolyte intakes and balances in volunteers and patients

TABLE A7.21

Low-Na^+ low-carbohydrate diet for volunteers

(Prepared by Dietetics Dept., St Mary's Hospital, W2)

	Weight (g)	Protein (g)	CHO_n (g)	Fat (g)	kcal	Na^+ (mg)	K^+ (mg)
Salt free bread	60	5.1	32.3	1.0	171	6.0	33
Salt free butter	10			8.2	74		
Lamb	50	13.0		9.0	133	32.5	155
Lettuce	15				2	1.4	36
Cucumber	10					1.3	1
Green Pepper	10					0.2	2
Potatoes	200	2.8	40.0		160	6.0	660
Orange	150		10.0		40	3.0	225
Chicken	50	13.2		1.6	71	35.5	165
Tomatoes	150		4.2		31	4.5	435
Apple	210		11.0		42	2.4	110
Tinned Fruit Salad	150	0.5	37.5		142	3.0	180
Double cream	50	0.7	1.0	24.1	223	13.3	40
Vegetable Oil	25			25.0	180		
Preliminary drink:							
200 ml Prosparol				100.0	900		
400 ml Deionized water							
2 sachets orange							
Vivonex flavourings							
Total :		35.3	136	169	2169	109	2042
Per cent :		7	26	67		4.7 (mmol)	56 (mmol)

To increase kcal intake : increase volume of drinks

Low-Na^+ high-carbohydrate diet for volunteers

(Prepared by Dietetics Dept., St Mary's Hospital, W2)

	Weight (g)	Protein (g)	CHO_n (g)	Fat (g)	kcal	Na^+ (mg)	K^+ (mg)
Salt free bread	100	8.5	53.8	1.7	282	14.0	50
Salt free butter	5			4.1	35		
Lamb	50	13.0		9.0	133	32.5	155
Lettuce	15				2	1.4	36
Cucumber	10					1.3	1
Green Pepper	10					0.2	2
Potatoes	200	2.8	40.0		160	6.0	660
Tinned Fruit salad	150	0.5	37.5		142	3.0	180
Chicken	50	13.2		1.6	71	35.5	165
Tomatoes	150		4.2		31	4.5	435
Apple	210		11.0		42	2.4	110
Banana	120	0.8	13.7		50	2.2	244
Supplementary drink:							
20 ml orange squash	20		5.7		21	6.0	4
300 g Maxijul-le	300		300		1200		
Deionised water to 600 ml							
2 tsps citric acid							
Total :		38.8	466	16	2169	109	2042
Per cent :		7	86	7		4.7 (mmol)	56 (mmol)

Low-Na^+ high-carbohydrate, potassium restricted diet for 2 volunteers

(Prepared by Dietetics Dept., St Mary's Hospital, W2)

	Protein (g)	CHO_n (g)	Fat (g)	kcal	Na^+ (mg)	K^+ (mg)
3 sachets Aminutrin	35.1			141		
200 mls milk	6.6	9.4	7.6	130	100	300
440 mg Maxijul-le		440		1760		
Distilled water to 2000 ml						
+ 4 sachets vivonex flavourings						
Total :	41.7	449.4	7.6	2031	100	300
Per cent :	7	86	7		4.3 (mmol)	5.6 (mmol)

TABLE A7.22

Na^+ balance data (mmol) during test diets in volunteers

	MM	AC	PH	JP	MG	LT	DC	SB	Mean ± SD
Day 1:	-62.1	-100.1	-103.8	-48.1	-56.8	-60.0	-70.8	-33.0	-66.8 ± 24.4
2:	-26.1	-63.7	-75.6	-71.8	-17.0	-27.1	-10.9	-7.0	-37.4 ± 28.3
3:	-34.7	-40.6	-23.7	-28.0	-11.3	-1.0	-22.9	-21.5	-23.0 ± 12.5
4:	-22.8	-20.2	-11.4	-33.6	-7.1	-13.7	+2.0	+1.0	-13.2 ± 12.1
5:	-13.7	-4.2	-1.7	-16.0	-8.4	-22.8	+8.8	+11.0	-5.9 ± 11.8
6:	-4.5	+0.8	-3.5	-1.2	-8.4	-34.7	+14.0	+13.1	-3.1 ± 15.1
7:	-1.0	-5.0	+0.9	-0.9	-6.7	-4.5	+5.2	+5.0	-0.9 ± 4.5
8:	+0.5	-2.3	+1.8	-4.3	-3.4	+2.5	+4.2	+4.4	+0.4 ± 3.4
9:	-1.7	+2.7	+1.4	-4.2	+4.2	+2.1	+2.3	+2.2	+1.1 ± 2.7
10:	-3.2	+1.6	+1.8	+8.2	-0.9	+1.8	-0.5	-1.3	+0.9 ± 3.4
11:	-3.0	-0.6	+3.8	+1.9	+2.1	+2.2	+3.2	+3.2	+1.6 ± 2.3
12:	-6.1	-1.3	+3.5	-2.3	+3.7	-2.7	+5.2	+2.7	+0.3 ± 4.0
13:	+2.3	+2.1	+3.2	+3.2	+3.9	+3.3	+4.2	+3.2	+3.2 ± 0.7
14:	+3.2	+0.3	+3.3	+4.1	+3.8	+4.2	+5.1	+4.2	+3.5 ± 1.4

TABLE A7.23

Plasma - Na^+ values (mmol/l) during test diets in volunteers

	MM	AC	PH	JP	MG	LT	DC	SB
Day 0:	144	137	145	145	137	141	142	140
1:	141	142	139	140	135	136	139	135
2:	143	136	139	142	138	135	141	138
3:	140	143	136	139	136	136	135	140
4:	140	142	138	140	139	141	141	137
5:	140	141	143	139	136	135	137	140
6:	135	141	142	138	138	136	138	138
7:	146	138	142	139	136	142	141	139
8:	142	135	141	137	139	141	143	139
9:	142	144	143	138	138	141	144	138
10:	143	136	141	139	137	143	141	140
11:	146	139	138	142	145	145	139	139
12:	140	141	136	139	135	142	134	137
13:	139	140	135	140	142	145	139	137
14:	142	138	142	147	136	145	138	139

Paired t-tests :

Day 0 vs 7 : $\bar{D}$ 1.00, S_D 3.03, t 0.81, df 5;
..... $p > 0.10$

Day 0 vs 14 : $\bar{D}$ -0.17, S_D 2.64, t -0.15, df 5;
..... $p > 0.10$

TABLE A7.24

K^+ balance data (mmol) during test diets in volunteers

	MM	AC	PH	JP	MG	LT	Mean ± SD	DC	SB	Mean ± SD
Day 1:	-13.2	+1.8	-4.0	-13.2	-9.8	-6.2	-7.4 ± 5.8	+4.2	+3.8	+4.02 ± 0.3
2:	+14.8	-7.3	-9.3	-14.8	-2.1	-6.1	-4.1 ± 10.2	+9.8	+8.2	+9.0 ± 1.1
3:	+3.4	-2.7	-3.9	+3.4	-12.8	-2.9	-2.6 ± 6.0	+11.2	+7.6	+9.4 ± 2.6
4:	-4.0	+0.1	+12.2	-4.0	-14.5	-6.7	-2.8 ± 8.8	+20.5	+10.2	+15.4 ± 7.3
5:	-6.6	+3.2	+19.7	-6.6	-4.5	-14.9	-1.6 ± 11.9	+22.6	+19.8	+21.2 ± 2.0
6:	+8.3	+9.1	+21.8	+8.4	-13.3	-24.2	+1.7 ± 17.0	+21.7	+18.8	+20.3 ± 2.1
7:	+2.5	+16.3	+5.2	+2.5	-16.8	-25.0	-2.6 ± 15.3	-16.3	-14.1	-15.2 ± 1.6
8:	-19.1	+0.9	+9.1	-19.2	-17.0	-19.2	-10.8 ± 12.5	-12.3	-18.5	-15.4 ± 4.4
9:	+3.0	+6.8	+6.1	+3.0	+8.8	+3.9	+5.3 ± 2.4	-11.9	-13.6	-12.8 ± 1.2
10:	-31.4	+8.1	+12.2	-31.4	+16.3	+10.2	-2.7 ± 22.4	-9.8	-10.2	-10.0 ± 0.3
11:	+27.6	+25.0	+11.0	+27.6	+24.5	+33.3	+24.8 ± 7.5	-7.7	-14.1	-10.9 ± 4.5
12:	+30.2	+20.0	+25.3	+30.2	+30.2	+16.1	+25.3 ± 6.1	-7.6	-	-
13:	+23.2	+27.4	+26.9	+23.3	+35.5	+40.4	+29.4 ± 7.0	-6.9	-	-
14:	+25.5	+27.1	+40.8	+33.1	+23.5	42.8	+32.1 ± 8.2	-6.8	-	-

TABLE A7.25

Plasma -K^+ values (mmol/l) during test diets in volunteers

	MM	AC	PH	JP	MG	LT	DC	SB
Day 0:	4.3	3.9	4.3	4.3	4.1	4.0	3.7	4.2
1:	3.7	3.5	3.3	4.2	3.9	4.0	4.2	4.1
2:	4.2	4.3	3.9	3.7	3.8	4.0	3.9	3.9
3:	4.1	3.6	3.5	3.6	4.1	3.9	3.7	4.2
4:	3.7	3.6	4.0	3.6	4.2	3.9	4.5	3.8
5:	3.8	4.1	4.1	4.2	4.2	3.8	4.2	4.1
6:	4.2	4.0	4.1	4.0	3.8	3.7	3.9	3.1
7:	4.1	3.9	4.0	4.1	3.9	3.8	3.9	3.6
8:	3.9	3.8	3.5	4.1	3.8	3.6	3.9	2.8
9:	4.1	4.1	3.6	3.7	3.9	3.5	3.8	2.9
10:	3.7	4.2	4.1	3.9	4.2	4.2	3.2	3.0
11:	3.8	3.9	4.2	3.9	3.8	4.1	3.0	3.1
12:	4.2	4.0	4.1	4.1	3.7	3.9	2.9	-
13:	4.1	3.8	3.8	4.2	3.6	3.8	3.1	-
14:	3.8	4.9	4.0	4.8	3.8	4.1	2.8	-

Paired t-tests:

Day 0 vs 7 : $\bar{D}$ 0.19, S_D 0.23, t 2.31, df 7;
..... p > 0.05

Day 0 vs 14 : $\bar{D}$ -0.08, S_D 0.57, t -0.36, df 5;
..... p > 0.01

TABLE A7.26

RER in 6 volunteers during test diets

Day :	0	4	7	11	14
MM	0.81	0.74	0.70	0.90	1.00
AC	0.82	0.75	0.80	0.92	0.99
PH	0.84	0.76	0.73	0.95	0.92
JP	0.85	0.77	0.73	0.89	0.93
MG	0.84	0.78	0.75	0.89	0.99
LT	0.86	0.78	0.77	0.88	0.99

Mean $\pm$ SD : 0.84 $\pm$ 0.02 ; 0.76 $\pm$ 0.02 ; 0.75 $\pm$ 0.04 ; 0.91 $\pm$ 0.03 ; 0.97 $\pm$ 0.04

TABLE A7.27

Regression relationship between ΔTBW (litres) and body weights, Δweight (kg) in 6 volunteers

ΔTBW:	ΔWeight:
2.4	2.2
1.1	1.4
2.4	2.9
1.3	1.7
2.3	3.8
1.3	1.9
2.0	2.2
1.2	1.6
2.3	2.2
1.1	1.4
2.6	2.7
1.4	1.8

..... r^2 = 0.63
t = 4.14
a = 0.33
b = 0.67
p < 0.005

95 per cent tolerance limits :

	ΔTBW:	
ΔWeight:	Upper limit:	Lower limit:
1.00	1.98	0.04
1.50	2.25	0.44
2.00	2.56	0.80
2.50	2.91	1.13
3.00	3.29	1.43
3.50	3.70	1.69
4.00	4.14	1.93

TABLE A7.28

Nitrogen balance data (g) in eight volunteers during test diets (derived from daily input and urinary urea excretion)

Day:	Subject: MM	AC	PH	JP	MG	LT	DC	SB
1	-1.43	-0.71	-3.92	-3.00	-1.44	-2.95	+2.70	-1.86
2	-3.59	-0.55	-4.83	-5.89	+2.50	-1.51	-1.86	+3.50
3	-0.51	-3.59	-4.94	-2.33	-1.86	-1.96	-3.76	-2.44
4	-0.35	-1.74	+1.03	-6.74	-3.49	-3.88	-1.83	-3.76
5	-1.74	-3.59	-4.15	-5.52	-3.67	-3.02	-4.79	-4.48
6	-3.59	-3.89	-3.98	-6.01	-3.76	+1.12	-3.67	-3.67
7	-3.89	-1.33	-4.09	-3.11	-4.79	-3.79	-3.49	-4.79
8	+4.74	+2.01	-1.01	-1.55	-1.13	-1.50	-1.00	-1.35
9	+4.89	+2.00	+2.87	+1.98	-1.08	+3.91	+2.49	+1.01
10	+5.03	+2.39	+2.12	+3.79	+3.95	+4.30	+2.99	+3.19
11	+5.03	+2.12	+2.34	+3.01	+4.30	+4.08	+3.50	+3.58
12	+5.39	+2.33	+1.89	+3.85	+4.76	+2.00	+2.13	+2.77
13	+5.33	+3.85	+2.56	+2.95	+3.84	+4.95	+2.66	+3.64
14	+5.39	+2.80	+1.88	+2.47	+4.91	+5.76	+2.43	+3.46

Daily weight changes due to water that is obligated to protein (assuming a ratio of 3g of water for each 1g of protein)

Day :		Day :	
1	-0.04 kg	8	-0.005 kg
2	-0.04 ""	9	+0.05 ""
3	-0.05 ""	10	+0.07 ""
4	-0.05 ""	11	+0.07 ""
5	-0.07 ""	12	+0.06 ""
6	-0.06 ""	13	+0.07 ""
7	-0.07 ""	14	+0.07 ""

TABLE A7.29

Clinical data of 2 patients with total dysphagia

Patient: WR Age: 51 Occupation: Ex-labourer Date of admission: 4.6.80

Active problems: (1) Dysphagia (2) Marked weight loss

Past Hx: 1976 - 'colon replacement' for benign oesophageal stricture as a result of hiatus hernia; weight : 44.5 kg

1979 - recurrent dysphagia; endoscopy - stricture at colo-gastrostomy; laparotomy - insertion of Celestin tube; weight : 42.0 kg.

Oct 1979 - recurrent dysphagia; replacement of Celestin tube; weight 36.3 kg

4 June 1980 - grossly wasted man; weight 32.3 kg.

Day:	0	1	2	3	4	5	6	7	8	9
Hb (g/dl)	12.0	11.5	11.7	9.7	9.8	10.6	8.3	12.1	11.5	11.7
WBC (x10³/µl)	13.7	12.5	14.5	10.6	9.8	10.9	10.8	10.7	12.0	8.6
PCV (%)	37.6	39.0	32.0	29.8	35.0	38.0	35.6	38.6	37.5	36.4
T-Pro (g/l)	69	-	-	65	-	-	71	-	-	63
Alb (g/l)	35	-	-	32	-	-	36	-	-	32
Bili (mmol/l)	4	-	-	2	-	-	4	-	-	3
Alk Phos (IU/l)	178	-	-	182	-	-	195	-	-	221
Ca^{2+} (mmol/l)	2.5	-	-	2.2	-	-	2.4	-	-	2.0
Phos (mmol/l)	1.4	-	-	0.8	-	-	1.6	-	-	0.2
s-Na^{+} (mmol/l)	124	130	125	130	128	126	125	134	139	138
s-K^{+} (mmol/l)	5.1	3.8	4.2	4.6	4.2	4.4	4.3	4.4	4.0	4.0
Glucose (mmol/l)	4.6	4.9	6.2	4.6	11.7	5.1	5.5	7.0	4.5	4.2
Urea (mmol/l)	13.5	9.3	5.6	3.3	1.7	1.5	1.1	1.3	2.4	3.2
s-Osm (mOsm/kg)	240	270	255	275	280	260	250	280	285	295
U_{Na^+} (mmol/day)	2	3	2	3	7	7	8	7	9	7
U_{K^+} (mmol/day)	64	44	23	20	12	17	26	32	16	18
U urea (mmol/day)	668	169	78	129	182	178	282	109	52	175

Patient: MO Age: 32 Occupation: Unemployed Date of admission: 24.6.80
Active problems: (1) Dysphagia (2) Marked weight loss
Past Hx: nil significant
Endoscopy June 1980 : tumour at lower third of oesophagus
Barium swallow : stricture at lower third of oesophagus

Day:	0	1	2	3	4	5	6	7	8	9
Hb (g/dl)	15.4	13.1	14.1	13.6	12.6	12.0	10.6	13.0	11.5	11.8
WBC ($x10^3/\mu l$)	10.4	9.8	8.9	9.1	9.9	7.5	9.1	9.9	10.1	9.6
PCV (%)	48.7	42.2	45.5	43.0	41.2	37.5	34.9	38.4	35.2	36.3
T-Pro (g/l)	74	-	-	68	-	-	59	-	-	65
Alb (g/l)	43	-	-	40	-	-	34	-	-	37
Bili (mmol/l)	7	-	-	7	-	-	3	-	-	4
Alk Phos (IU/l)	85	-	-	126	-	-	134	-	-	150
Ca^{2+} (mmol/l)	2.5	-	-	2.3	-	-	2.6	-	-	2.7
Phos (mmol/l)	1.4	-	-	1.3	-	-	1.2	-	-	1.5
s-Na^+ (mmol/l)	136	134	136	133	131	135	133	131	130	135
s-K^+ (mmol/l)	4.4	4.5	4.7	4.6	4.2	4.5	4.3	4.4	5.0	4.6
Glucose (mmol/l)	6.1	6.0	9.2	6.7	6.9	9.3	3.8	3.9	5.6	6.7
Urea (mmol/l)	6.8	3.6	2.7	2.1	2.9	1.5	3.7	6.2	5.5	6.1
s-Osm (mOsm/kg)	273	270	290	285	279	292	289	285	279	292
U_{Na^+} (mmol/day)	3	8	5	2	1	6	5	3	3	8
U_{K^+} (mmol/day)	28	12	13	5	10	13	6	22	44	56
U urea (mmol/day)	278	389	265	122	76	175	52	109	282	626

APPENDIX 8.1

Details of 2 patients given 'GKI' therapy

Patient: WJ Age: 87 Sex: Female Date of admission: 30.10.81

Active problem: Epigastric pains for investigation

Past Hx: Epigastric pains for 10 years ? peptic ulcer; on no medication

Physical exam: T 36°C; BP 150/95 mmHg; PR 90/min regular.
JVP not raised; chest - equal expansion.

Abdomen: mild epigastric tenderness; no masses felt; normal bowel sounds; no peritonism; per rectal exam - soft faeces

Chest x-ray, Plain abdominal x-rays, ECG; within normal limits

Management: nil by mouth; IV-Dextrose/Saline

Biliary scan: normal

Endoscopy: to be arranged

Day:	30/10	31/10	1/11	2/11	3/11	4/11	5/11	6/11	7/11
Hb (g/dl)	14.2	13.5	13.6	13.0	12.5	12.5	13.8	14.9	13.9
WBC ($\times 10^3/\mu l$)	6.8	9.4	11.1	9.0	8.5	9.4	10.8	9.8	9.9
s-Na^+ (mmol/l)	128	112	108	110	117	115	122	125	126
s-K^+ (mmol/l)	3.8	3.0	4.1	3.2	3.1	2.7	3.6	3.8	5.1
s-urea (mmol/l)	6.1	5.4	4.9	3.3	3.9	3.4	4.1	3.1	2.9
s-glucose (mmol/l)	7.6	6.9	7.2	7.0	6.8	6.6	6.5	7.9	8.8
s-Osm (mOsm/kg)	257	223	220	225	227	228	268	275	282
u-Osm (mOsm/kg)	545	601	596	584	585	436	444	492	492
pO_2	-	-	78	-	-	-	-	-	-
pCO_2	-	-	36	-	-	-	-	-	-
pH	-	-	7.4	-	-	-	-	-	-
HCO_3	-	-	23	-	-	-	-	-	-
s-amylase (IU/l)	210	180	-	190	-	-	-	-	-
Ca^{2+} (mmol/l)	2.5	-	-	2.3	-	-	-	-	-
Phos (mmol/l)	0.8	-	-	1.2	-	-	-	-	-
T-Pro (g/l)	67	-	-	54	-	-	-	-	65
Alb (g/l)	41	-	-	33	-	-	-	-	37
Bili (mmol/l)	8	-	-	7	-	-	-	-	5
Alk Phos (IU/l)	82	-	-	95	-	-	-	-	112
Cum. water bal (ml/day)		+1305	+3130	+3260	+2471	+2311	+2089	+2104	+1985	+1845
Cum. Na^+ bal (mmol/day)		+155	+189	+84	+15	+17	+13	+36	+40	+13
cum. K^+ bal (mmol/day)		+13	+7	+4	+77	+92	+50	+78	+85	+90

* 2-11 to 6-11 : Central venous line
20% dextrose solution at 1000 ml/12 hr + 80 mmol KCl/l

Insulin requirements as dictated by s-glucose and u-glucose

Patient: EG Age: 66 Sex: Female Date of admission: 1.9.81

Active problems: Increasing dysphagia; weight loss;

Past Hx: Oesophageal dilatation 1977

Steps in management:

2. 9.81 - Pharyngoscopy and Laryngoscopy - large tumour of right pyriform fossa extending to oesophagus.

8. 9.81 - Pharyngo-laryngo-oesophagectomy with colonic replacement.

17.11.81 - Laparotomy; gastric 'pull-up' due to failed colonic replacement.

8.12.81 - Died

Day:	22/11	23/11	24/11	25/11	26/11	27/11	28/11	29/11	30/11
Hb (g/dl)	11.0	10.8	9.2	9.5	12.0	12.9	12.6	11.6	12.0
WBC (x10³/µl)	10.6	10.5	14.8	15.0	17.3	11.1	13.0	13.5	12.9
s-Na^+ (mmol/l)	128	128	124	125	127	132	136	135	135
s-K^+ (mmol/l)	4.3	3.6	3.7	3.4	3.2	3.4	3.0	3.0	3.7
s-urea (mmol/l)	5.6	4.9	4.6	5.0	5.0	3.9	5.8	6.2	10.1
s-glucose (mmol/l)	7.2	7.9	8.9	7.6	6.1	7.1	3.9	7.1	7.4
s-Osm (mOsm/kg)	259	257	249	251	254	265	292	289	293
u-Osm (mOsm/kg)	511	545	533	642	561	722	769	640	640
pO_2	-	-	94	-	-	-	-	-	-
pCO_2	-	-	34	-	-	-	-	-	-
pH	-	-	7.5	-	-	-	-	-	-
HCO_3	-	-	22	-	-	-	-	-	-
s-amylase (IU/l)	-	-	-	-	-	-	-	-	-
Ca^{2+} (mmol/l)	2.1	-	-	2.1	-	-	2.6	-	-
Phos (mmol/l)	0.9	-	-	0.8	-	-	1.1	-	-
T-Pro (g/l)	67	-	-	54	-	-	62	-	-
Alb (g/l)	30	-	-	27	-	-	31	-	-
Bili (mmol/l)	11	-	-	14	-	-	12	-	-
Alk Phos (IU/l)	450	-	-	450	-	-	450	-	-
Cum. water bal (ml/day)	+1120	+1560	+1566	+2610	+2530	+1890	+1990	+1640	+1880
Cum. Na^+ bal (mmol/day)	+75	+90	+120	+95	+45	+50	+65	+50	+50
cum. K^+ bal (mmol/day)	+26	+26	+32	+40	+32	+60	+65	+72	+65

* 25-11 to 29-11 : Central venous line
20% dextrose solution at 1000 ml/12 hr
+ 80 mmol KCl/l

Insulin requirements as dictated by s-glucose and u-glucose

APPENDIX 9.1

Calculation for rabbit small bowel anastomoses studies

TABLE A9.11

Duration and volume of intravenous Hartmann's infusion in group 2 animals

No:	Weight: (kg)	5 ml/kg/hr during operation (ml)	Infusion to 48 hrs post-op (ml)
1	2.2	16.50	183.50
2	2.4	18.00	182.00
3	2.5	18.75	181.25
4	2.6	19.50	180.50
5	2.3	17.25	182.75
6	2.5	18.75	181.25
7	2.6	19.50	180.50
8	2.7	20.25	179.75
9	2.4	18.00	182.00
10	2.5	18.75	181.25
11	2.5	18.75	181.25
12	2.6	19.50	180.50
13	2.7	20.25	179.75
14	2.5	18.75	181.25
15	2.5	18.75	181.25
16	2.6	19.50	180.50
17	2.7	20.25	179.75
18	2.5	18.75	181.25

No:	Weight: (kg)	5 ml/kg/hr during operation (ml)	Infusion to 48 hrs post-op (ml)
19	2.4	18.00	182.00
20	2.5	18.75	181.25
21	2.2	16.50	183.50
22	2.4	18.00	182.00
23	2.5	18.75	181.25
24	2.6	19.50	180.50
25	2.3	17.25	182.75
26	2.5	18.75	181.25
27	2.6	19.50	180.50
28	2.7	20.25	179.75
29	2.4	18.00	182.00
30	2.5	18.75	181.25
31	2.6	19.50	180.50
32	2.7	20.25	179.75
33	2.5	18.75	181.25
34	2.5	18.75	181.25
35	2.6	19.50	180.50
$\bar{x} \pm SD$	2.51 $\pm$ 0.13	18.81 $\pm$ 0.99	181.19 $\pm$ 0.99

TABLE A9.12

Mean urine volume (ml/hr) for 18 hrs post operatively

Group 1	Group 2
2.0	2.2
2.1	2.4
2.1	2.5
2.1	2.5
2.2	2.5
2.3	2.5
2.4	2.5
2.5	2.6
2.5	2.6
2.5	2.6
2.6	2.6
2.6	2.6
2.6	2.7
2.7	2.8
2.7	2.8
2.7	2.8
2.8	2.8
2.8	2.8
$\bar{x} \pm$ SD 2.46 $\pm$ 0.26	2.60 $\pm$ 0.16

Mann Whitney U : U = 113.5
z = 1.53
p : NS

TABLE A9.13

Wet/Dry ratios in Control Group (n = 50)

1	5.2944	26	5.0381
2	5.5119	27	5.0885
3	5.6492	28	5.3170
4	5.7844	29	5.2476
5	5.0475	30	5.3120
6	4.2826	31	4.2701
7	5.9412	32	4.9940
8	4.9665	33	4.6849
9	5.1155	34	4.8698
10	5.7920	35	4.6959
11	5.2685	36	4.4190
12	5.6853	37	4.9781
13	4.6077	38	5.3733
14	5.0175	39	5.9803
15	4.1902	40	5.5835
16	4.5845	41	5.0070
17	5.7582	42	4.3733
18	5.2052	43	4.2944
19	5.0050	44	4.5119
20	4.9070	45	4.7155
21	4.8037	46	5.2675
22	5.3262	47	5.0700
23	5.2413	48	5.5124
24	5.2327	49	5.2431
25	5.2301	50	5.2445

$\bar{x}$: 5.0908, range 4.1902 - 5.9803

TABLE A9.14

Per cent weight change above normal due to water (Group 1) (mean ± SD)

	0 hr	6 hr	Day 1	2	3	4	5
A	7.7 ± 1.4	4.9 ± 1.2	5.8 ± 3.0	7.7 ± 1.5	9.0 ± 2.1	9.2 ± 1.3	9.8 ± 2.4
B	8.1 ± 1.7	6.0 ± 1.1	6.2 ± 1.9	8.3 ± 1.7	7.0 ± 1.9	2.0 ± 1.7	0.6 ± 1.4

Per cent weight change above normal due to water (Group 2)

	0 hr	6 hr	Day 1	2	3	4	5
A	17.8 ± 1.0	10.0 ± 0.7	11.6 ± 2.3	11.0 ± 1.3	14.1 ± 1.8	14.3 ± 0.9	14.8 ± 2.8
B	15.9 ± 1.3	11.8 ± 2.6	11.0 ± 2.0	11.4 ± 0.2	9.4 ± 3.2	3.8 ± 1.5	3.3 ± 1.1

GLOSSARY OF ABBREVIATIONS AND SYMBOLS

ADH:	antidiuretic hormone	g:	gram	mOsm:	milli-osmole	SEM:	standard error of the mean
AVP:	arginine vasopressin	G:	gravity	ml:	milli-litre	std:	standard
AA:	amino acid	H_{diet}:	low-sodium high-carbhydrate diet	min:	minute	TBW:	total body water
ATP:	adenosine triphosphate			Na^+:	sodium ion	TCF:	transcellular fluid
ATPase:	adenosine triphosphatase	H_2O:	water	Na_e:	exchangeable body sodium	t:	t value for student's t-test
Bal:	balance	^3H_2O:	tritiated water				
Calc-Osm:	calculated osmolality	HCO_3^-:	bicarbonate ion	N_2:	nitrogen	U_{osm}:	urinary osmolality
C_{osm}:	osmolal clearance	h:	hour	NS:	not significant	U_{Na}:	urinary sodium
C_{H_2O}:	free water excretion	ICF:	intracellular fluid	Obs-Osm:	observed osmolality	U_K:	urinary potassium
		ICW:	intracellular water	Osm:	osmolality	u:	u value for Mann Whitney U test
Cl^-:	choride ion	IVT:	intravenous therapy	O_{osm}:	osmolal excretion		
CO_2:	carbon dioxide	K^+:	potassium ion	O_2:	oxygen	V_u:	urinary volume
Cr:	chromium	K_e:	exchangeable body potassium	op:	operation	wt:	weight
Ci:	curie			P_{osm}:	plasma osmolality	yr:	year
^0C:	degree centigrade	k:	kilo	P:	probability	z:	z value for Mann Whitney U test
Ca:	carcinoma	kcal:	kilocalorie	p:	plasma		
DDAVP:	Desmopressin, Ferring	kPa:	kiloPascal	RER:	respiratory exchange ratio	Δ:	change
d:	day	Li^+:	lithium ion			μ:	micro
df:	degrees of freedom	L_{diet}:	low-sodium low-carbohydrate diet	REE:	resting energy expenditure	<:	less than
ECF:	extracellular fluid					>:	greater than
ECW:	extracellular water	l:	litre	r:	correlation coefficient	$\propto$:	proportional
EDTA:	ethylenediaminetetra-acetic acid	MBq:	mega-Becquerel	rpm:	revolutions per minute	$\bar{x}$:	mean
		MJ:	mega joule	s:	serum	/:	per
GKI:	glucose-potassium-insulin	mV:	millivolt	SW:	serum water	%:	per cent
		mmol:	millimole	SD:	standard deviation		