HYPERNATRAEMIC DEHYDRATION IN INFANTS WITH DIARRHOEAL DISEASE.

Ivor Dennis Hill.
M.B. Ch.B. (Cape Town) F.C.P. (Paed.)
D.C.H. (S.A.)

Thesis submitted in part fulfillment of the requirements for the degree Doctor of Medicine University of Cape Town.

September 1981.
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Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.
TO MY WIFE BARBARA, MY SONS KEVIN AND GARICK
AND LITTLE CHILDREN EVERYWHERE.
Acknowledgments.

I am deeply indebted to both Professor Malcolm Bowie and Dr. Michael Mann. Professor Bowie has helped me in my career and is largely responsible for my interest in Paediatric Gastroenterology. He encouraged me to do research and his expert guidance and advice have been of the utmost importance to my career and this project. I sincerely appreciate all his help and continued interest in my activities. Dr. Mann has been a major source of advice, encouragement and uncomplaining help. His willingness to impart his knowledge and his meticulous attention to detail have been invaluable to my work. I wish to express my gratitude to both these men.

My thanks are due to Mrs. Lyn Moore, Mrs. Pam Burns and Miss Gillian Peat of the Institute of Child Health research laboratory for their help in the biochemical analysis of the various specimens.

I am grateful to Dr. John Ireland for his advice and encouragement and for allowing me access to the patients in the Drip Room. I would also like to thank the Paediatric Nurse Associates and staff of the Drip Room for referring patients to me.
The sisters in ward R2 and the nurses in the Metabolic Unit deserve a special word of praise for their care of the patients and the careful collection of specimens.

I am grateful to the parents who allowed their children to participate in the investigations. Without them this project would not have been possible.

Professor G.M. Berger and the staff of the Chemical Pathology laboratory performed all the routine investigations on the patients in the Drip Room.

I wish to thank Mrs. Elizabeth Michel for all her work in typing this manuscript.

The work was done in the Institute of Child Health, Department of Paediatrics and Child Health, University of Cape Town. The patients were admitted to the Metabolic Unit and the Drip Room at the Red Cross War Memorial Children's Hospital. Much needed financial support was received from the South African Medical Research Council, the Atomic Energy Board and the Mobil Research Associateship. This is gratefully acknowledged.

Finally I wish to thank my wife Barbara. She has provided constant encouragement and help and has been most patient throughout.
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Abstract.

Hyponatraemic dehydration has long been recognised as a serious complication of diarrhoea in young children but there is still much about the condition which is incompletely understood. The inability to predict which infants with diarrhoea will become hyponatraemic makes a prospective study of the factors involved in the pathogenesis of the condition impossible. The events during recovery must to some extent be the reverse of those occurring during development. Their study during rehydration should lead to an improved understanding of the pathogenesis of hyponatraemia secondary to diarrhoeal disease.

Such a study was undertaken on a group of infants with hyponatraemic dehydration. The results were compared to those of a group of infants with non hyponatraemic dehydration who were similarly managed and studied. All non hyponatraemic infants and the majority of hyponatraemic infants have a total body sodium deficit at the time of admission. In the hyponatraemic infants there is a greater loss of water than sodium from the body. In a few, hyponatraemia may be associated with a normal or even excess body sodium. This may be the result of prior excessive ingestion of exogenous sodium. Complex shifts of endogenous sodium and water between the body fluid compartments apparently occur during development of
hyperna
traemia. In some the movement of sodium is into the
cells and may limit the height of the rise in the serum sodium
concentration. In others transfer of endogenous sodium is into
the extracellular fluid compartment and may aggravate the
hyperna
traemia. The factors responsible for these shifts are not
known but may be related to acidosis and increased adrenal
cortical activity.

Recovery from hyperna
traemic dehydration is a dynamic process
involving a number of different mechanisms. Early in the course
of rehydration renal sodium excretion appears important in
lowering the serum sodium concentration. Most infants with
diarrhoea are capable of appropriate renal sodium excretion and
hyperna
traemic infants can produce urinary sodium concentrations well in excess of plasma levels shortly after
starting intravenous fluid therapy. The urinary sodium excretion
is accompanied by relatively greater retention of administered
water than sodium. There is dilution of the sodium in the
extracellular fluid space and a further lowering of the serum
sodium. The effect of renal sodium excretion is short lived and
by the end of twenty four hours of therapy all infants (even
those with an apparent initial excess body sodium) have a
positive sodium retention. This, with the relatively greater
water retention, obscures the importance of renal sodium
excretion in the initial phase of returning serum sodium to
normal levels.
Following the first twenty four hours of rehydration there is a prolonged phase of adjustment during which time body sodium status is returned to normal. This entails positive sodium retention in most infants to replace an initial sodium deficit. In a small number there is a negative sodium balance to correct an initial sodium excess.

The most serious effects of hypernatraemia are related to changes in the central nervous system with features of dysfunction including coma and convulsions. When coma and convulsions occur prior to admission and the initiation of treatment they are poor prognostic features. Such convulsions are caused by structural brain damage due to intracranial bleeding and have a high death rate. Convulsions occurring only after starting treatment do not have such a poor prognostic significance. They may be caused by factors unrelated to the hypernatraemia per se or may be precipitated by such treatable causes as hypocalcaemia. Their importance lies in the potential they have for causing residual damage and long term morbidity.

To avoid convulsions which may be caused by improper therapy, numerous fluid schedules have been recommended. All rely on early recognition of the hypernatraemic infant to effect a
modification of treatment. Recognition of hypernatraemia by clinical means is difficult as no features are pathognomonic of the condition. The most important clue is the presence of features of central nervous system dysfunction. However, unless the serum sodium concentration is determined on every infant with dehydrating diarrhoea many with this electrolyte disturbance will go undetected. Routine sodium determination on all infants admitted with dehydrating diarrhoea is not possible in all areas. Therefore it is imperative to have a fluid therapy schedule which satisfies the needs of the non hypernatraemic infant and at the same time minimises the risk of iatrogenically induced complications in the hypernatraemic infant.

The fluid schedule at present in use at the Children's Hospital fulfills these requirements. It has been used successfully in children with non hypernatraemic dehydration for years and the study has shown it to be associated with a much lower mortality and morbidity in hypernatraemia than occurs elsewhere. The scheme obviates the urgent need to recognise the hypernatraemic child, is simple to apply and is recommended for all infants requiring intravenous fluids for dehydration due to diarrhoeal disease. It is in particular recommended for use in areas where large numbers of children require treatment annually.
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**Chapter 1.**

Aspects of the pathogenesis and pathophysiology of hypernatraemic dehydration secondary to diarrhoeal disease.

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1.1. The nature of the fluid losses during diarrhoea.

The loose or watery stools characteristic of acute infectious diarrhoea result in excessive loss of both water and electrolyte from the body. One of the electrolytes lost is sodium but its concentration in stool water is invariably below that of serum. Other major sources of loss are mainly water. Insensible losses from the lungs are sodium free and loss through the skin is hyponatraemic relative to serum. These may be greatly increased by tachypnoea or hyperpyrexia both of which often accompany diarrhoeal disease. The net effect is a disproportionately greater loss of water than sodium from the body. Unreplaced the loss of water will result in dehydration and because of the relatively lesser sodium loss a rise in serum sodium concentration occurs. Partial replacement of the losses with low concentration or sodium free solutions prevents this situation arising. Dehydration is then accompanied by a serum sodium concentration which remains within the accepted normal range of one hundred and thirty to one hundred and fifty millimole per litre.

When dehydration is associated with a serum sodium concentration exceeding one hundred and fifty millimole per litre, the condition is known as 'hypernatraemic dehydration'. Other terms such as hypertonic or hyperosmolar dehydration
have been used. These are unsatisfactory as they do not distinguish hypernatraemia from conditions with a raised serum osmolality but a normal sodium concentration (e.g. diabetic hyperglycaemia with ketoacidosis).

1.2 **Pathogenesis of hypernatraemic dehydration.**

Because of the disproportionately greater loss of water than sodium in diarrhoea, hypernatraemic dehydration might be expected to be the most common form of dehydration. In practice this is not so and most series report hypernatraemia in only ten to thirty per cent of cases of diarrhoeal disease. Most dehydration is normonatraemic and the homeostatic mechanisms of thirst and renal water conservation appear mainly responsible for the maintenance of normal serum sodium concentration. It is an apparent failure of homeostasis which results in hypernatraemia.

An adequate intake of fluid of low or absent sodium content must be a significant factor in the pathogenesis of hypernatraemia. It may occur as a result of either anorexia or vomiting both of which frequently accompany diarrhoeal disease. Small infants are unable to attend to their own water requirements and their inability to communicate their
needs may result in a further inadvertant limitation of free water intake. The result is insufficient replacement of the water losses sustained during diarrhoea.

The exact role of the kidneys in the pathogenesis is less certain. There are three ways in which they might participate in the development of, or aggravate existing hypernatraemia. The infant kidney may be unable to concentrate urine above seven hundred milliosmoles per litre.\(^{22, 105, 107, 127}\) This is only half the maximum concentrating ability of the adult kidney\(^{22}\) and in order to excrete a given solute load twice as much water would be required. Because of this, where feeds contain a solute load in excess of the infants needs the kidney becomes a source of excess water loss.\(^{125}\) In health enough free water is ingested to cover the renal losses but where losses are increased as in diarrhoeal disease, water intake becomes inadequate.\(^{24, 125}\)

Even in health the infant is believed to be unable to excrete an excess sodium load.\(^{61, 135}\) The suggested ceiling for renal sodium excretion is five to ten millimoles per kilogram per day.\(^{135}\) Where sodium intake exceeds this level some will be retained. Renal sodium clearance is dependant on both glomerular filtration and tubular reabsorption.\(^{130, 140}\) and
multiple complex regulatory mechanisms exist to determine the final urinary concentration of this ion.\textsuperscript{106, 140} In early infancy glomerular filtration is relatively less than that of adults\textsuperscript{5, 107, 129, 140} while tubular reabsorption is much the same.\textsuperscript{129, 140} This apparent overdevelopment of tubular reabsorptive activity relative to glomerular function would favour sodium retention.\textsuperscript{104} Alone it does not fully explain the difference in sodium clearance between adults and young infants.\textsuperscript{140} Recent experimental work in dogs subjected to saline infusion has demonstrated proximal renal tubular response in newborns to be similar to that of adults.\textsuperscript{87, 140} Distal tubular response differed and the newborn puppies appeared unable to limit sodium reabsorption to the same degree as adult dogs.\textsuperscript{87} The difference in distal tubular function between adults and newborns may account for the latter's inability to adequately increase sodium clearance when intake is excessive.

A third possible renal mechanism promoting excess water loss is as osmotic diuresis due to the raised serum sodium concentration per se.\textsuperscript{33, 46, 152} In experimental animals it has been shown that in hypernatraemia there is a failure to concentrate urinary sodium and the ratio of urine to plasma sodium rarely exceed 1.0.\textsuperscript{46} This resembles the observation that some infants excrete dilute urine in the face of hypernatraemia.\textsuperscript{43a, 151} It would aggravate the disproportionately greater loss of water compared to sodium occurring during diarrhoeal disease.
Controversy surrounds the relative importance of these renal factors in the pathogenesis of hypernatraemic dehydration. The limited ability of the infants kidney to concentrate urine is a firmly established fact in the neonatal period and particularly in preterm infants. It is caused by the relatively lower glomerular filtration rate and reduced tubular excretory capacity of the newborn. While it is generally accepted that all aspects of renal function have matured by two years of age, the minimum age at which individual aspects of renal function mature is uncertain. Some have claimed that glomerular filtration rate may reach adult levels by as early as ten weeks of age and tubular excretory capacity by thirty weeks.

There is also a possibility that the diarrhoea and dehydration and not renal immaturity is responsible for the failure to concentrate urine. Pratt et al demonstrated that healthy infants aged thirty to sixty-five days produce urine osmolalities as high as 1 200 milliosmoles per litre when subjected to water deprivation. In contrast during dehydration due to diarrhoea and vomiting there appears to be a disturbance in tubular reabsorption of water and failure of urinary concentration. The disturbance may be due to a potassium deficiency which frequently accompanies diarrhoeal disease.
Similarly the inability of infants beyond the neonatal period to excrete sodium appropriately may be related to the diarrhoea and dehydration and not to immaturity of renal function. Rubin et al have demonstrated a sodium excretory ability equal to that of adults in healthy infants aged one to nine months. During dehydration following diarrhoea a number of factors may account for a low urine to plasma sodium ratio.

1. Glomerular filtration rate may be decreased by a fall in intravascular volume. Consequently filtered sodium is decreased and this results in greater tubular reabsorption of the fraction of filtered sodium.

2. Because of the diarrhoea there is a loss of potassium from the body and the kidney fails to clear sodium effectively during potassium deficiency.

3. In the dehydrated individual the output of urinary minerals is affected by factors other than their serum concentrations. Aldosterone affects sodium excretion and in response to a fall in extracellular fluid volume it is produced promoting renal tubular reabsorption of sodium.
The studies in which hypernatraemia was shown to cause an osmotic diuresis in experimental animals must also be questioned. During these experiments there were changes in both extracellular fluid volume and glomerular filtration rate. Subsequent work by Kamm and Levinsky eliminated the changes in the extracellular fluid volume and the glomerular filtration rate and showed that hypernatraemia per se resulted in a decreased tubular reabsorption of sodium. This appeared to be mediated through a local effect of the raised serum sodium concentration on the tubules increasing the rate of sodium elimination from the body.

1.3. Total body sodium in infants with hypernatraemic dehydration

Although the serum sodium concentration is raised in infants with hypernatraemic dehydration the loss of sodium in the diarrhoeal stools results in a deficit of total body sodium. Most authors believe this and while balance studies during rehydration of hypernatraemic infants support this view these have been limited in both number and duration.

It is possible that there is also an abnormal distribution of the remaining body sodium. Acidosis and some hormones of the
adrenal cortex appear capable of causing a transfer of sodium from bone and intracellular fluid to the extracellular fluid.\(^8, 17, 63, 83, 91, 92, 116, 142\) Infants with dehydrating diarrhoeal disease often have a metabolic acidosis.\(^6, 65, 67\) Whether this causes such a transfer of sodium, and if so, how significant it will be in raising the sodium concentration of the extracellular fluid is at present not known.

1.4. Normal body sodium distribution and exchangeable sodium

Sodium in the body is largely confined to bone, cartilage and extracellular fluid.\(^31, 119, 128\) Only a very small fraction is present in the intracellular fluid.\(^128\) Bone sodium consists of a fluid phase which is readily exchangeable with the extracellular fluid sodium and a crystal phase which exchanges only slowly or not at all.\(^54, 100, 128\) The body sodium which is metabolically active is confined to the extracellular fluid, cartilage and the fluid phase of bone.\(^53, 54\) This is known as the exchangeable sodium.\(^121\)

Exchangeable sodium can be accurately measured by means of isotopic dilution of radioactive \(^{24}\text{Na}.\(^37, 38, 50a, 94, 111\) Compared with results of carcass analysis exchangeable sodium in adults accounts for about two thirds of the total body sodium.\(^51\) In newborn infants exchangeable sodium and total
body sodium are virtually the same.\textsuperscript{50b} There are two reasons for the difference between adults and infants. Firstly the water content of bone is high at birth and falls progressively with age.\textsuperscript{52} The crystal phase of bone is initially very small. Secondly the proportion of the skeleton which is cartilage in the newborn is much larger than that of the adult and up to thirty four per cent of the sodium content of the skeleton may be in cartilage in the very young infant.\textsuperscript{52, 143}

The difference between healthy adults and infants is emphasised when exchangeable sodium is expressed in millimoles per unit of body weight. In the adult the mean value is 40 millimoles per kilogram.\textsuperscript{50a} In the newborn it may be as high as eighty six millimoles per kilogram and declines in a curvilinear fashion until adult values are reached near puberty.\textsuperscript{50b} Regardless of age it is possible to predict the exchangeable sodium using formulas incorporating the body weight of the individual.\textsuperscript{50b} In healthy infants there is very good correlation between the predicted and measured values for exchangeable sodium.

This change with age does not negate the usefulness of the exchangeable sodium as a measurement. It represents that portion of body sodium which may be affected by acute metabolic disturbances.\textsuperscript{38, 53, 121} It can be used to detect changes in sodium content due to disease of recent onset and limited duration.\textsuperscript{121}
1.5. Factors affecting sodium content of bone

Although it is now accepted that bone sodium in the fluid phase plays a role in general sodium metabolism factors affecting the mobilisation of skeletal sodium are controversial. Experimentally some hormones of the adrenal cortex appear capable of transferring sodium from bone and intracellular fluid to the extracellular fluid. In 1954 Bergstrom claimed a thirty to fifty per cent decline of the original bone sodium content occurred with acidosis. The magnitude of these changes have since been questioned but other workers have confirmed that some loss of sodium from bone occurs with acidosis or hyponatraemia while some is gained during hypernatraemia. The relative importance of acidosis versus the serum sodium concentration as the main controlling factor in the mobilisation of bone sodium remains unresolved.

Changes in bone sodium content in infants are also more rapid and of greater magnitude than in adults. This may be due to the greater rapidity with which acidosis develops in infants as compared to adults.
1.6. Effect of hypernatraemia on the distribution of body water

The raised sodium concentration of hypernatraemia has a profound effect on the distribution of the body water. Sodium is the principle cation of the extracellular fluid and for practical purposes moves freely between the intravascular and interstitial fluid spaces. These two subdivisions of the extracellular fluid can be considered as a single space as far as the effects of this electrolyte are concerned. It constitutes ninety per cent of the osmotically active particles in the extracellular fluid and is responsible for maintaining the volume of this space.

In contrast to the extracellular fluid, sodium is present in very low concentrations in the intracellular fluid and contributes little to intracellular osmolality. It is actively excluded from the intracellular fluid by the action of an energy dependant sodium pump in the cell membrane, and thus acts as an impermeable solute.

Water, unlike sodium, diffuses rapidly and freely across the cell membrane separating intracellular from extracellular fluid. Transfer of water is the chief means of maintaining osmotic equilibrium between the various fluid compartments. The direction of water movement is determined by the osmotic gradient across the cell membrane. A rise in the osmotic pressure of the extracellular fluid results in a movement of water from the intracellular to the extracellular fluid space to maintain osmotic equilibrium.
Much of present knowledge of fluid and electrolyte changes occurring during diarrhoeal disease comes from studies of patients in whom dehydration was associated with a normal serum sodium concentration (iso- or normonatraemic dehydration). The osmolality of the extracellular fluid remains normal in these patients and no osmotic gradient results between the extra- and intracellular fluids. Fluid is lost from the extracellular fluid space but there is little or no loss from the intracellular fluid (figure 1.1). The loss of extracellular fluid volume affects both the interstitial and intravascular fluids. When dehydration occurs rapidly the circulating blood volume falls precipitously and shock ensues early in the course of the illness.

In contrast to normonatraemic dehydration, knowledge of the fluid and electrolyte changes of hypernatraemic dehydration comes largely from work in experimental animal models, circumstantial clinical evidence and physiological principles. The rise in sodium concentration causes an increase in the osmolality of the extracellular fluid and creates an osmotic gradient across the cell membrane. To restore osmotic equilibrium water is transferred from the intracellular to the extracellular fluid space. This results in partial correction of the extracellular fluid volume deficit at the expense of the intracellular fluid (figure 1.2).
Figure 1.1.
Changes in Extra & Intracellular Fluid Volume.
Normonatraemic Dehydration.
Figure 1.2.
Changes in Extra & Intracellular Fluid Volume.
Hypernatraemic Dehydration.

ECF  ICF

ECF  ICF

H₂O
Because of this transfer of water hypernatraemia is believed to result in a proportional or relatively greater loss of intracellular as compared to extracellular fluid volume. Work on experimental animals supports this belief. As the clinical features associated with dehydration reflect loss of water from the extracellular fluid, the relative preservation of this volume limits the appearance of signs of dehydration despite a significant loss of total body water. Similarly the preservation of the intravascular volume prevents hypovolaemic shock occurring until late in the course of the illness. Characteristically infants with hypernatraemic dehydration manifest few of the clinical features associated with dehydration and are seldom shocked despite a significant loss of body weight.

Recently it has become apparent that not all cells respond to a rise in extracellular fluid osmolality by water loss alone. Where hypernatraemia develops abruptly osmolality equalises primarily by water movement and the loss of intracellular fluid volume described occurs in all cells. If hypernatraemia develops more gradually some cells are able to adapt by an increased intracellular solute concentration and prevent water loss to the extracellular fluid (figure 1.3). The acquired intracellular osmotically active particles are known as
'idiogenic osmoles'. They are thought to arise from the release of previously bound osmotically inactive intracellular cations and the breakdown of complex phosphates and proteins to smaller osmotically active molecules. Their function appears protective and aimed at preserving cellular volume in the face of a rising osmolality in the external environment. The cells of the brain and red blood cells appear best able to manufacture idiogenic osmoles whereas others (eg. muscle) have only a limited capacity to do so.
Figure 1.3. Changes in Extra & Intracellular Fluid Volume. Hypernatraemic Dehydration: Effect of Idiogenic Osmoles.
Chapter 2.

Clinical aspects and management of hypernatraemic dehydration.

2.1. Incidence of hypernatraemia.
   - seasonal variation in incidence.

2.2. Diagnosis of hypernatraemia.
   - anorexia and vomiting.
   - salt/solute ingestion.
   - age and sex.
   - nutritional status.
   - skin changes.
   - CNS dysfunction.
   - coma and convulsions.

2.3. Mortality and morbidity due to hypernatraemia.

2.4. Fluid therapy in hypernatraemic dehydration.

2.5. Summary.
2.1. Incidence

Hypernatraemia is said to occur in four to sixty three percent of hospital admissions for diarrhoeal disease. 6, 10, 12, 22, 32, 35, 41, 44, 48, 49, 57, 65, 67, 74, 79, 84, 97, 120, 126, 136, 147, 151 This wide variation in incidence is due to a few reports 6, 10, 22, 79 and most authors have found between ten and thirty per cent of children admitted with diarrhoea to have a serum sodium concentration greater than one hundred and fifty millimoles per litre. Recently it has been suggested that there has been a decline in the incidence of hypernatraemia over the past decade. 74, 103, 141, 154 The increased use of modified cows milk formulas with a low solute content and campaigns promoting breast feeding have been proposed as the factors responsible for this apparent decline but their relative importance remains controversial.

A marked seasonal variation has been noted in some areas with up to seventy five per cent of the cases being admitted during the winter months. 12, 22, 49 'Epidemics' have been described during winter in these regions and at times ninety to one hundred per cent of admissions for diarrhoea may be hypernatraemic. 12 In other areas no seasonal influence on the incidence has been noted. 97
2.2. **Diagnosis of hypernatraemia**

Early recognition of the hypernatraemic individual has been stressed as desirable as it allows for appropriate modification of treatment.\(^2\)\(^0\), \(^4\)\(^7\), \(^6\)\(^7\) There are a number of features associated with but none specific to the condition. Consequently there is conflict of opinion as to the relative ease with which the clinical diagnosis can be made.

Bruck et al felt a clinical diagnosis was possible in almost all cases.\(^1\)\(^2\) Others found it difficult to distinguish hypernatraemic from non-hypernatraemic dehydration and the condition was often only recognised when the serum sodium concentration was determined.\(^6\), \(^1\)\(^0\), \(^1\)\(^7\), \(^6\)\(^7\), \(^9\)\(^7\) Although the relative importance of individual features remains controversial their presence in an infant with diarrhoeal disease should arouse suspicion of the diagnosis.

A history of severe anorexia or excessive vomiting is often described in these patients and may point to a severely limited fluid intake prior to admission.\(^1\)\(^2\), \(^4\)\(^8\), \(^6\)\(^9\), \(^9\)\(^7\), \(^1\)\(^5\)\(^1\) Specific questioning may produce evidence of prior ingestion of excessive salt or high solute containing feeds. Some have emphasised this as being an important factor\(^2\)\(^2\), \(^3\)\(^2\), \(^4\)\(^8\), \(^6\)\(^9\), \(^1\)\(^3\)\(^5\), \(^1\)\(^4\)\(^6\), \(^1\)\(^4\)\(^7\), \(^1\)\(^5\)\(^1\) while others feel it to be of little value.\(^1\)\(^2\), \(^9\)\(^7\)
The age of the patient is noteworthy. Young infants, particularly those under one year of age, appear most at risk of developing hypernatraemia as a complication of diarrhoeal disease. \[12, 32, 48, 67, 69, 147, 151\] This is probably because their greater surface area to body mass ratio results in a relatively greater insensible water loss than that of the older child. \[36\] Males are also more often affected than females but the reasons for this are unknown. \[12, 115, 136\]

Well nourished infants are usually affected and it appears most uncommon for malnourished infants to develop hypernatraemia. \[6, 126, 136\] Plasma sodium levels in malnutrition are usually low and when dehydration occurs rarely exceed one hundred and forty millimole per litre. \[81\] Compared to well nourished individuals extra and intracellular water is relatively greater in the malnourished. \[58, 66, 68, 109\] The factors promoting hypernatraemia in the well nourished infant may only return the sodium concentration to the normal range in the malnourished. \[136\]

On examination the infants often appear extremely thirsty. \[48, 69\] Clinical features of dehydration are seldom prominent except for the mucous membranes which are noticeably dry. \[17, 20, 41, 67, 69, 74, 97, 135, 151\] The skin and subcutaneous tissues may impart a peculiar inelastic feel often described as 'woody' or
'doughy' 48, 67, 74 This is claimed to be a useful diagnostic sign by some while others have found it to be either inconsistent or of no value in distinguishing the hypernatraemic state. 6, 10, 41, 147, 151

Hyperpnoea is frequently described in these infants 12, 41, 97, 136 although Weil and Wallace noted this feature in only one of twenty six patients studied. 151 It may be due to an accompanying metabolic acidosis 127 or an associated pneumonia and as a result water loss via the lungs may be increased two or three fold. 12, 75

Many infants with hypernatraemic dehydration are said to manifest signs of central nervous system dysfunction. 10, 12, 17, 20, 35, 41, 45, 48, 67, 69, 97, 135, 151 This has been the most consistent change noted by almost all the workers in this field and is regarded as the most useful clinical clue to the diagnosis. These signs have usually been present in at least two thirds of the cases studied. 12, 35, 41, 45, 97, 151

Prominent are lethargy with varying degrees of depressed level of consciousness. The infants are usually sleepy but may be easily roused. When awake there is marked irritability often associated with a high pitched shrill cry. There may also be noticeable hypo- or hypertonia with exaggeration of the deep tendon reflexes. Tremulousness of the limbs on movement is also
well described. The exact cause of the central nervous system signs is unknown but from work in experimental animals it is postulated to be due to increased intracellular ion concentration with cellular dehydration.21, 138 In addition sludging in the cerebral vessels with stasis and anoxia may be partially responsible.23

Coma and convulsions with hypernatraemic dehydration have been described. The convulsions may be a presenting feature in some22, 35, 79, 97 but more commonly occur during rehydration with parenteral fluids.12, 32, 41, 79, 97, 151

Those occurring prior to starting treatment appear to be particularly serious as there is a high death rate in these infants.45, 79, 98, 151 Such seizures are believed to be due to structural brain damage caused by subdural and intracerebral bleeds.115 It is postulated that this follows tearing of the bridging veins and cerebral vessels occurring when there is shrinkage of the brain within the rigid bony cranium.43b, 64, 96 This is due to a decrease in intracellular volume and follows on the transfer of water from cells to the extracellular space to maintain osmotic equilibrium during the development of hypernatraemia. When present it implies that hypernatraemia occurred rapidly and idiogenic osmoles were not formed in sufficient numbers to protect cerebral cell volume.40, 138
finding of extensive intracerebral bleeds at post mortem, and work on experimental animals, support this view on the etiology of these seizures. 26, 43a, 43b, 45, 64, 96, 138

Convulsions occurring for the first time after the start of parenteral fluid therapy are not associated with a high mortality. 13, 48, 97, 151 They are believed to be due to cerebral edema and consequent intracellular chemical derangement. 73, 144 This edema would occur when there is a rapid reduction in extracellular fluid osmolality following the administration of large volumes of relatively hyponatraemic fluid over a short period of time. Intracellular fluid osmolality then becomes greater than extracellular and osmotic equilibrium is restored by transfer of water into the cells. Having previously preserved a normal cell volume by the production of idiogenic osmoles cerebral cells are suddenly expanded by water transfer and this is thought to lower the seizure threshold. 144

Hypocalcaemia has also been noted in association with hypernatraemia 17, 41, 42, 67, 74 but the role of a low serum calcium concentration in the pathogenesis of the convulsions is generally believed to be negligible. 43a, 47 Regardless of the etiology, the majority of infants with convulsions occurring only during treatment appear to recover completely. However a small
number are associated with permanent neurological sequelae\textsuperscript{43a} and prevention and early termination of seizures during treatment of hypernatraemic dehydration is essential.

2.3. Mortality and long term morbidity

Death has been reported to occur in four to forty three per cent of infants with hypernatraemia.\textsuperscript{10, 20, 22, 32, 35, 45, 48, 79, 135} Some of the high figures quoted have exaggerated the mortality as the patients were of a selected series.\textsuperscript{10, 22, 35, 45} A mortality in the region of ten per cent appears to be the most commonly reported. Compared to the mortality in infants with non-hypernatraemic dehydration, or to the overall mortality of diarrhoeal disease, that for patients with hypernatraemia is usually considerably higher.\textsuperscript{3, 17, 26, 32, 41, 79, 97}

The long term morbidity associated with hypernatraemic dehydration is equally important. Most serious are permanent sequelae from damage to the central nervous system. These occur in four to thirty per cent of cases.\textsuperscript{22, 35, 74, 79, 98, 115} They may manifest as a persistent epileptic disorder, mental retardation or motor disorders ranging from monoplegia to spastic quadriplegia. The permanence implies irreversible structural brain damage, possibly the result of intracranial bleeding or cerebral venous thrombosis.\textsuperscript{74}
There is also a strong association between hypernatraemia and peripheral gangrene. Sludging and thrombosis secondary to hyperviscosity is postulated to occur in these cases. In some instances this has resulted in amputation of a portion of the affected limb.

2.4. Fluid therapy in hypernatraemic dehydration

The patient with hypernatraemic dehydration needs water and sodium to replace the existing deficit, the ongoing abnormal loss and to supply daily maintenance requirements. Although there is a loss of sodium, that of water is relatively greater. It seems logical to use a fluid with a very low sodium content for rehydration of these infants but a number of problems may be encountered with this form of treatment. The most serious are related to the central nervous system. Convulsions or exaggeration of existing signs of central nervous system dysfunction are frequently described.

Fluids which are sodium free or very low in sodium content cause a rapid decline in the extracellular sodium concentration and osmolality. Intracellular osmolality then exceeds that of the
extracellular space and water moves into the cells to restore osmotic equilibrium. Because cell volume in the brain is to some extent preserved by the production of idiogenic osmoles further movement of water into the cells produces cerebral edema. This appears to be responsible for the convulsions.

Strong evidence against the use of sodium free fluids comes from a study by Bruck et al. Comparing initial rehydration with ten per cent dextrose water as opposed to a sodium containing solution they noted that convulsions occurred only with the former. It is also claimed that the likelihood of convulsions increases as the sodium concentration of the administered fluid falls below fifty millimoles per litre.

The use of fluids with a sodium concentration above fifty millimoles per litre does not preclude convulsions as the rate of administration is also implicated in their pathogenesis. Rapid infusion of a large volume of fluid which is slightly hyponatraemic relative to serum will also cause a precipitous fall in sodium concentration and consequent cerebral edema.

Gradual rehydration with a slow decline in the patient's sodium concentration is advocated as the optimal form of therapy. A fall in serum sodium concentration of less than point five
millimoles per hour is recommended. A more rapid rate appears to greatly increase the incidence of convulsions. With slow rehydration cerebral cells have time to make the necessary ionic adjustments to lower intracellular osmolality. This limits water movement into the cells as extracellular fluid osmolality drops to normal. The mechanisms involved in the decline of intracellular osmolality are probably the reverse of those occurring in the production of idiogenic osmoles.

A problem arises when the patient is shocked and needs intravenous fluids rapidly. Restoration of an adequate circulating blood volume must take priority but rapid infusion of large volumes of hyponatraemic solutions is unsafe. In this situation the patient should receive a rapid infusion with a solution containing sodium in a concentration similar to normal serum. Plasma, plasma volume expanders and normal saline are among the fluids recommended. Once shock is corrected the remaining fluid deficit may be more gradually replaced.

A major difficulty in fluid therapy in hypernatraemic dehydration is the clinical estimation of the degree of fluid deficit. Fluid loss with diarrhoeal disease can be accurately determined only if the patients weight is known immediately prior to the onset of the illness. As such weights are rarely available water losses have to be estimated
on the basis of the clinical signs of dehydration. These signs include loss of skin and tissue turgor, dry mucous membranes, sunken eyes and a depressed fontanelle. They are directly related to the decrease in volume of the extracellular fluid. When the signs are first evident the degree of water loss is judged to be five per cent and when marked, ten per cent of body weight. Replacement requirements are then calculated as fifty or one hundred millilitres per kilogram respectively.

In hypernatraemia because of the fluid shift from the intracellular space there is relative preservation of extracellular fluid volume until late in the course of the disease. The clinical signs of dehydration are often minimal or absent. Consequently dehydration and water requirements are frequently underestimated despite a severe decrease in total body water.

Because of the problems associated with therapy many fluid regimes have been described for treating hypernatraemic dehydration. Rehydration by means of ad libitum oral fluids has been recommended as the most physiological form of treatment. No calculations of fluid requirements are involved and it has been claimed to be the least likely to cause convulsions. It is frequently not possible to use only oral fluids because of the presence of shock, coma or convulsions or persistent vomiting.
limiting oral fluid intake.

Recommended intravenous fluid schedules are varied and often cumbersome to apply in practice. All advocate that fluids for rehydration contain sodium but the suggested concentrations ranged from fifteen to eighty millimoles per litre. There is also considerable variation in the method of calculating fluid requirements and their subsequent rate of administration. Conversely most authors agree that in the absence of shock fluid deficits should be gradually replaced over forty eight to seventy two hours.

Attention to other aspects of management is also important. Most infants with dehydrating diarrhoeal disease have a metabolic acidosis on admission to the hospital. This may be exaggerated in the hypernatraemic state and appears related to the hypertonicity of the extracellular fluid and not the sodium concentration per se. A mild metabolic acidosis (base excess less than minus ten millimoles per litre) will correct spontaneously during rehydration. When more severe, partial correction with intravenous alkali is adviseable. The amount of alkali administered is calculated to half correct the base deficit. The administration of intravenous sodium bicarbonate in this manner is effective and does not appear to affect the serum sodium concentration significantly.
The majority of children with acute diarrhoeal disease also have a low total body potassium. There is no correlation between serum concentration and total body potassium and infants with normal serum values may have significant potassium depletion. Potassium is important in maintaining normal renal tubular function, and providing intracellular ions during rehydration of hypernatraemic children. Supplemental administration is recommended in all cases of hypernatraemic dehydration secondary to diarrhoeal disease. Where possible it should be given orally and when given intravenously should not exceed a concentration of forty millimoles per litre in the infusate.

A low serum calcium concentration in hypernatraemic individuals has been described. On occasions hypocalcaemia has been associated with convulsions but generally no untoward effects have been ascribed to the low serum concentrations. The low calcium level usually corrects spontaneously but to avoid possible tetany the addition of calcium gluconate to the intravenous fluids during rehydration has been advocated on occasions.
2.5. Summary

During diarrhoeal disease water loss is relatively greater than sodium loss. This predisposes towards hypernatraemia where the sodium concentration is greater than one hundred and fifty millimoles per litre. Because sodium is the principal osmotically active particle in the extracellular fluid and is largely excluded from the intracellular fluid by the sodium pump, hypernatraemia has a profound effect on body water distribution.

Water and sodium losses in diarrhoeal disease are from the extracellular fluid. When dehydration is associated with a normal sodium concentration there is a decrease in the volume of the extracellular fluid with little change in that of the intracellular fluid. As the sodium concentration rises increased extracellular fluid osmolality promotes the movement of water from cells to the extracellular fluid to restore osmotic equilibrium. This results in the volume of the extracellular fluid being relatively preserved while that of the intracellular fluid decreases.

Not all cells respond to a rise in extracellular fluid osmolality by water movement alone. Certain cells such as those of the brain have the ability to raise intracellular osmolality by the production of idiogenic osmoles. This limits movement of water out of the cells and preserves cell volume in the face of hypernatraemia. Idiogenic osmole production can only occur to the degree that will protect cell volume if the hypernatraemia develops slowly.
Because of the nature of the losses in diarrhoea, hypernatraemia might be expected to be the most common variety of dehydration. Owing to the efficiency of the homeostatic mechanisms of thirst and renal water conservation this is not so. It is the failure of homeostasis that appears to result in hypernatraemia.

The role of the kidney in the pathogenesis of hypernatraemia is uncertain. Some evidence suggests that the kidney might be a source of excess water loss aggravating the hypernatraemia, but this is controversial.

Despite the high serum sodium concentration the patients are believed to be depleted of body sodium. The raised sodium concentration may be partly the result of a mobilisation of endogenous sodium into the extracellular fluid. Bone sodium is a possible source of the endogenous load but the factors governing its movement are not clear.

Hypernatraemia occurs in ten to thirty per cent of admissions for diarrhoea. Clinical diagnosis is generally difficult as there are no features specific to the condition. The most commonly encountered changes are the signs of central nervous system dysfunction. Convulsions are not infrequent and their occurrence before or after starting therapy have a different prognostic significance. The mortality and morbidity in hypernatraemia is higher than with other forms of dehydration.
Improper fluid therapy may be associated with convulsions. Both the composition and the rate of the infusion are implicated in the pathogenesis of seizures. Shock has to be corrected rapidly but thereafter correction of the dehydration should be gradual to avoid convulsions. All fluid administered during rehydration should contain sodium.
Chapter 3.

Design and Purpose of the Study.

Introduction.

Part 1.

3.1. To investigate the pattern of renal sodium excretion and determine sodium retention during recovery in infants with hypernatraemic dehydration.

3.2. To examine the exchangeable sodium on admission in infants with hypernatraemic dehydration.

3.3. To measure blood volume and the change in the main body fluid compartments occurring during rehydration of infants with hypernatraemic dehydration.

3.4. To investigate the possible role of an endogenous sodium transfer being partially responsible for the raised sodium concentration in the extracellular fluid of infants with hypernatraemic dehydration.
Part 2.

3.5. To determine the incidence and seasonal variation of hypernatraemic dehydration in association with diarrhoeal disease.

3.6. To establish the clinical features most useful in distinguishing hypernatraemic from non hypernatraemic infants.

3.7. To determine the prognostic significance of coma and convulsions.

3.8. To assess the efficacy of a standard fluid therapy regimen for all infants with dehydrating diarrhoeal disease.
Introduction.

A number of important aspects of the pathophysiology and pathogenesis of hypernatraemic dehydration in diarrhoeal disease of infants remain to be clarified. Balance studies in some 41, 151 have shown sodium retention during recovery from hypernatraemia and this implies an initial total body sodium deficit. Others 32, 151 have shown a loss of sodium during recovery implying an initial total body sodium excess. Such studies have been limited in numbers and duration and while it is generally believed that children with hypernatraemic dehydration are total body sodium depleted this has not been adequately investigated. Sodium retention in some could be due to an inability to excrete sodium. This would result in an excessive accumulation of the ion.

The ability of the kidney to adequately excrete sodium and the importance of the kidney as a source of continued excess water loss needs investigation. Renal sodium excretion might have important therapeutic implications for the electrolyte composition of fluids used in rehydration.

The effect of hypernatraemic dehydration on extra- and intracellular fluid volume needs to be determined. The circumstantial belief that intracellular is proportionately or
even relatively more depleted than extracellular fluid volume may not always be correct.\textsuperscript{18} The possibility of endogenous transfer of sodium to the extracellular fluid contributing to hypernatraemia has not been explored.

The first part of the study was designed to investigate aspects of the pathophysiology and pathogenises of hypernatraemic dehydration outlined above. The second established the incidence of hypernatraemia in Cape Town and attempted to define those clinical features most useful in distinguishing hypernatraemic from non hypernatraemic dehydration. The prognostic significance and possible etiology of convulsions was investigated and the mortality and short term morbidity established. A standard fluid therapy regimen for infants with non hypernatraemic dehydration was used and its suitability in treating hypernatraemia assessed.
Part 1.

3.1. **To investigate the pattern of renal sodium excretion and determine sodium retention during recovery in infants with hypernatraemic dehydration.**

Infants with hypernatraemic dehydration are said to lack the ability to adequately excrete sodium in the urine. This belief is based largely on the examination of initial urine specimens in hypernatraemic infants and on experimental work in dogs rendered hypernatraemic by saline administration.

Whether the hyponatraemic urine found on admission in hypernatraemic infants is due to an immaturity of renal function, an osmotic diuresis from the hypernatraemia per se or a transient renal dysfunction due to the diarrhoea and dehydration is uncertain. If only a transient disturbance restoration of normal renal function and sodium excretion might be an important factor in the recovery of these infants. Continued limitation of sodium excretion and excessive urinary water loss could retard recovery. These would be important factors in determining the most appropriate sodium concentration of the fluid to be administered parenterally during rehydration.
To investigate the ability of the infants kidney to excrete sodium and the role of renal function in aiding recovery, a group of patients with hypernatraemic dehydration was studied.

Renal sodium excretion was analysed from the time of admission until the serum sodium had fallen and remained below one hundred and fifty millimoles per litre for about ninety hours. The pattern of urinary sodium concentration was related to changes in that of the serum. Sodium retention was measured during the period of study. The results were compared to those from a group of infants recovering from non hypernatraemic dehydration who were managed in the same way.

3.2. To determine the exchangeable sodium on admission in infants with hypernatraemic dehydration.

Exchangeable body sodium consists of the sodium in the extracellular fluid, cartilage and the fluid phase of bone. It is that portion of total body sodium which is affected by acute metabolic disturbances.

It may be accurately determined by a dilution technique using the radioactive isotope $^{24}\text{Na}$. The method is relatively simple but equilibration of isotope within the body requires about eighteen to twenty one hours. This is a disadvantage in an infant where the sodium status is changing
continuously with rehydration. The exchangeable sodium in the infant with hypernatraemic dehydration cannot be measured directly on admission. It has to be derived from the measured value obtained at eighteen to twenty one hours after admission and the sodium retention measured during this period.

To determine the body sodium status of infants with hypernatraemic dehydration following diarrhoea, exchangeable sodium was measured in a small group of these children. In each case the calculated value at admission was compared to that predicted from the infants rehydrated body weight and to reported values for infants without diarrhoea. The predicted value was derived from the formula of Forbes and Perley and the rehydrated weight was taken as the stable weight when off intravenous fluids.

3.3. To measure blood volume on admission and the change in the main body fluid compartments occurring during rehydration of infants with hypernatraemic dehydration.

Loss of sodium and water isotonic with plasma results in a decrease in the volume of the extracellular fluid with no change in that of the intracellular fluid. When only water is lost the concentration of the sodium remaining in the extracellular fluid rises and water is transferred from the intracellular fluid
to maintain osmotic equilibrium. Pure water loss affects both the extra- and intracellular fluid volumes. Because the intracellular fluid volume is larger than the extracellular the absolute loss of water from the former must exceed that of the latter if osmotic equilibrium is to be maintained. Conversely relative loss of water must be identical and the ratio of their volumes remains unchanged.

When water loss is disproportionately greater than sodium the concentration of the remaining sodium in the extracellular fluid rises and transfer of water from the intracellular to the extracellular fluid occurs. The fluid loss may be regarded as an isotonic fraction from the extracellular fluid and a pure water fraction from both the intra- and extracellular fluid in proportion to their relative sizes. Under these circumstances the extracellular fluid is relatively more depleted than the intracellular.

Transfer of endogenous sodium to the extracellular fluid occurring at this stage (for example by mobilisation from bone stores) would raise the osmolality further and more water would leave the cells to restore osmotic equilibrium. The depleted extracellular fluid volume would be partially restored and a stage would be reached when intracellular fluid volume was relatively more depleted than extracellular.
Blood and extracellular fluid volume may be determined during the acute stage of hypernatraemic dehydration. Blood volume can be measured accurately using $^{99\text{Tc}}$ labelled erythrocytes. Many methods exist for the measurement of extracellular fluid volume but for simplicity and accuracy, determination of the thiosulphate space is probably the best. During rehydration changes in the extracellular fluid volume may be measured directly by repeated thiosulphate space determinations. Corresponding changes in total body water may be regarded as proportional to changes in body weight. In such short term studies changes in lean body mass do not have to be taken into account. Intracellular fluid volume changes can thus be derived from the difference between the change in extracellular fluid volume and that of total body weight.

Blood volume and thiosulphate space were measured on admission in a small group of children with hypernatraemic dehydration. The thiosulphate space measurement was repeated after a period of rehydration. Change in body weight during this time was determined and the change of the intracellular fluid volume was calculated. The results permitted the effect of hypernatraemic dehydration on both the extra- and intracellular fluid volumes to be assessed.
To investigate the possible role of an endogenous sodium transfer being partially responsible for the raised sodium concentration in the extracellular fluid of infants with hypernatraemic dehydration.

The sodium content of the extracellular fluid may be determined from the product of the absolute volume of this space and the serum sodium concentration. During recovery from hypernatraemic dehydration repeated measurements of extracellular fluid volume and serum sodium concentration permit changes in the sodium content of the extracellular fluid to be established.

An increase in extracellular fluid sodium content may be due to administration of exogenous sodium, an endogenous sodium transfer from some body store or a combination of these mechanisms. A decrease in extracellular fluid sodium content may follow excretion of sodium, transfer of sodium out of the extracellular fluid to another site or a combination of these factors.

In order to establish which factors are responsible for changes in extracellular fluid sodium content it is necessary to know the total retention of sodium by the body in the period under study. For example a positive retention of sodium equal to the
increase in extracellular fluid sodium content implies exogenous sodium administered remained entirely confined to the extracellular fluid. Sodium retention exceeding the increase in extracellular fluid sodium content suggests the exogenous sodium administered was partly retained in the extracellular fluid space while the rest was transferred to some other site such as the bone or the intracellular fluid.

If events during recovery are the reverse of those occurring during development of hypernatraemic dehydration their study will aid in the understanding of the pathogenesis of the condition. Accordingly sodium retention and change in extracellular fluid sodium content during a period of rehydration were studied in a group of infants recovering from hypernatraemic dehydration. Extracellular fluid volume was measured on admission and repeated after a period of intravenous fluid therapy. Sodium content of the extracellular fluid was calculated on each occasion and compared to the retention of sodium during the same time. The possible changes involved in returning serum sodium concentration to normal were examined.
Part 2.

3.5 To determine the incidence and seasonal variation of hypernatraemic dehydration in association with diarrhoeal disease.

Studies from unselected groups on the incidence of hypernatraemic dehydration secondary to diarrhoeal disease are limited. The majority of reports on the incidence are based on the study of selected groups of more severely ill infants. Selection on this basis might include many hypernatraemic infants as they often manifest signs of central nervous system dysfunction and appear extremely ill on admission. This may exaggerate the incidence of the electrolyte disturbance.

There is discrepancy between reports on the effects of climatic changes on the incidence of hypernatraemia. Some authors have found a marked seasonal variation while others have not.

To establish more precisely the incidence of hypernatraemic dehydration a large number of unselected children were assessed prospectively. All children with dehydrating diarrhoea requiring admission to the Drip Room at the Childrens Hospital over a twelve month period were assessed. Serum sodium concentration was determined on every child and any with a level exceeding
one hundred and fifty millimoles per litre was included in the study. To assess seasonal variation of the condition the monthly incidence of hypernatraemia among the infants admitted with diarrhoeal disease was determined.

3.6. To establish the clinical features most useful in distinguishing hypernatraemic from non hypernatraemic infants.

Early recognition of the infant with hypernatraemic dehydration is frequently stressed as important as it enables modification of treatment. Determination of serum sodium concentration is the only certain means of confirming the diagnosis. This is not widely available as a routine investigation particularly in the less developed areas of the world where dehydrating diarrhoea is a major problem. Recognition of the hypernatraemic infant in these areas is largely dependant on clinical features. Opinions differ over the ease with which the diagnosis can be made clinically but the majority of authors have found it difficult. To determine those clinical features most reliable in the diagnosis a large number of hypernatraemic children were assessed. Detailed histories were obtained from the parent or guardian and each case was carefully examined for those features which have been associated with this electrolyte
disturbance. The incidence of positive findings was compared to that of a group of infants with non hypernatraemic dehydration assessed in the same way.

3.7. To determine the prognostic significance of coma and convulsions.

Coma and convulsions occurring prior to admission and treatment of the infant with hypernatraemic dehydration are said to carry a poor prognosis. They probably result from intracranial bleeding. Extensive bleeding results in death of the patient while lesser degrees may cause permanent central nervous system dysfunction.

In contrast convulsions occurring for the first time only after starting fluid therapy may not have such a poor prognosis. They are believed to result from reversible cerebral changes associated with rapid fluid and electrolyte shifts. The majority of affected infants seem to recover completely.

In an attempt to establish the prognostic significance of coma and convulsions all hypernatraemic infants admitted during a twelve month period were assessed. Any with one or other of these central nervous system features was included. In the
event of death a post mortem examination was performed providing parental consent was obtained.

Where convulsions occurred only after starting treatment an attempt was made to relate their onset to the duration of fluid therapy, the volume of fluid administered, the initial serum sodium concentration and the rate of fall of the serum sodium concentration. As far as possible other causes for the convulsions were excluded. An attempt was made to follow up all affected children for as long as possible after discharge from hospital.

3.8. To assess the efficacy of a standard fluid therapy regimen for all infants with dehydrating diarrhoea.

If a standard fluid schedule can be successfully used for all infants with dehydrating diarrhoea regardless of the serum sodium concentration, the need to recognise the hypernatraemic individual becomes less important. The large number of children each year that need parenteral fluid therapy for diarrhoea dictates that the regimen used be simple. The effectiveness of the scheme presently in use at the Children's Hospital for the treatment of infants with non hypernatraemic dehydration is reflected by a mortality consistently in the region of one percent over the last five years. This compares
favourably with that of the management of dehydrating diarrhoea anywhere in the world. 3, 41, 79, 97, 114, 126

The scheme is simple and based in the first instance on the treatment of shock and partial correction of severe acidosis. Thereafter all intravenous fluids are administered as a standard electrolyte and dextrose solution given at a constant calculated rate. All calculations of fluid requirements are based on the clinical features of the degree of dehydration and the body weight.

To establish the efficacy of such a fluid schedule in hypernatraemia a large number of children with hypernatraemic dehydration secondary to diarrhoeal disease were managed in this way. Blood was taken at regular intervals to monitor the return of serum sodium to normal levels. Any adverse reactions that might be attributed to the parenteral fluid therapy were recorded. For comparison a group of children with non hypernatraemic dehydration managed according to the standard schedule was similarly assessed and followed up until discharge from the hospital.
Chapter 4.

Patients and Methods.

Part 1.

4.1. Clinical material.
- criteria for patient selection.

4.2. Urinary sodium excretion and sodium retention during recovery.

4.3. Determination of exchangeable sodium and blood volume on admission, change in extracellular fluid volume during rehydration and transfer of sodium between the various body stores during recovery from hypernatraemic dehydration.
- measured exchangeable sodium.
- predicted exchangeable sodium.
- measurement of blood volume.
- measurement of ECFV.
- sodium content of ECFV.
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4.1. **Clinical material.**

The investigations were undertaken on twenty four infants with acute dehydrating diarrhoeal disease requiring admission to the Drip Room at the Red Cross War Memorial Childrens Hospital. Fourteen, designated the hypernatraemic group, were selected because their serum sodium concentration on admission exceeded one hundred and fifty millimoles per litre. The remaining ten comprised the non hypernatraemic group. As soon as the initial serum sodium concentration was available the infant was transferred to the metabolic unit and nursed on a metabolic bed for the period of study. Of the fourteen hypernatraemic and ten non hypernatraemic patients all were included in a study of urinary sodium excretion and (with the exception of one non hypernatraemic patient) of sodium retention during recovery. Seven of the hypernatraemic patients also had exchangeable sodium, blood and extracellular fluid volume and sodium transfer measured during rehydration.

The following general criteria were used for selecting the patients:

1. Only male infants were chosen to facilitate separate collection of stools and urine.
2. A history of recent onset of diarrhoea with or without vomiting.
3. Clinical evidence of dehydration requiring admission to hospital for rehydration with intravenous fluids.
4. The absence of an associated systemic infection such as pneumonia.

Written consent for inclusion in the study was obtained from the accompanying parent.

4.2. **Urinary sodium excretion and sodium retention during recovery.**

The time of starting the study was designated zero hours and blood was taken at this stage for serum sodium determination. Routine investigation and management of the infants was as outlined in part two of the study.

Each stool and urine specimen passed was collected separately. The time of passing the specimen was noted and the volume of each urine and weight of individual stool specimens recorded. In the hypernatraemic group the study continued throughout the period of hypernatraemia and for about ninety hours after the serum sodium had fallen and remained below one hundred and fifty millimoles per litre. In the non hypernatraemic group the
collection of specimens continued for about ninety hours after starting the study.

Sodium concentration was determined on an aliquot of each stool and urine. The sodium content of each specimen was calculated as the product of the sodium concentration and the volume or weight of the specimen. The pattern of renal sodium excretion was determined by first plotting the sodium concentration and then the sodium content of each urine specimen against the time that the specimen was passed. In each case the excretory pattern was related to the patient's serum sodium concentration determined at intervals during the period of study. Urinary sodium excretory patterns in hypernatraemic infants were compared to those in the infants with non hypernatraemic dehydration.

The volume of all fluid administered intravenously was accurately determined by weighing the containers when full and again when empty and recording the difference. The volume of all fluid given orally was similarly determined by weighing the feeding bottles before and after feeds. An aliquot of the intravenous fluids and each feed was withdrawn for determination of sodium concentration before the initial weighing of the containers. The absolute amount of sodium given could then be calculated.
Total sodium intake during the period of study was calculated from the sum of all sodium administered both intravenously and orally. Sodium retention was determined by subtracting from the intake all sodium lost in the stools and urine. Sodium retention of the hypernatraemic group was compared to that of the non hypernatraemic.

4.3. Determination of exchangeable sodium and blood volume on admission, change in extracellular fluid volume during rehydration and transfer of sodium between the various body fluid stores during recovery from hypernatraemic dehydration.

During the investigation of renal sodium excretion and sodium retention seven of the hypernatraemic infants were also involved in these additional studies. The rate of intravenous fluid administration in these infants was controlled by means of an IVAC drip rate controller. The time of any adjustment to the rate was recorded. The time of administering each feed was noted. This information permitted calculation of sodium intake for any specified time interval during the study.

Radioactive sodium ($^{24}$Na) in a dose of 0.5 microcurie per kilogram body weight was injected intravenously immediately after taking the first blood sample at zero hours. Blood was
taken by venisection at four hourly intervals thereafter for
between twenty two and twenty five hours. When taking blood
care was taken to avoid using the site where the $^{24}$Na had been
injected. The time of taking each sample was recorded. Serum
sodium concentration was determined on each specimen and an
aliquot of serum was immediately counted for specific activity of
$^{24}$Na. An aliquot of each stool and urine passed during this
period was also counted for specific activity.

A standard sample of the $^{24}$Na was counted at regular intervals
to allow for appropriate correction for decay to be made.
Serum $^{24}$Na disappearance curves were constructed and the point
of apparent equilibration of the injected $^{24}$Na determined. The
volume of distribution of the $^{24}$Na at equilibration was obtained
from the following equation.

$$\frac{\text{\textit{Na counts injected} } - \text{\textit{Na counts excreted (in stools and urine)}}}{\text{\textit{Na counts per millilitre serum}}}$$

Exchangeable sodium was calculated as the product of the
volume of distribution of $^{24}$Na (in litres) and the serum sodium
centration at the time of equilibrium. To derive the
exchangeable sodium value on admission the sodium retention
between zero hours and the time of equilibration was subtracted
from the measured exchangeable sodium value. The result was expressed in millimoles per kilogram body weight to facilitate comparison between the patients.

Following recovery the infants rehydrated weight (i.e. the stable weight off intravenous fluids) was used to determine the predicted exchangeable sodium for the individual. The predicted value was obtained from the equation of Forbes and Perley\textsuperscript{50b} as follows:

\[
\text{Exchangeable sodium} = 0.281 \times (\text{weight in grams})^{0.829}
\]

The value obtained was expressed in millimoles per kilogram body weight and was compared to that calculated for the time of admission. A comparison was also made with reported values of exchangeable sodium for healthy infants of the same age.\textsuperscript{50b}

Blood and extracellular fluid volume was measured within half an hour of starting the study. Blood volume was determined by means of technecium (\textsuperscript{99m}Tc) labelled erythrocytes using a commercial kit (TCK, CIS-Sorin). The blood volume was expressed in millilitres per kilogram body weight for ease of comparison between patients. The results were compared to the reported normal values for infants without diarrhoea.

Extracellular fluid volume was measured by determining the thiosulphate space in a manner similar to that described by
Friis-Hansen. The extracellular fluid volume measurement was repeated after about twenty four hours in six of the patients. At this stage all had improved both clinically and biochemically. In one infant (patient no. 3 of table 5.1) the second extracellular fluid volume measurement was deferred for sixty nine hours because of convulsions and the general poor clinical state of the infant prior to this time. Extracellular fluid volume was recorded both as an absolute volume and as a percentage of body weight. The change in extracellular fluid volume between the two measurements of the thiosulphate space was calculated in each case.

The infant was weighed immediately prior to each extracellular fluid volume measurement and any change in body weight recorded. This was taken to represent a change in total body water. The difference between the change in total body water and extracellular fluid volume represented a change in intracellular fluid volume. In each case the change in extracellular fluid volume was compared to the corresponding change in intracellular fluid volume. The effects of hypernatraemic dehydration on the volume of the two major body fluid compartments was assessed.

Serum sodium concentration was determined at the time of each extracellular fluid volume measurement. Sodium content of the
extracellular fluid was calculated as the product of the serum sodium concentration and the absolute volume (in litres) of the extracellular fluid space. The change in sodium content between the two extracellular fluid volume measurements was determined.

Sodium retention between the extracellular fluid volume measurements was calculated from the sodium intake via intravenous and oral fluids less the sodium loss in the stools and urine during this time. Sodium retention was compared to the change in extracellular fluid sodium content. The data was analysed for possible mechanisms involved in returning sodium concentration to normal during recovery from hypernatraemic dehydration.
Part 2.

4.4. Incidence and clinical features associated with hypernatraemic dehydration

All children admitted with dehydrating diarrhoeal disease to the Drip Room between 1st March 1978 and 28th February 1979 had serum sodium concentrations determined on admission. Those with an initial level above one hundred and fifty millimoles per litre were referred to the author as soon as the serum sodium concentration was known for assessment and supervision of further management. The monthly incidence of hypernatraemic dehydration was determined by expressing the number of hypernatraemic admissions each month as a percentage of the total admissions for diarrhoeal disease. The results were analysed to assess whether seasonal climatic variation had any effect on the incidence of hypernatraemia.

Fifty consecutive children requiring admission for dehydrating diarrhoea between 0900 hours and 1700 hours Mondays to Fridays and in whom the initial serum sodium concentration was less than one hundred and fifty millimoles per litre were similarly referred. They were assessed and their management supervised in the same way as the hypernatraemic infants.

4.5. Data Collection

The notes of the admitting medical officer were examined to see if the diagnoses of hypernatraemia had been clinically suspected.
prior to receiving the results of the serum sodium concentration. The age, sex and height were recorded and the infants were weighed on admission and at least daily thereafter.

In the history particular note was made of anorexia with decreased fluid intake prior to admission. The possible administration of excess salt or solute was ascertained by obtaining details of the volume and composition of all fluids given to the infant during the previous forty eight hours.

The patients were fully examined. Dehydration was clinically assessed on the basis of loss of tissue turgor, dryness of mucous membranes, sunken eyes and a depressed fontanelle. This was estimated and recorded as not dehydrated if none of the features was present, five per cent dehydrated if they were apparent and ten per cent dehydrated if they were marked. Shock was recorded if there was poor peripheral capillary perfusion as judged by a capillary filling time that was greater than four seconds.

Any infant suspected clinically of having a pulmonary infection had a chest x-ray for confirmation. Tachypnoea was attributed to an associated chest infection only in those cases with radiological evidence of consolidation.
Particular attention was paid to the status of the central nervous system. Alteration in the level of consciousness was noted and recorded as follows:

1. Drowsy but rouseable.
2. Depressed level of consciousness but with purposeful response to painful stimuli.
3. Depressed level of consciousness with semi-purposeful response to painful stimuli only.
4. Coma with no response to painful stimuli.

Other features recorded included hyper- and hypotonia, hyperreflexia and convulsions.

The rehydrated weight was recorded after treatment as the stable weight when off intravenous fluids and in the absence of edema. The actual degree of dehydration on admission was calculated in retrospect from the admission and rehydrated weights. This was compared to the clinical estimate of dehydration made at the initial examination. If the clinical estimate differed by more than 2.5 per cent from the calculated dehydration this was considered significant and recorded. The nutritional status of the infant was retrospectively assessed using the rehydrated weight and the Boston percentile charts of weight for age.
Prior to discharge from hospital the infants were examined for features suggestive of residual central nervous system dysfunction. Any suspected of having such features were requested to attend a follow-up clinic conducted by the author. Their further progress was monitored and where necessary they were referred to the developmental clinic for assessment and further management.

4.6. Data Analysis.

To establish those clinical features most useful in distinguishing hypernatraemic from non-hypernatraemic infants the two groups were compared for the following:

- **a.** Age
- **b.** Sex
- **c.** Nutritional status
- **d.** A history of anorexia
- **e.** A history of prior ingestion of excess salt or solute
- **f.** A 'doughy' feel to the skin
- **g.** An associated chest infection confirmed radiologically
- **h.** Features of central nervous system dysfunction

The number of infants in each group in whom the degree of dehydration was clinically underestimated was compared.
Coma or convulsions occurring prior to treatment were recorded separately from those occurring for the first time after the start of parenteral fluid therapy. The time of occurrence of the coma or convulsions was related to the subsequent clinical course of the infant. In those occurring for the first time after the start of intravenous fluids an attempt was made to relate the onset to the initial serum sodium concentration, the amount of intravenous fluid received, the rate of decline of the serum sodium concentration and the serum calcium concentration.

Mortality among the hypernatraemic infants was compared to that for all infants with diarrhoea as well as that for infants with non hypernatraemic dehydration requiring admission to the Drip Room during the twelve month period. Morbidity, which included features of residual central nervous system dysfunction, peripheral gangrene or any complication which might have resulted from the fluid therapy was determined for both hyper- and non hypernatraemic infants. The two groups were compared for morbidity.

In all comparisons between the two groups the Chi square test was used.
4.7. Investigation and management.

On admission blood was taken for estimation of acid base status and serum electrolytes. These were repeated as often as necessary to monitor the patients progress and ensure the serum sodium concentration in the hypernatraemic infants fell and remained below one hundred and fifty millimoles per litre. Total protein, serum albumin and calcium were determined in a large number of the hypernatraemic patients. Other investigations were performed where clinically indicated.

Fluid therapy was the same for all patients. Any infant assessed clinically as being shocked was given an initial intravenous infusion of an isonatraemic plasma volume expander (Haemacceil). A volume of twenty millilitres per kilogram body weight was infused as rapidly as possible and assessment of response was based on improvement in capillary perfusion. If still inadequate a further ten millilitres per kilogram body weight was infused rapidly. Any infant with persistent poor capillary perfusion thereafter had a central venous catheter inserted for the monitoring of central venous pressure. Further fluid and drug therapy for the treatment of shock in these cases was guided by the central venous pressure.

Severe metabolic acidosis (pH < 7.25) was partially corrected with intravenous sodium bicarbonate. The amount of an eight
per cent solution calculated to half correct the base deficit was
given as a bolus injection over a five minute period.

After correction of shock, or where this was not initially
present, all fluids given intravenously were as half strength
Darrow's solution in five per cent dextrose water. The volume
of fluid for rehydration was calculated on the basis of the
clinical assessment of dehydration. Fifty millilitres per kilogram
body weight was given for five per cent and one hundred
millilitres per kilogram for ten per cent dehydration. This
volume plus a maintenance volume of one hundred and twenty
millilitres per kilogram body weight per day was infused at a
constant rate over the next twenty four hours.

Providing vomiting or abdominal distension did not occur oral
half strength Darrows in five per cent dextrose water was given
at three hourly intervals starting three to twelve hours after
admission. With the introduction of oral fluids the volume of
fluid given intravenously was reduced so that the total daily
volume did not exceed the calculated requirements.

The infants were assessed at three to four hourly intervals and
fluid requirements recalculated. Providing there was clinical
and biochemical improvement oral feeds of a low solute cows milk protein formula (S26) were introduced about twenty four hours after admission. Parenteral antibiotics were given only if clinically indicated.
### Chapter 5.

**Results.**

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Part 1.

Individual details of the infants in this part of the study are shown in table 5.1. In the hypernatraemic patients initial serum sodium concentration ranged from 151 to 177 millimoles per litre and in the non hypernatraemic from 120 to 147 millimoles per litre.

The median for the degree of dehydration, calculated in retrospect from the admission and rehydrated weight, was 8.9 per cent (range 4.1 to 12.7%) in the hypernatraemic and 6.3 per cent (range 4.6 to 10.7%) in the non hypernatraemic group. As a group the hypernatraemic were significantly more dehydrated than the non hypernatraemic. (Mann-Whitney u test \( p<0.01 \)).

5.a Urinary sodium excretion and sodium retention during recovery

Urinary excretory patterns of sodium concentration and sodium content in the hypernatraemic patients are shown in figures 5.1 to 5.14 and those for the non hypernatraemic patients in figures 5.15 to 5.24. Because the volume of individual urine specimens remained fairly constant in a particular infant the excretory pattern for sodium concentration resembled that for sodium content in each case.
Table 5.1. Individual details of the patients

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Hypernatraemic group

1. 1.25 2800 3100 163/4.7
2. 9.50 7880 8220 165/2.3
3. 8.00 6650 7200 170/3.9
4. 1.25 3480 3900 151/4.5
5. 5.75 7100 7600 156/4.3
6. 9.00 8390 9200 177/3.0
7. 2.00 2930 3300 162/4.4
8. 10.25 9700 10500 172/3.3 Pos.
9. 13.25 9870 10600 161/2.4 Pos.
10. 3.00 4840 5520 154/4.1
11. 4.25 4220 4700 158/4.5 Pos.
12. 4.75 4690 5150 167/5.0
13. 3.75 5750 6150 158/3.0 Pos.
14. 6.00 6420 7350 153/3.7

Non hypernatraemic group

15. 5.75 6200 6580 126/3.4
16. 6.00 6580 7000 143/3.1
17. 11.25 8510 9200 142/3.5
18. 3.25 5400 5800 147/4.0
19. 6.00 7200 7600 136/3.4
20. 2.00 3130 3400 120/4.9
21. 5.00 2760 3100 132/5.8
22. 16.00 7750 8120 140/3.7
23. 16.50 7050 7530 135/3.3
24. 1.50 2300 2450 143/3.4
Figure 5.1a: Patient 1. Urine & Serum Sodium Concentrations against Time
Figure 5.1b: Patient 1. Urine Sodium Content & Serum Sodium Concentration against Time.
Figure 5.2a: Patient 2. Urine & Serum Sodium Concentrations against Time.
Figure 5.2b: Patient 2. Urine Sodium Content & Serum Sodium Concentration against Time.
Figure 5.3a: Patient 3. Urine & Serum Sodium Concentrations against Time
Figure 5.3b: Patient 3. Urine Sodium Content & Serum Sodium Concentration against Time
Figure 5.4a: Patient 4. Urine & Serum Sodium Concentrations against Time
Figure 5.4b: Patient 4. Urine Sodium Content & Serum Sodium Concentration against Time.

---

Note: The graph shows the relationship between urine sodium content and serum sodium concentration over time. The x-axis represents time in hours, while the y-axis represents the concentration levels. The data points indicate a significant increase in serum sodium concentration compared to urine sodium content over the observed period.
Figure 5.5a: Patient 5. Urine & Serum Sodium Concentrations against Time
Figure 5.5b: Patient Urine Sodium Content & Serum Sodium Concentration against Time.
Figure 5.6a: Patient 6. Urine & Serum Sodium Concentrations against Time
Figure 5.6b: Patient 6. Urine Sodium Content & Serum Sodium Concentration against Time
Figure 5.7a: Patient 7. Urine & Serum Sodium Concentrations against Time
Figure 5.7b: Patient 7. Urine Sodium Content & Serum Sodium Concentration against Time

HOURS

URINE

SERUM

200 175 150 125 100

20 15 10 5 0

0 25 50 75 100 125 150
Figure 5.8a: Patient 8. Urine & Serum Sodium Concentrations against Time.
Figure 5.8b: Patient 8. Urine Sodium Content & Serum Sodium Concentration against Time

![Graph showing Urine Sodium Content & Serum Sodium Concentration against Time]
Figure 5.9a: Patient 9. Urine & Serum Sodium Concentrations against Time
Figure 5.9b: Patient 9. Urine Sodium Content & Serum Sodium Concentration against Time.
Figure 5.10a: Patient 10. Urine & Serum Sodium Concentrations against Time

---

**Urine Sodium Concentration**

- 0 to 50 mmol/l
- 50 to 100 mmol/l
- 100 to 150 mmol/l
- 150 to 200 mmol/l
- 200 to 250 mmol/l
- 250 to 300 mmol/l
- 300 to 350 mmol/l
- 350 to 400 mmol/l

**Serum Sodium Concentration**

- 100 to 125 mmol/l
- 125 to 150 mmol/l
- 150 to 175 mmol/l
- 175 to 200 mmol/l

---

**Hours**

- 0 to 150 hours

---

Legend:

- Dashed line: Urine
- Solid line: Serum
Figure 5.10b: Patient 10. Urine Sodium Content & Serum Sodium Concentration against Time.
Figure 5.11: Urine & Serum Sodium Concentrations against Time

\[ \text{Urine Sodium Concentrations} \]

\[ \text{Serum Sodium Concentrations} \]
Figure 5.1b: Patient 11: Urine Sodium Content & Serum Sodium Concentration against Time
Figure 5.12a: Patient 12. Urine & Serum Sodium Concentrations against Time
Figure 5.12b: Patient 12. Urine Sodium Content & Serum Sodium Concentration against Time.
Figure 5.13a: Patient 13. Urine & Serum Sodium Concentrations against Time
Figure 5.13b: Patient 13. Urine Sodium Content & Serum Sodium Concentration against Time
Figure 5.14a: Patient 14. Urine & Serum Sodium Concentrations against Time
Figure 5.14b: Patient 14. Urine Sodium Content & Serum Sodium Concentration against Time
Figure 5.15a: Patient 15. Urine & Serum Sodium Concentrations against Time
Figure 5.15b: Patient 15. Urine Sodium Content & Serum Sodium Concentration against Time.
Figure 5.16a: Patient 16. Urine & Serum Sodium Concentrations against Time
Figure 5.16b: Patient 16. Urine Sodium Content & Serum Sodium Concentration against Time
Figure 5.17a: Patient 17. Urine & Serum Sodium Concentrations against Time
Figure 5.17b: Patient 17. Urine Sodium Content & Serum Sodium Concentration against Time
Figure 5.18a: Patient 18. Urine & Serum Sodium Concentrations against Time.

- **Urine**
  - 400
  - 350
  - 300
  - 250
  - 200
  - 150
  - 100
  - 50
  - 0

- **Serum**
  - 200
  - 175
  - 150
  - 125
  - 100
  - 75
  - 50
  - 25
  - 0

**HOURS**
- 250
- 200
- 150
- 100
- 50
- 0

- **Sodium Levels**
  - 0
  - 50
  - 100
  - 150
  - 200
  - 250
  - 300
  - 350
  - 400

- **X** marks the sodium levels on both urine and serum.

- **Legend:**
  - Solid line: Urine
  - Dashed line: Serum
Figure 5.18b: Patient 18. Urine Sodium Content & Serum Sodium Concentration against Time.
Figure 5.19a: Patient 19. Urine & Serum Sodium Concentrations against Time.

The graph shows the sodium concentrations in both urine and serum over time. The x-axis represents time in hours, ranging from 0 to 400, while the y-axis shows sodium concentration levels. The data points indicate fluctuations in sodium levels at different time intervals.
Figure 5.19b: Patient 19. Urine Sodium Content & Serum Sodium Concentration against Time.
Figure 5.20a: Patient 20. Urine & Serum Sodium Concentrations against Time
Figure 5.20b: Patient 20. Urine Sodium Content & Serum Sodium Concentration against Time.
Figure 5.21a: Patient 21. Urine & Serum Sodium Concentrations against Time
Figure 5.21b: Patient 21. Urine Sodium Content & Serum Sodium Concentration against Time
Figure 5.22a: Patient 22. Urine & Serum Sodium Concentrations against Time.
Figure 5.23a: Patient 23. Urine & Serum Sodium Concentrations against Time

- **Urine Sodium Concentrations** are indicated by X markers along the dashed line.
- **Serum Sodium Concentrations** are indicated by markers along the solid line.

The graph shows the fluctuations in sodium concentrations over time, withURINE concentrations generally lower than SERUM concentrations.
Figure 5.23b: Patient 23. Urine Sodium Content & Serum Sodium Concentration against Time
Figure 5.24a: Patient 24. Urine & Serum Sodium Concentrations against Time.
Figure 5.24b: Patient 24. Urine Sodium Content & Serum Sodium Concentration against Time
Eleven of the 14 hypernatraemic patients had comparable urinary sodium excretory patterns during recovery. Initial urine sodium concentrations tended to be low with a urine to plasma (u/p) sodium ratio less than 1. After a few hours of rehydration with intravenous fluids the urine sodium concentration rose and the u/p sodium ratio exceeded 1. The fall in serum sodium concentration to below 150 millimoles per litre coincided with the peak level of urinary sodium concentration.

In three cases (patients 6, 10 & 14) urinary sodium excretory patterns did not resemble that of the majority of the hypernatraemic group. Despite a single late peak in the urine sodium concentration in patient 10 the u/p sodium ratio in these patients remained below 1 at all times. There was no apparent correlation between the fall in serum sodium concentration and the output of sodium in the urine in these 3 patients.

Eight of the 10 non hypernatraemic patients had similar urinary sodium excretory patterns. In contrast to the majority of the hypernatraemic patients the u/p sodium ratio in these infants remained below 1 throughout the period of study. In 3 cases (patients 15, 20 & 21) urinary sodium concentrations were very low. These infants also had the lowest recorded serum sodium concentrations in the group (table 5.1).
The remaining non hypernatraemic patients (nos. 18 & 19) had urinary sodium excretory patterns that resembled the majority of the hypernatraemic group. In one (patient 18) serum sodium concentration rose briefly from 147 to 152 millimoles per litre shortly after admission and the peak in urinary sodium concentration coincided with the return of serum sodium to below 150 millimoles per litre.

Total loss of sodium via stools and urine, total sodium intake via intravenous and oral fluids and the calculated total retention of sodium and retention per kilogram body weight for the period of study in 23 of the 24 patients are shown in table 5.2. In one infant (patient 15) the stools were discarded in error prior to the weight of the specimens being recorded.

Ten of the hypernatraemic and all the non hypernatraemic infants had positive sodium retention during recovery. Of the remaining 4 hypernatraemic infants 2 (patients 9 & 13) had virtually zero sodium retention and 2 (patients 2 & 5) had negative retention. Four infants (patients 8, 9, 11 & 13) had a definite history of excessive salt or solute ingestion prior to admission (table 5.1). They all had a positive sodium retention whereas the two with negative sodium retention gave no such history.
The difference between the two groups for sodium retention per kilogram body weight was not significant, (Mann-Whitney u test $p > 0.05$).
Table 5.2. Total intake and loss of sodium via stool and urine and sodium retention in hyper- and non hypernatraemic infants recovering from diarrhoea.

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Stool losses (mmol)</th>
<th>Urinary losses (mmol)</th>
<th>Total losses (mmol)</th>
<th>Total intake (mmol)</th>
<th>Sodium retention (mmol)</th>
<th>Sodium retention (mmol) per kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypernatraemic group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>3.1</td>
<td>51.5</td>
<td>54.6</td>
<td>68.4</td>
<td>13.8</td>
<td>4.7</td>
</tr>
<tr>
<td>2.</td>
<td>14.1</td>
<td>204.1</td>
<td>218.2</td>
<td>200.9</td>
<td>-</td>
<td>17.3</td>
</tr>
<tr>
<td>3.</td>
<td>14.9</td>
<td>141.8</td>
<td>156.7</td>
<td>186.5</td>
<td></td>
<td>29.8</td>
</tr>
<tr>
<td>4.</td>
<td>3.9</td>
<td>45.9</td>
<td>50.8</td>
<td>94.7</td>
<td></td>
<td>43.9</td>
</tr>
<tr>
<td>5.</td>
<td>6.2</td>
<td>108.4</td>
<td>114.6</td>
<td>104.8</td>
<td>-</td>
<td>9.8</td>
</tr>
<tr>
<td>6.</td>
<td>173.5</td>
<td>105.6</td>
<td>279.1</td>
<td>366.1</td>
<td></td>
<td>87.0</td>
</tr>
<tr>
<td>7.</td>
<td>73.9</td>
<td>40.2</td>
<td>114.1</td>
<td>166.1</td>
<td></td>
<td>52.0</td>
</tr>
<tr>
<td>8.</td>
<td>10.8</td>
<td>140.9</td>
<td>151.7</td>
<td>185.3</td>
<td></td>
<td>33.6</td>
</tr>
<tr>
<td>9.</td>
<td>42.7</td>
<td>77.5</td>
<td>120.3</td>
<td>121.3</td>
<td>1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>10.</td>
<td>100.9</td>
<td>31.9</td>
<td>132.8</td>
<td>204.9</td>
<td>72.1</td>
<td>13.0</td>
</tr>
<tr>
<td>11.</td>
<td>20.5</td>
<td>105.3</td>
<td>125.8</td>
<td>167.1</td>
<td></td>
<td>41.3</td>
</tr>
<tr>
<td>12.</td>
<td>86.2</td>
<td>103.6</td>
<td>189.8</td>
<td>284.2</td>
<td></td>
<td>94.4</td>
</tr>
<tr>
<td>13.</td>
<td>94.1</td>
<td>86.7</td>
<td>180.8</td>
<td>182.8</td>
<td>2.0</td>
<td>0.3</td>
</tr>
<tr>
<td>14.</td>
<td>60.2</td>
<td>52.2</td>
<td>112.4</td>
<td>192.7</td>
<td></td>
<td>80.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non hypernatraemic group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>------</td>
<td>1.1</td>
<td>------</td>
<td>107.8</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>36.0</td>
<td>104.3</td>
<td>140.3</td>
<td>177.4</td>
<td>37.1</td>
<td>5.3</td>
</tr>
<tr>
<td>17.</td>
<td>41.7</td>
<td>51.2</td>
<td>92.9</td>
<td>249.8</td>
<td>156.8</td>
<td>17.0</td>
</tr>
<tr>
<td>18.</td>
<td>28.8</td>
<td>60.3</td>
<td>89.1</td>
<td>125.4</td>
<td></td>
<td>36.3</td>
</tr>
<tr>
<td>19.</td>
<td>23.7</td>
<td>120.7</td>
<td>144.4</td>
<td>215.8</td>
<td></td>
<td>71.4</td>
</tr>
<tr>
<td>20.</td>
<td>136.8</td>
<td>1.4</td>
<td>138.2</td>
<td>223.5</td>
<td></td>
<td>85.3</td>
</tr>
<tr>
<td>21.</td>
<td>29.9</td>
<td>4.2</td>
<td>34.1</td>
<td>81.2</td>
<td></td>
<td>47.1</td>
</tr>
<tr>
<td>22.</td>
<td>35.6</td>
<td>59.9</td>
<td>95.5</td>
<td>113.5</td>
<td></td>
<td>18.0</td>
</tr>
<tr>
<td>23.</td>
<td>100.7</td>
<td>123.1</td>
<td>223.8</td>
<td>313.1</td>
<td></td>
<td>89.3</td>
</tr>
<tr>
<td>24.</td>
<td>4.8</td>
<td>31.4</td>
<td>36.2</td>
<td>72.0</td>
<td></td>
<td>35.8</td>
</tr>
</tbody>
</table>

*Sodium retention is positive unless otherwise shown.
5.b Exchangeable sodium in infants with hypernatraemic dehydration

The measured value for exchangeable sodium, the value calculated for time zero hour and the predicted value for each of the 7 infants in this part of the study are shown in table 5.3. With the exception of patient 5 the predicted values were higher than those calculated for zero hour. In figure 5.25 the calculated values of exchangeable sodium at zero hour are compared to the reported values for healthy children without diarrhoea. Only one infant (patient 5) had an exchangeable sodium above the reported value for healthy children.

5.c Blood volume in infants with hypernatraemic dehydration

Four infants (patients 2, 4, 6 & 7) were shocked on admission to the Drip Room. They received an initial rapid infusion of a plasma volume expander prior to starting the study. None were clinically shocked at the start of the investigation.

Blood volume measured shortly after admission to the metabolic unit are shown in table 5.4. In two cases (patients 1 & 2) the blood volume was well below the normal range of 70 to 85 millilitres per kilogram body weight while in a further two (patients 3 & 6) it was just below the lower limit of normal. Patients 4 & 5 had a blood volume slightly above the upper limit of normal and in patient 7 the value was well above this limit.
Table 5.3. Exchangeable sodium levels in infants with hypernatraemic dehydration

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Exchangeable Na (measured)</th>
<th>Exchangeable Na (calculated)</th>
<th>Exchangeable Na (predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (mmol)</td>
<td>Per kg. (mmol)</td>
<td>Total (mmol)</td>
</tr>
<tr>
<td>1.</td>
<td>198.9</td>
<td>64.2</td>
<td>183.3</td>
</tr>
<tr>
<td>2.</td>
<td>538.0</td>
<td>65.5</td>
<td>468.4</td>
</tr>
<tr>
<td>3.</td>
<td>477.0</td>
<td>66.3</td>
<td>400.8</td>
</tr>
<tr>
<td>4.</td>
<td>245.0</td>
<td>62.8</td>
<td>183.0</td>
</tr>
<tr>
<td>5.</td>
<td>623.6</td>
<td>82.1</td>
<td>594.3</td>
</tr>
<tr>
<td>6.</td>
<td>591.0</td>
<td>64.2</td>
<td>459.2</td>
</tr>
<tr>
<td>7.</td>
<td>243.2</td>
<td>73.7</td>
<td>218.6</td>
</tr>
</tbody>
</table>

*Value calculated for the time of admission - zero hour.
+The predicted values are based on the fully rehydrated weight of the infant.
Figure 5.25: Exchangeable Sodium (ES) in Healthy Infants & Infants with Hypernatraemic Dehydration

* Known Values: Children without diarrhoea
* Derived Values: Children with Hypernatraemic Dehydration on admission.
Table 5.4. Blood volume in infants with hypernatraemic dehydration.

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Blood vol. (ml/kg)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>49.6</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>45.6</td>
<td>Received 80 ml Haemaccel</td>
</tr>
<tr>
<td>3.</td>
<td>64.0</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>90.0</td>
<td>Received 60 ml Haemaccel</td>
</tr>
<tr>
<td>5.</td>
<td>88.0</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>65.0</td>
<td>Received 150 ml Haemaccel</td>
</tr>
<tr>
<td>7.</td>
<td>116.0</td>
<td>Received 60 ml Haemaccel</td>
</tr>
</tbody>
</table>
5.d Extracellular fluid volume changes during rehydration in infants with hypernatraemic dehydration

The extracellular fluid volume measurements, serum sodium concentration, sodium content of the extracellular fluid and sodium retention during the period between the extracellular fluid volume measurements are shown in table 5.5. Changes in total body weight, extracellular fluid volume and the calculated change in intracellular fluid volume are shown in table 5.6. The absolute volume of the extracellular fluid and the total body weight increased in every case during the period between the two measurements. As a percentage of body weight the initial extracellular fluid volume was in the reported normal range in four (patients 1, 4, 5 & 7) and decreased in the remainder. Following rehydration it was within the normal range in 6 infants and increased in one (patient 7). Intracellular fluid volume increased in three infants (patients 1, 4 & 5) decreased in three (patients 2, 6 & 7) and remained virtually unchanged in one (patient 3). During this period serum sodium concentration decreased in all cases. Sodium content of the extracellular fluid increased in six and decreased in one (patient 5) while sodium retention was positive in all cases.
Table 5.5 Extracellular fluid volume measurements, serum sodium concentration, sodium content of the extracellular fluid and sodium retention during recovery in infants with hypernatraemic dehydration.

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Weight (gms)</th>
<th>ECFV ml.</th>
<th>%body wt.</th>
<th>Serum Na content (mmol)</th>
<th>Sodium Change of ECFV content (mmol)</th>
<th>Sodium retention (mmol)+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>a 2800</td>
<td>857</td>
<td>30.6</td>
<td>171</td>
<td>146.5</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>b 2930</td>
<td>936</td>
<td>31.9</td>
<td>149</td>
<td>150.8</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>a 7800</td>
<td>2058</td>
<td>26.0</td>
<td>165</td>
<td>339.6</td>
<td>86.7</td>
</tr>
<tr>
<td></td>
<td>b 8220</td>
<td>2786</td>
<td>33.9</td>
<td>153</td>
<td>426.3</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>a 6650</td>
<td>1774</td>
<td>26.7</td>
<td>170</td>
<td>301.6</td>
<td>109.9</td>
</tr>
<tr>
<td></td>
<td>b 7780</td>
<td>2939</td>
<td>37.8</td>
<td>140</td>
<td>411.5</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>a 3480</td>
<td>1165</td>
<td>33.5</td>
<td>153</td>
<td>178.2</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>b 3800</td>
<td>1257</td>
<td>33.0</td>
<td>146</td>
<td>178.8</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>a 7100</td>
<td>2257</td>
<td>31.8</td>
<td>156</td>
<td>352.1</td>
<td>- 7.6</td>
</tr>
<tr>
<td></td>
<td>b 7630</td>
<td>2426</td>
<td>31.8</td>
<td>142</td>
<td>344.5</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>a 8390</td>
<td>1805</td>
<td>21.5</td>
<td>177</td>
<td>319.5</td>
<td>228.0</td>
</tr>
<tr>
<td></td>
<td>b 8900</td>
<td>3359</td>
<td>37.7</td>
<td>163</td>
<td>547.5</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>a 2930</td>
<td>1028</td>
<td>35.1</td>
<td>162</td>
<td>166.5</td>
<td>89.7</td>
</tr>
<tr>
<td></td>
<td>b 3200</td>
<td>1697</td>
<td>53.0</td>
<td>151</td>
<td>256.2</td>
<td></td>
</tr>
</tbody>
</table>

*a and b refer to the times of the first and second extracellular fluid volume measurements.
+Figures in these columns are positive unless shown otherwise.
Table 5.6. Measured change in total body weight and extracellular fluid volumes and calculated change in intracellular fluid volume during rehydration of infants with hypernatraemic dehydration

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Change in body wt. (ml)</th>
<th>Change in ECFV (ml)</th>
<th>Change in ICFV (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>130</td>
<td>79</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>340</td>
<td>728</td>
<td>-388</td>
</tr>
<tr>
<td>3</td>
<td>1130</td>
<td>1165</td>
<td>-35</td>
</tr>
<tr>
<td>4</td>
<td>320</td>
<td>92</td>
<td>228</td>
</tr>
<tr>
<td>5</td>
<td>530</td>
<td>169</td>
<td>361</td>
</tr>
<tr>
<td>6</td>
<td>510</td>
<td>1554</td>
<td>-1044</td>
</tr>
<tr>
<td>7</td>
<td>270</td>
<td>669</td>
<td>-399</td>
</tr>
</tbody>
</table>

*Unless otherwise shown all changes are positive and refer to an increase in volume.*
5.e Incidence of hypernatraemia.

During the twelve months 3889 children with diarrhoea were admitted to the Drip Room. In 147 the initial serum sodium concentration was greater than 150 millimoles per litre. This represents a 3.8 per cent incidence of hypernatraemic dehydration among infants presenting with dehydrating diarrhoeal disease.

The percentage of infants each month who were hypernatraemic on admission is shown in figure 5.26. The lowest monthly incidence was 2 per cent in December and the highest was 7.3 per cent in June but no definite seasonal pattern could be established. In terms of absolute numbers most hypernatraemic patients were admitted from the beginning of January through to the end of April. During this period there were 75 hypernatraemic patients representing 51 per cent of the total. In the same four months 2036 children were admitted to the Drip Room with dehydrating diarrhoea which is 52 per cent of the total for the year.

In only seven cases did the notes of the admitting medical officer indicate that hypernatraemia was clinically suspected on admission. In the remaining 140 children the diagnosis was not established until the result of the initial serum sodium concentration was known.
Figure 5.26: Monthly Incidence of Hypernatraemia
Clinical features

The age range of the hypernatraemic infants was 0.75 to 16.75 months (mean 6.0 months) and that of the non hypernatraemic was 0.75 to 59.25 months (mean 10.6 months). In table 5.7 the numbers in each group who were either above or below 6 months of age are shown. A significantly greater proportion of the infants in the hypernatraemic group were below 6 months of age.

No sex predilection was evident in the hypernatraemic group. There was a slight male predominance in the non hypernatraemic group but this was not significant (table 5.8).

The number of patients with a rehydrated weight above 80 percent of expected weight for age (Boston 50th percentile) and the number below this level for both groups of patients is shown is table 5.9. Rehydrated weight was taken as the stable weight of the infant while off intravenous fluids and in the absence of edema. Relatively fewer of the hypernatraemic group were underweight for age but the difference between the two groups was not statistically significant.
A definite history of anorexia was obtained in 23.8 per cent of the hypernatraemic group and 19.9 per cent had a history of excessive salt or solute intake prior to admission. The corresponding figures for the non hypernatraemic group were 12 and 8 per cent respectively. These differences were not statistically significant (tables 5.10 and 5.11).

A doughy feel to the skin was found in only 3 patients in the hypernatraemic group while none of the non hypernatraemic group exhibited this sign.

In the hypernatraemic group 21 per cent had radiological evidence of pulmonary consolidation. This was significantly more than the 2 per cent with positive x-ray findings in the non hypernatraemic group. (p < 0.01).
Table 5.7. Age distribution of hyper- and non hypernatraemic patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Under 6 mths</th>
<th>Over 6 mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernatraemic group</td>
<td>94 (63.9%)</td>
<td>53 (36.1%)</td>
</tr>
<tr>
<td>Non hypernatraemic group</td>
<td>19 (38.0%)</td>
<td>31 (62.0%)</td>
</tr>
</tbody>
</table>

\[ x^2 = 9.25 \]

\[ p < 0.01. \]

Table 5.8. Sex ratio in hyper- and non hypernatraemic patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernatraemic group</td>
<td>74</td>
<td>73</td>
<td>147</td>
</tr>
<tr>
<td>Non hypernatraemic group</td>
<td>29</td>
<td>21</td>
<td>50</td>
</tr>
</tbody>
</table>

\[ x^2 = 0.60 \]

\[ p > 0.05. \]
Table 5.9. Distribution of weight as a percentage of expected weight for age.

<table>
<thead>
<tr>
<th></th>
<th>Percentage expected wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Under 80%</td>
</tr>
<tr>
<td>Hypernatraemic group.</td>
<td>46</td>
</tr>
<tr>
<td>(31.5%)</td>
<td>(68.5%)</td>
</tr>
<tr>
<td>Non hypernatraemic group.</td>
<td>22</td>
</tr>
<tr>
<td>(45.8%)</td>
<td>(54.2%)</td>
</tr>
</tbody>
</table>

$x^2 = 2.66$
$p > 0.05$

Table 5.10. Incidence of history of anorexia with decreased fluid intake prior to admission in infants with hypernatraemic and non hypernatraemic dehydration.

<table>
<thead>
<tr>
<th>History of anorexia</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernatraemic group.</td>
<td>35</td>
<td>112</td>
</tr>
<tr>
<td>(23.8%)</td>
<td>(76.2%)</td>
<td></td>
</tr>
<tr>
<td>Non hypernatraemic group.</td>
<td>6</td>
<td>44</td>
</tr>
<tr>
<td>(12.0%)</td>
<td>(88.0%)</td>
<td></td>
</tr>
</tbody>
</table>

$x^2 = 2.48$
$p > 0.05$
Table 5.11. Incidence of a history of excessive salt or solute intake prior to admission in patients with hypernatraemic and non hypernatraemic dehydration.

<table>
<thead>
<tr>
<th>History of ingestion.</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernatraemic group.</td>
<td>29 (19.7%)</td>
<td>118 (80.3%)</td>
</tr>
<tr>
<td>Non hypernatraemic group.</td>
<td>4 (8.0%)</td>
<td>46 (92.0%)</td>
</tr>
</tbody>
</table>

χ² = 2.89
p > 0.05

Table 5.12. Underestimation of dehydration by clinical criteria in hyper- and non hypernatraemic patients.

<table>
<thead>
<tr>
<th>Degree of underestimation.</th>
<th>Hypernatraemic group</th>
<th>Non hypernatraemic group</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 - 4.9%</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>5.0 - 9.9%</td>
<td>53</td>
<td>7</td>
</tr>
<tr>
<td>10% and over</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

*n represents the number of patients assessed in each group.
χ² = 19.35
p < 0.001.
Due to failure to record the admission weight accurately in some cases and uncertainty about the fully rehydrated weight in others the actual degree of dehydration could not be retrospectively calculated in all hypernatraemic individuals. Adequate data on 138 infants was available and in these the actual degree of water loss on admission was compared to the estimated loss. In table 5.12 the number of patients in each group in whom dehydration was significantly underestimated (ie more than 2.5% underestimation) is shown. In the hypernatraemic group dehydration was underestimated in 72.5 per cent of cases. This is significantly more than the 36 per cent in whom dehydration was underestimated in the non hypernatraemic group.

Details of the features of central nervous system dysfunction are shown in table 5.13. Abnormal findings were present in 38 per cent of the hypernatraemic individuals and 4 per cent of the non hypernatraemic. This difference is highly significant.

Details of the 9 patients who had a convulsion prior to admission or were comatose on arrival at hospital are shown in table 5.14. Six died shortly after admission. There was no apparent relationship between the coma or convulsions and the level of the serum sodium concentration on admission. Five of these infants had a preceeding history of diarrhoea of less than
24 hours duration and 4 died. With one exception (case 73 table 5.14) they had marked signs of dehydration or were clinically shocked on arrival. The relatively short history of diarrhoea in more than half these cases and the marked signs of dehydration with shock in most suggest that water loss had been both acute and severe. None of the non hypernatraemic group were in coma or had convulsions prior to admission.

Six hypernatraemic infants had convulsions for the first time after starting intravenous fluid therapy (table 5.15). The duration of intravenous fluid administration prior to the onset of seizures ranged from 5 to 36 hours and there was no relationship between the amount of fluid infused and the convulsions.

There was no difference between the initial serum sodium concentration in those infants who had convulsions during recovery and those who did not (Mann-Whitney u test $p > 0.05$). Serum sodium concentration in 2 of the 6 who had convulsions during treatment declined at a rate exceeding 0.5 millimoles per hour. In the remainder it was less than this value.

In 5 of the 6 infants serum calcium concentration determined shortly after admission was less than 2.00 millimoles per litre. In contrast in 76 infants who did not have convulsions only 13
had a serum calcium concentration less than 2.00 millimoles per litre (table 5.16). The association between convulsions and a serum calcium concentration less than two millimoles per litre was highly significant ($p < 0.001$).

Three of these infants had a lumbar cerebro-spinal fluid which was compatible with an aseptic meningitis. In two (cases 19 & 62 table 5.15) the CSF protein was normal while in the third (case 125) it was twice the upper level of normal. In all cases convulsions were of short duration and rapidly terminated with intravenous Diazepam. None of the non hypernatraemic infants had convulsions during recovery.

There were 8 deaths in the hypernatraemic group, a mortality of 5.4 per cent. In the two cases who had not had convulsions nor were comatose on admission, post mortem revealed an extensive suppurative pneumonia and death could not be attributed directly to hypernatraemia. The remaining six infants (mentioned previously) had convulsions prior to or were in coma on arrival (table 5.14). Post mortem in four showed gross cerebral edema with cerebral venous thromboses and intracranial haemorrhage. Consent for autopsy was refused in the remaining two.
Table 5.13. Patients presenting with features of CNS dysfunction in hyper- and non hypernatraemic dehydration.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hypernatraemia</th>
<th>Non hypernatraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsy but rouseable</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Jittery hypertonic or hyperreflexic</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Coma and/or convulsions</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>2</td>
</tr>
<tr>
<td>Number of cases assessed</td>
<td>147</td>
<td>50</td>
</tr>
<tr>
<td>Percentage positive</td>
<td>38</td>
<td>4</td>
</tr>
</tbody>
</table>

\[ x^2 = 19.27 \]

\[ p < 0.001 \]
Table 5.14. Details of patients presenting with coma or convulsions.

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Age (mths)</th>
<th>CNS feature</th>
<th>Initial serum Na.</th>
<th>Duration of diarrhoea (hours)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4.75</td>
<td>Coma</td>
<td>157</td>
<td>&lt; 48</td>
<td>Normal</td>
</tr>
<tr>
<td>13</td>
<td>6.50</td>
<td>Convulsion</td>
<td>152</td>
<td>&lt; 24</td>
<td>Died</td>
</tr>
<tr>
<td>21</td>
<td>7.50</td>
<td>Coma</td>
<td>164</td>
<td>&gt; 96</td>
<td>Previous known spastic C.P.</td>
</tr>
<tr>
<td>27</td>
<td>6.50</td>
<td>Convulsion</td>
<td>160</td>
<td>&lt; 24</td>
<td>Normal</td>
</tr>
<tr>
<td>46</td>
<td>2.75</td>
<td>Coma</td>
<td>154</td>
<td>&lt; 24</td>
<td>Died</td>
</tr>
<tr>
<td>58</td>
<td>5.00</td>
<td>Coma</td>
<td>178</td>
<td>&lt; 24</td>
<td>Died</td>
</tr>
<tr>
<td>73</td>
<td>14.00</td>
<td>Convulsion</td>
<td>168</td>
<td>&lt; 48</td>
<td>Died</td>
</tr>
<tr>
<td>105</td>
<td>12.00</td>
<td>Coma</td>
<td>170</td>
<td>&lt; 24</td>
<td>Died</td>
</tr>
<tr>
<td>140</td>
<td>8.00</td>
<td>Coma</td>
<td>151</td>
<td>&lt; 72</td>
<td>Died</td>
</tr>
<tr>
<td>Pt. no.</td>
<td>Age (mths)</td>
<td>L.P.</td>
<td>Duration of therapy (hours)</td>
<td>Na at seizure</td>
<td>Initial Na</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
<td>------</td>
<td>-----------------------------</td>
<td>---------------</td>
<td>------------</td>
</tr>
<tr>
<td>17</td>
<td>5.50</td>
<td>N</td>
<td>20.0</td>
<td>156</td>
<td>161</td>
</tr>
<tr>
<td>19</td>
<td>3.75</td>
<td>A.M.</td>
<td>29.5</td>
<td>151</td>
<td>178</td>
</tr>
<tr>
<td>62</td>
<td>3.25</td>
<td>A.M.</td>
<td>12.5</td>
<td>172</td>
<td>174</td>
</tr>
<tr>
<td>93</td>
<td>10.00</td>
<td>N.D.</td>
<td>5.0</td>
<td>161</td>
<td>164</td>
</tr>
<tr>
<td>102</td>
<td>0.75</td>
<td>N.D.</td>
<td>36.0</td>
<td>158</td>
<td>154</td>
</tr>
<tr>
<td>125</td>
<td>11.25</td>
<td>R.P.</td>
<td>148</td>
<td>154</td>
<td>154</td>
</tr>
</tbody>
</table>

*L.P. - lumbar puncture (N - normal; A.M. - aseptic meningitis, R.P. - raised protein, N.D. - not done).*

"Ca/Mg - Serum calcium and magnesium in mmol/l."
Table 5.16. Distribution of serum calcium concentration in hypernatraemic infants with and without convulsions during intravenous fluid therapy.

<table>
<thead>
<tr>
<th></th>
<th>With convulsions</th>
<th>Without convulsions</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients assessed</td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td>Serum Ca greater than 2 mmol/l</td>
<td>0</td>
<td>63</td>
</tr>
<tr>
<td>Serum Ca less than 2 mmol/l</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

$x^2 = 14.16$

$p < 0.001$
There were no deaths in the non hypernatraemic group studied. Of the 3889 children admitted to the Drip Room during the year there were a total of 18 deaths giving a mortality of 0.5 per cent. Excluding the hypernatraemic patients there were 10 deaths among the remaining 3742 non hypernatraemic admissions, a mortality of 0.3 per cent. The mortality in hypernatraemia was significantly greater than that for either diarrhoeal disease in general or for non hypernatraemic dehydration (tables 5.17 and 5.18).

Three hypernatraemic infants were assessed clinically as having residual central nervous system dysfunction at the time of discharge. The first, aged one month, had a convulsion for the first time after starting intravenous fluid therapy (case 102 table 5.15) and was noted to have a right hemiparesis postictally. A brain scan at this stage failed to demonstrate venous blood flow through the superior sagittal sinus and the possibility of a superior sagittal sinus thrombosis was entertained. On discharge some weeks later the infant was alert and active but had a persistent right sided weakness. He was referred to the developmental clinic where regular intensive physiotherapy was given. At 7 months of age the residual weakness was barely detectable and a repeat brain scan at this stage was entirely normal. When last seen at 21 months of age
no weakness was demonstrable and he was assessed as functioning developmentally at an 18 month level.

The second child aged 6 months had a history suggestive of a short lived convulsion prior to admission. No further convulsions were witnessed during recovery from hypernatraemia. An EEG performed shortly after admission showed generalised slowing, more marked on the left and in keeping with a metabolic encephalopathy. A brain scan showed a small superficial area of decreased uptake on the left with patchy areas of decreased uptake in the right frontal and left parietal regions. At the time of discharge the infant was alert and active but had generalised mild hypotonia with slightly brisk tendon reflexes. At follow up there was gradual improvement and when last seen at 14 months of age no abnormal features were clinically detectable.

The third infant, aged 3 months, did not have convulsions but during recovery was noted to have generalised persistent hypotonia with brisk tendon reflexes. An EEG performed shortly after admission was normal and a brain scan showed multiple small areas of patchy increased uptake particularly in the right temporal region. When seen one month later there had been some improvement in tone but the reflexes were still brisk. The patient subsequently failed follow up.
None of the patients had peripheral gangrene during the year of study. No patient in the non hypernatraemic group had clinical features of residual central nervous system dysfunction. There were no other complications in either group which could have resulted from therapy. Thus morbidity in the hypernatraemic group was 2 per cent.
Table 5.17. Mortality due to diarrhoeal disease compared to that for hypernatraemic dehydration in infants.

<table>
<thead>
<tr>
<th></th>
<th>Alive</th>
<th>Died</th>
<th>Total</th>
<th>% mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infants with diarrhoeal disease.</td>
<td>3871</td>
<td>18</td>
<td>3889</td>
<td>0.46</td>
</tr>
<tr>
<td>Infants with hypernatraemic dehydration.</td>
<td>139</td>
<td>8</td>
<td>147</td>
<td>5.44</td>
</tr>
</tbody>
</table>

\[ x^2 = 47.37 \]

\[ p < 0.001 \]

Table 5.18. Mortality due to hypernatraemic dehydration compared to that for non hypernatraemic dehydration.

<table>
<thead>
<tr>
<th></th>
<th>Alive</th>
<th>Died</th>
<th>Total</th>
<th>% mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants with hypernatraemic dehydration.</td>
<td>139</td>
<td>8</td>
<td>147</td>
<td>5.44</td>
</tr>
<tr>
<td>Infants with non hypernatraemic dehydration.</td>
<td>3732</td>
<td>10</td>
<td>3742</td>
<td>0.28</td>
</tr>
</tbody>
</table>

\[ x^2 = 71.37 \]

\[ p < 0.001 \]
Chapter 6.

Discussion.

Part 1.

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6.2. Sodium retention during recovery.

6.3. Body sodium status in infants with hypernatraemic dehydration.

6.4. Possible mechanisms responsible for returning sodium concentration to normal during recovery from hypernatraemic dehydration.

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Summary and conclusions.
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Summary and conclusions. 197
6.1. Urinary sodium excretion in hyper- and non hypernatraemic infants.

The striking feature in the pattern of urinary sodium excretion in the majority of hypernatraemic infants was their ability to produce a urine with a sodium concentration well above that of plasma. Levels of urinary sodium achieved were similar to the maximum produced in sodium loaded adults. The peaks in urinary sodium concentration usually occurred within a few hours of commencing intravenous fluid therapy and coincided with the fall in serum sodium concentration to below 150 millimoles per litre. The absolute excretion of sodium was also greatest during the period of peak urinary sodium concentration. These facts do not appear to have been adequately documented previously. They suggest that renal sodium excretion is important during recovery from hypernatraemia.

It is currently believed that in hypernatraemia urinary sodium concentration is invariably below that of serum and that renal mechanisms play little part in recovery. Previous studies on renal sodium excretion in infants recovering from hypernatraemic dehydration have been of a
limited nature. The conclusions were based largely on findings in single urine samples or twenty four hour urine collections, and the excretory patterns demonstrated in this series emphasise the potential pitfalls of analysing collective or isolated urine samples. Peaks in urinary sodium concentration may be missed and account for the misconceptions that exist.

The initial low urinary sodium concentrations demonstrated in some of the hypernatraemic patients have been noted previously by Weil and Wallace. Renal dysfunction was suggested as a cause of the low levels of sodium in the urine. It has been noted before to occur in disease states resulting in dehydration and is believed to be transient in nature. The findings in the majority of hypernatraemic infants in this series supports the belief that it is a transient phenomenon.

Factors thought to be responsible for the initial low urinary sodium concentrations include a decreased glomerular filtration rate with increased reabsorption of the fraction of filtered sodium, an excessive reabsorption of sodium due to increased aldosterone secretion resulting from a low plasma volume and inadequate tubular excretion of sodium due to potassium deficiency. The low circulating blood volume demonstrated in the majority of infants studied could cause a low glomerular filtration rate and
increased aldosterone secretion. In addition it is probable that the infants had a low total body potassium as this frequently occurs during diarrhoeal disease.\textsuperscript{102} Return of normal renal sodium excretion might depend on the restoration of the glomerular filtration rate and early administration of potassium supplements.

In the present study an inadequate circulating blood volume was vigorously corrected whenever clinically suspected. Potassium administration in the form of intravenous half strength Darrows solution was initiated early in the course of rehydration. Both these factors may have been responsible for the early return of appropriate renal sodium excretion demonstrated in the majority of infants with hypernatraemic dehydration.

Once present a high urinary sodium concentration persisted until serum sodium concentration had returned within the normal range. This is contrary to the experimental work of Finberg et al who reported that in dogs hypernatraemia per se resulted in an osmotic diuresis with a failure to concentrate urine sodium to levels above those of plasma.\textsuperscript{46} It is in agreement with the findings of Kamm and Levinsky who noted that in the presence of a normal glomerular filtration rate, urine sodium concentrations were greatly elevated in hypernatraemia.\textsuperscript{82} They
suggested that this was due to decreased tubular reabsorption of sodium, apparently a locally mediated effect of the hypernatraemia on the kidney.

In three hypernatraemic infants (patients 6, 10 and 14) urinary sodium excretion differed from the majority. Urinary sodium concentrations remained inappropriately low throughout the period of study. Unlike the rest of the hypernatraemic patients in whom the diarrhoea resolved prior to terminating the study these three had persistent severe diarrhoea throughout the period of investigation. Two (patients 6 and 10) had extremely high stool sodium losses (table 5.2). In these this may have affected the renal sodium excretion but it does not readily account for patient 14 whose stool sodium losses were not excessive. A more likely explanation for the abnormal excretory pattern in all three infants would be persistence of a low total body potassium affecting the ability of the infants kidneys to excrete sodium appropriately.9, 15, 25, 56, 76, 132 Large amounts of potassium are lost in diarrhoeal stools and total body potassium repletion is related to cessation of the diarrhoea.102 However, as no measurements of total body potassium were made during the study this possibility remains speculative.

In contrast to the hypernatraemic infants urinary sodium concentration in most non hypernatraemic infants at all times
remained below that of serum. Eight of ten infants recovering from non hypernatraemic dehydration had comparable patterns of urinary sodium excretion. As in the majority of the hypernatraemic group renal sodium excretion in most infants with non hypernatraemic dehydration appears appropriate during recovery. Three (patients 15, 20 and 21) in particular support this view. They had extremely low concentrations of sodium in their urine in keeping with their initial low serum sodium concentrations. This is indicative of efficient sodium conservation by the kidney.

Two infants in the non hypernatraemic group (patients 18 and 19) had excretory patterns dissimilar from the rest but resembling the majority of the hypernatraemic group. The reason for this pattern in one (patient 19) is unexplained. The other (patient 18) had a brief rise in serum sodium concentration to hypernatraemic levels shortly after admission. This could have accounted for the pattern of renal sodium excretion in this particular infant.

The results suggest the majority of hypernatraemic infants recovering from dehydrating diarrhoea are capable of appropriate renal sodium excretion which is in keeping with their serum sodium concentrations. In addition the return of serum sodium concentration to normal levels during recovery
from hypernatraemic dehydration is apparently aided by excretion of sodium in the urine. Where urinary sodium concentration in hypernatraemic infants remained low despite therapy there was persistence of severe watery diarrhoea. Persistent diarrhoea may be casually related to the apparent renal dysfunction and prolong the period of hypernatraemia (as occurred in patient 10). In such cases stopping the diarrhoea might be an important aspect of therapy for this electrolyte disturbance.

6.2. Sodium retention during recovery.

In calculating sodium retention no attempt was made to take into account the loss of sodium in the sweat. At normal body temperature these losses are very small and generally less than one millimole per kilogram body weight per day.\(^\text{16, 61, 86, 110}\)

It was assumed that under the stable environmental conditions existing in the metabolic unit sweat sodium losses in the infants studied would be constant and insufficient to affect the results significantly.

Ten of the fourteen hypernatraemic patients had a significant positive sodium retention during recovery (table 5.2). This suggests they had an initial total body sodium deficit. While it is generally believed that infants with hypernatraemic dehydration secondary to diarrhoeal disease are total body sodium depleted\(^\text{10, 12, 41, 48, 67, 69, 151}\) this has not been adequately demonstrated previously.
In two (patients 9 and 13) there was virtually zero sodium retention and another two (patients 2 and 5) were in negative sodium retention during recovery. The zero retention suggests an initial normal body sodium while the negative retention suggests an initial excess of total body sodium.

These results support the belief that the majority of infants with hypernatraemic dehydration secondary to diarrhoeal disease are total body sodium depleted contrary to the belief of Darrow and Welsh.32 A smaller number of infants with hypernatraemia (four of fourteen or twenty eight per cent of this series) may not be sodium depleted or may actually have an excess of body sodium at the time of admission. This is surprising in view of the nature of the fluid and electrolyte losses in diarrhoeal disease. Administration of exogenous sodium prior to admission is the usual explanation given for the lack of sodium depletion in these cases.22, 32, 151 In patients 9 and 13 such a history was obtained and might explain their apparent normal body sodium on admission. However no such history was obtained from the patients with negative sodium retention while two infants with a positive sodium retention had a definite history of prior excess salt ingestion. A history of excess exogenous sodium ingestion is not a reliable indicator of body sodium status in infants with hypernatraemic dehydration.
All the non hypernatraemic infants assessed had a significant positive sodium retention during recovery. The non hypernatraemic infants retained more sodium than the hypernatraemic group but the difference was not statistically significant. As a group the hypernatraemic was more dehydrated than the non hypernatraemic. Water losses must have been relatively greater in the hypernatraemic infants while sodium loss was much the same in both. If the initial degree of dehydration had been of similar severity in both groups it is likely that the non hypernatraemic infants would have had relatively greater sodium deficits and retained more sodium during recovery. The findings suggest that water loss in hypernatraemic dehydration is disproportionately greater than sodium loss and the sodium loss is relatively less than that sustained by infants with non hypernatraemic dehydration.

6.3 Body sodium status in infants with hypernatraemic dehydration.

The positive sodium retention demonstrated during recovery in the majority of the infants in this study implied they were total body sodium depleted. To confirm this in hypernatraemic infants the content of the metabolically active pool of sodium in the body on admission was determined.
In the healthy growing individual total body sodium increases in a predictable manner with increasing body weight.\textsuperscript{50a, 50b} In contrast the proportion of body sodium readily available to the metabolic pool decreases with age from birth to early adolescence.\textsuperscript{52} During this period a greater proportion of sodium is incorporated into the crystal phase of bone. This is only very slowly exchangeable and unaffected by acute disturbances in sodium homeostasis.\textsuperscript{53, 54, 55, 128}

The exchangeable sodium represents the metabolically active sodium in the body and comprises that found in the extracellular fluid, cartilage, intracellular fluid and a portion of the sodium in bone which is readily exchangeable.\textsuperscript{53, 54, 121} Acute disturbances in sodium homeostasis are reflected in the exchangeable sodium\textsuperscript{53, 121} and its measurement was used to assess the sodium status of the infants with hypernatraemic dehydration following diarrhoeal disease.

Exchangeable sodium is accurately and relatively easily measured by means of isotopic dilution of radioactive \textsuperscript{24}Na.\textsuperscript{37, 38, 50a, 94, 111} A disadvantage of this method is that equilibration of the isotope in the body requires 18 to 24 hours.\textsuperscript{37, 50a, 100} Correction for excretion of \textsuperscript{24}Na in the stools and urine during the period of equilibration is an essential part of the measurement.
The infants in this study were all dehydrated on admission and required intravenous fluid therapy. The intravenous fluid contained sodium and an alteration of the exchangeable sodium during rehydration would be expected. Therefore exchangeable sodium corresponding to the time of admission in these infants could not be measured directly but had to be derived from the measured value at 18 to 24 hours and the sodium retention during the period of equilibration.

To assess the magnitude of change in body sodium in hypernatraemic dehydration the exchangeable sodium calculated for the time of admission was compared to that predicted for each infant. This predicted value was calculated from the weight of the patient when fully hydrated and no longer requiring intravenous fluid therapy. A further comparison was made between the calculated exchangeable sodium for the time of admission and known measured values for infants of the same age.

With the exception of patient 5 (table 5.3) the infants all had exchangeable sodiums on admission lower than the predicted value for their rehydrated weight. This confirms that the majority of infants who develop hypernatraemia during diarrhoeal disease are total body sodium depleted. It supports the suggestion that the sodium retention demonstrated in these infants during recovery is due to an initial body sodium deficit. A net loss of sodium from the body must occur during development of the electrolyte disturbance.
In one infant (patient 2) the results of the exchangeable sodium determination conflicted with the noted negative sodium retention during recovery. Exchangeable sodium in this case was lower than the predicted values and known values for infants of the same age group suggesting an initial body sodium deficit. However during recovery there was a negative sodium retention suggesting an initial excess of body sodium. The pattern of urine sodium excretion in this infant differed from the majority of infants with hypernatraemia. There was a late second peak of sodium excretion when the urine sodium concentration again exceeded plasma levels despite the fact that serum sodium concentration had fallen and remained below 150 millimoles per litre for about fifty hours prior to the second rise in the urine sodium concentration. The reason for this apparent "salt wasting" by the kidney is not known but it may account for the negative sodium retention that occurred. The initial body sodium deficit demonstrated appears to have got worse during recovery. A longer period of investigation in this infant might have shown a positive retention of sodium.

In patient 5 the exchangeable sodium calculated on admission was higher than the predicted value and the known measured values for infants of the same age (figure 5.25). This confirms that a small number of cases of hypernatraemic dehydration have an initial increase in body sodium. Cases such as this
may represent examples of true salt poisoning and the negative retention of sodium during recovery supports this belief. In patient 5 a detailed history of the composition of all fluids administered during the 48 hours prior to admission failed to disclose any excessive salt ingestion. In this infant the reason for the apparent excess of sodium remains unclear.

6.4. **Possible mechanisms responsible for returning sodium concentration to normal during recovery from hypernatraemic dehydration.**

There are at least three possible mechanisms which either singly or in combination could result in the raised sodium concentration found in infants with hypernatraemic dehydration.

A disproportionately greater loss of water than sodium from the body would result in an absolute deficit of total body sodium but an increase in the concentration of that remaining. This is believed to be the mechanism responsible for the majority of cases\textsuperscript{10, 12, 22, 41, 48, 67, 69, 151} and the exchangeable sodium measurements and sodium retention during recovery support this belief. During recovery both water and sodium would be retained and the fall in sodium concentration would largely follow the relatively greater retention of water with dilution of the sodium in the extracellular fluid.
Retention of an exogenous sodium load would aggravate the situation described above. If net sodium retention occurred the hypernatraemic dehydration could be associated with an absolute increase in total body sodium. Patient 5 may represent an example of such a case. During recovery there should be retention of water with net loss of sodium and the fall in sodium concentration would result from a combination of excretion and dilution of sodium in the extracellular fluid.

Finally a shift of endogenous sodium, mobilised from some body store such as bone, to the extracellular fluid may contribute to the raised sodium concentration. This mechanism has been suggested but little evidence to support the possibility has been documented. Recovery in these infants would entail both dilution of the sodium in the extracellular fluid and movement of sodium out of this compartment not entirely accounted for by excretion.

Because it is not possible to predict which infants with diarrhoeal disease will become hypernatraemic a prospective investigation of the factors responsible for the raised sodium concentration is not possible. The events during recovery must to some extent be the reverse of those during development of hypernatraemia and their study provides a means of establishing which mechanisms are operative in a particular infant. By comparing the change in sodium content of the extracellular fluid to the "sodium retention" during the period between two extracellular fluid space determinations it was
possible to relate the fall in serum sodium concentration to the effects of dilution, excretion and movement of sodium out of the extracellular fluid space. This method does not provide a quantitative estimate of the mechanisms involved but merely establishes their relative importance.

Three patterns of change in the sodium content of the extracellular fluid and sodium retention emerged. Patients 1, 4 and 5 had little change in the sodium content of the extracellular fluid during rehydration, positive sodium retention during the same period and a fall in the serum sodium concentration (table 5.5).

In these cases it would seem that while the sodium was initially delivered to the extracellular fluid in the form of intravenous and oral fluids, an amount equivalent to that retained was transferred out of the extracellular fluid to some other site such as bone or the intracellular fluid. The sodium content of the extracellular fluid remained almost unchanged during this period. The fall in sodium concentration in these infants must then have been largely a dilutional effect with relatively greater water than sodium retention. Excretion appears to have played little part in reducing the sodium concentration of the extracellular fluid. This is contrary to the urinary sodium excretory findings which suggested that renal sodium excretion is initially important in lowering the serum sodium concentration in the majority of hypernatraemic infants. This apparent conflict of results will be examined in more detail later.
The positive sodium retention demonstrated during the period between the first and second thiosulphate injections (ie. the initial period of rehydration) was expected in patient 1 and 4. They had an exchangeable sodium on admission that was lower than their predicted values suggesting an initial body sodium deficit. In patient 5 the positive retention was surprising as the exchangeable sodium on admission in this infant suggested an initial excess of body sodium. Excretion of sodium and negative sodium retention was expected to be important in correcting the hypernatraemia in patient 5. Negative retention did not occur until after the first twenty four hours of rehydration when the serum sodium concentration was already below 150 millimoles per litre. A delay in excreting a sodium load has been shown to occur in normal infants and adults. It is attributed to an initial inadequate sodium output possibly due to increased adrenal cortical activity causing increased tubular reabsorption of sodium. In view of the fact that patient 5 was able to produce urine with a sodium concentration well in excess of that of plasma while still hypernatraemic, it is difficult to accept this as the cause for the overall delayed excretion of the excess sodium in this case.

In patient 3 an increase in the sodium content of the extracellular fluid equal to the amount of sodium retained occurred over the period of rehydration. This suggests that all
the sodium retained was confined to the extracellular fluid space. The fall in serum sodium concentration that occurred must have been largely the result of a relatively greater water retention with dilution of the extracellular fluid. Excretion and transfer of sodium out of the extracellular fluid space did not appear to be significant factors in lowering the sodium concentration of this infant. In patients 2 and 6 an increase in the sodium content of the extracellular fluid and positive sodium retention accompanied the fall in serum sodium concentration. In both infants the increase in the sodium content of the extracellular fluid exceeded the amount of sodium retained. Changes similar to these have previously been noted by Katcher et al. They suggest that all the sodium retained during the period of rehydration remained in the extracellular fluid and in addition some endogenous sodium was transferred to this space. The fall in serum sodium concentration in these infants was again explained as being entirely due to dilution of the sodium in the extracellular fluid by relatively greater water retention.

Patient 7 had changes similar to those of patients 2 and 6. However in this infant the second extracellular fluid measurement was exceptionally large (table 5.5). While there was no objective evidence to confirm the possibility, it is likely that there was an error in the measurement of the second
thiosulphate space. If true this would exaggerate the sodium content of the extracellular fluid following the period of rehydration. Taking this into consideration the sodium content of the extracellular fluid was recalculated on the basis of an extracellular fluid volume of 35 per cent (ie. the same as the percentage for the initial extracellular fluid volume). Under these circumstances patient 7 had similar changes to those of patients 1, 4 and 5 in that the sodium content of the extracellular fluid remained virtually unchanged while there was a positive sodium retention. Regardless of which extracellular fluid volume is correct the fall in sodium concentration in this infant was also due to relatively greater water retention with dilution of extracellular fluid sodium and excretion appeared to be unimportant.

In all seven infants there was a positive retention of sodium during the first twenty four hours of rehydration and recovery from hypernatraemia. It appears that the fall in sodium concentration is largely the result of relatively greater water retention and dilution of sodium in the extracellular fluid. Combining these findings with those of the sodium retention during recovery it can be deduced that in the majority of infants hypernatraemic dehydration secondary to diarrhoeal disease follows a disproportionately greater loss of water than sodium from the body. In some the raised sodium concentration
may be further elevated by transfer of endogenous sodium into the extracellular fluid space, patients 1, 4 and 5 being examples. In others the height of the elevation may be limited by transfer of sodium out of the extracellular fluid to some other body compartment, patients 2 and 6 being examples. The factors determining this movement of endogenous sodium between the various body fluid compartments and bone are not known. They may be related to acidosis\(^7,\,8,\,31,\,92,\,142,\,157\) and increased adrenal cortical activity\(^{17,\,91}\) which promotes transfer of sodium from bone to the extracellular fluid space, or to potassium deficiency with movement of sodium from the extracellular fluid into the cells to partially offset the loss of intracellular cation.\(^{29}\)

6.5. **Effect of hypernatraemic dehydration on blood and extracellular fluid volume.**

The infusion of intravenous fluids both prior to and during the study period meant continuous changes in the volumes of the various body fluid compartments would occur. This influenced the choice of method for measuring the blood and extracellular fluid volumes and providing no sacrifice of the accuracy of the determination was involved; the most rapid was chosen.

All the infants had received intravenous fluids prior to the measurement of blood and extracellular fluid volume. Four (patients 2, 4 6 and 7) were clinically shocked on admission to the Drip Room and received a rapid infusion with a plasma
volume expander (table 5.4). It was not possible to correct for the fluid already given and this undoubtably affected the results.

The fluid administered prior to measuring the blood volume was believed to be largely confined to the intravascular fluid compartment. If this is so it could be expected to affect the measurement of the blood and total extracellular fluid volume but not that of the interstitial fluid volume. A correlation was found between the blood and initial total extracellular fluid volumes in these infants (Spearman rank correlation coefficient \( p \leq 0.05 \)) and with the exception of patient 1 the infants with the largest extracellular fluid volumes (patients 1, 4, 5 & 7) also had the largest blood volume.

There was no correlation between the blood and interstitial fluid volume (ie. the extracellular fluid volume less the blood volume). This supports the assumption that the fluid infused prior to the start of the study was largely confined to the intravascular fluid compartment.

In view of this interpretation of the blood volume results is difficult. In some cases of hypernatraemia the dehydration obviously results in intravascular volume depletion, as four patients (1, 2, 3 and 6) had blood volumes below the normal
range of 70 to 85 millilitres per kilogram body weight. In others there appears to be relative preservation of the blood volume at the expense of the other body fluid compartments. An example is patient 5 who did not receive a plasma volume expander prior to the study but had a blood volume above the upper limit of normal at the time of being significantly dehydrated (tables 5.4 and 5.6). No conclusions can be drawn from the very high values obtained in patients 4 and 7. Both had previously received a plasma volume expander which may have caused prolonged elevation of their blood volume.

The change with rehydration in the volumes of the various body fluids did not follow a uniform pattern. In three (patients 1, 4 and 5) the initial extracellular fluid volume expressed as a percentage of body weight was within the normal range for age. With rehydration there was a considerable increase in both the absolute volume of the extracellular fluid and the total body weight but very little change in the extracellular fluid volume as a percentage of body weight (tables 5.5 and 5.6). This suggests that water retained by these infants was distributed throughout the various body fluid compartments in proportion to their relative sizes. It also implies that during the development of hypernatraemic dehydration water loss was not solely from the extracellular fluid but affected both the intra- and extracellular fluid
In a further three (patients 2, 3 and 6) the extracellular fluid volume increased both in absolute amount and as a percentage of body weight. In one (patient 3) the increase in total body water (i.e. the increase in total body weight) during the rehydration period was almost identical to the absolute increase in extracellular fluid volume (table 5.6). All the fluid retained during rehydration in this infant appears to have been confined to the extracellular fluid space. A situation where extracellular fluid loss is greater than intracellular in hypernatraemic dehydration has been noted previously. Patient 3 provides a further example of this pattern. The preservation of the intracellular fluid volume in this case implies that an increase in the intracellular fluid osmolality occurred in parallel with that of the extracellular fluid during the development of hypernatraemia. As no endogenous redistribution of sodium was demonstrated during recovery in this infant (table 5.5) the most likely explanation for the intracellular volume preservation was the production of intracellular "idiogenic osmoles".

In the other two (patients 2 and 6) the absolute increase in the volume of the extracellular fluid exceeded the increase in total body water. In these infants it appears that not only was the retained fluid confined to the extracellular fluid compartment,
but a net transfer of water from the intracellular to the extracellular fluid space occurred. It is noteworthy that patients 2 and 6 also apparently transferred endogenous sodium into the extracellular fluid space during the same period (table 5.5). Similar changes attributed to such an endogenous redistribution of sodium, chloride and water have been reported previously. These findings suggest that during the development of dehydration there must have been a movement of endogenous sodium and water from the extracellular to the intracellular fluid space. The amount of sodium involved in this redistribution is insufficient to entirely account for the volume of water apparently transferred into the cells. Some other source of intracellular osmotically active particles (such as "idiogenic osmole" production) must have contributed towards promoting the shift of fluid into the cells.

In patient 7 the initial extracellular fluid volume as a percentage of body weight was within the normal range. Following the period of rehydration there was a very large increase in both the absolute volume of the extracellular fluid and the percentage of body weight accounted for by this volume (table 5.5). Excessive expansion of the extracellular fluid space due to overhydration would account for the figure of 530 millilitres per kilogram body weight obtained on the second extracellular fluid volume determination. However under these
circumstances there should be clinical evidence of edema. This was not present and is an unlikely explanation for the high extracellular fluid volume obtained in this infant. Overestimation of the size of the extracellular fluid space due to loss of normal anatomical boundaries is another possibility. This has been shown to occur during the early stages of rehydration of infants with dehydrating diarrhoea when thiocyanate is used for the extracellular fluid volume measurement. It is unlikely that the thiosulphate ion used would cause such a large error particularly as it did not occur in the other six infants. In them the second measurements were comparable to those of normal and underweight infants. An error in the second thiosulphate space measurement seems the most likely explanation for the abnormally high second volume. No evidence for this was found. The findings in this infant remain unexplained.
Summary and conclusions.

The majority of infants recovering from dehydrating diarrhoea are capable of appropriate renal sodium excretion providing shock is vigorously corrected and potassium loss replaced. In hypernatraemic infants recovery is characterised by excretion of urine with a sodium concentration well in excess of that of the serum soon after commencing intravenous fluid therapy. High urinary sodium concentrations persist until the serum sodium concentration is less than 150 millimoles per litre and appears to be a factor in returning serum sodium to normal levels.

During complete recovery the majority of infants presenting with hypernatraemic dehydration have a positive sodium retention. This implies an initial depletion of body sodium existed. In a smaller number there is virtually zero retention or even negative retention of sodium during recovery. This suggests an initial excess of body sodium and may arise as a result of high exogenous sodium intake prior to admission.

Exchangeable sodium determinations in infants with hypernatraemic dehydration substantiate the deductions made from the sodium retention during recovery. On admission the majority of infants have exchangeable sodium levels lower than those predicted from the fully rehydrated body weight and those
reported in healthy infants of the same age. In a smaller number the exchangeable sodium is higher than both the predicted and reported values.

Recovery from hypernatraemia secondary to dehydrating diarrhoea is characterised by a positive retention of sodium and water during the first 24 hours in all cases. The positive retention of sodium occurs regardless of whether or not there is an initial apparent excess of body sodium.

In many an endogenous redistribution of water and sodium between the various body fluid compartments occurs with rehydration. In some, movement of the water and sodium is from the extracellular to the intracellular fluid while in others it is in the opposite direction. In a small number no apparent redistribution of endogenous sodium and water takes place.

The fall in sodium concentration of the extracellular fluid occurring during the first 24 hours of rehydration appears to be mainly due to relatively greater water than sodium retention and dilution of the extracellular fluid. The sodium retention and change in sodium content of the extracellular fluid demonstrated by these infants suggest renal excretion is unimportant in returning sodium concentration to normal levels. This is in conflict with the pattern of urinary sodium excretion.
However recovery needs to be viewed as a dynamic process involving a number of mechanisms in combination and the following is a possible sequence of events.

Early in the course of rehydration and recovery, and as long as the serum sodium concentration exceeds 150 millimoles per litre, the kidney is able to increase sodium excretion and is an important factor in lowering the sodium concentration of the extracellular fluid. This is probably a locally mediated effect of the hypernatraemia on the renal tubules. Simultaneously the administration of relatively low sodium containing intravenous fluids results in progressive retention of both sodium and water but with a relative excess of water. This causes dilution and promotes a further lowering of the sodium concentration in the extracellular fluid. As the extracellular fluid sodium concentration falls renal sodium excretion decreases and eventually ceases to be a factor in lowering the extracellular fluid sodium concentration.

The phase of relatively greater water than sodium retention and dilution of extracellular fluid continues for at least 24 hours. Sodium retained during this time eventually exceeds the amount initially excreted in the urine giving an erroneous impression that renal excretion is not important during recovery.
Some time after the first 24 hours, when the volume of the various body fluid compartments have been restored to near normal levels, there begins a prolonged phase of gradual sodium adjustment. During this period the body stores of sodium (and no doubt other minerals as well) are returned to normal. In the majority this phase involves positive sodium retention to correct an initial deficit. In a small number there is a negative retention to eliminate an initial excess of the ion.

As the events during recovery are to some extent the reverse of those during development, the results of this study provide a clearer understanding of the pathogenesis and pathophysiology of hypernatraemic dehydration secondary to diarrhoeal disease in children. In the majority the raised sodium concentration occurs largely as a result of a disproportionately greater loss of water than sodium from the body. Hypernatraemia in these infants is accompanied by a total body sodium deficit. In a small number the dehydration is accompanied by a normal or even excessive body sodium. These infants may represent examples of excessive ingestion of exogenous sodium although a history to support this possibility is not always forthcoming.

In many infants a redistribution of endogenous sodium and water accompanies the relatively greater loss of water than sodium from the body. In some sodium and water moves from the
extracellular to the intracellular fluid. This prevents intracellular dehydration from occurring and may limit the height of the sodium concentration in the extracellular fluid. In others sodium and water moves from intracellular to extracellular fluid. Such a movement is accompanied by loss of intracellular fluid volume and may further increase the sodium concentration of the extracellular fluid. Dehydration in these infants involves a loss of water from both the intra- and extracellular fluids.

Finally a small number of infants do not have a redistribution of endogenous sodium and water. The relatively greater water than sodium loss in these infants occurs entirely from the extracellular fluid. Intracellular fluid volume is unchanged. A progressive increase in intracellular osmolality must occur to maintain osmotic equilibrium during development of the hypernatraemia. The production of intracellular idiogenic osmoles could account for this apparent increase in intracellular osmolality.

The factors responsible for the transfer of endogenous sodium and water between the various body fluid compartments are not known. Acidosis, increased adrenal cortical hormone release and total body potassium deficiency may all affect the distribution of sodium and water in the body. To what extent these factors
are operative in infants with hypernatraemic dehydration secondary to diarrhoeal disease remains to be determined.
Part 2.

6.6. Incidence and seasonal variation of hypernatraemic dehydration.

The incidence of hypernatraemia (3.8 per cent) in this series of infants with diarrhoeal disease is similar to a previous report from this hospital\(^6\) and one other report from elsewhere\(^{103}\) but lower than most other reports.\(^{10, 12, 22, 32, 35, 41, 57, 67, 74, 84, 97, 136, 147, 151}\) A number of factors may account for the discrepancy.

A decline in the incidence of hypernatraemic dehydration over the past decade has been suggested.\(^{74, 103, 141, 154}\) As most series were reported prior to 1970 this could account for the difference in the figures obtained. The apparent decline has been attributed to the less frequent use of unmodified (high solute) cows milk formulas,\(^{74, 103, 141}\) an increased incidence of breast feeding,\(^{141}\) a delay in introducing solid feeds and a campaign against the over concentration of milk feeds.\(^{141}\) The relative importance of these factors in reducing the incidence of hypernatraemia is controversial and infants on a low solute cows milk formula, apparently made up in the correct concentration, may still develop hypernatraemia.\(^{154}\)
The lesser incidence of administration of over concentrated feeds is the only factor that may have influenced the occurrence of hypernatraemia locally. Very few infants in the community which this hospital serves are still breast fed by three months of age\(^{123}\) and the relatively high cost of low solute formula milks probably limits their use by the majority. Therefore a decline in incidence is unlikely to account for the relatively small numbers of hypernatraemic infants in this series.

Hypernatraemia is said to be very uncommon in the malnourished infant.\(^{6, 126, 136}\) If true there should be a low incidence of the electrolyte disturbance in a community with a high prevalence of malnutrition. In this series almost half the infants in the non hypernatraemic group had a rehydrated weight below 80 per cent of expected weight for age and may be classified as malnourished (table 5.9). The group was unselected and can be considered representative of all infants admitted with non hypernatraemic dehydration to the Drip Room. As non hypernatraemic dehydration occurs in 96 per cent of infants requiring admission, malnutrition is common in children with dehydrating diarrhoea in Cape Town. A similar finding was previously reported from this unit.\(^6\) The high incidence of malnutrition may partly account for the low incidence of hypernatraemia.
A more likely explanation for the lower incidence in this series is the unselected nature of the patients investigated. Many earlier reports have been of a selected nature and often only the more severely ill infants with diarrhoea had serum sodium determinations. Infants with hypernatraemic dehydration frequently appear extremely ill as they often manifest signs of central nervous system dysfunction. Selection of patients on this basis would exaggerate the incidence of the electrolyte disturbance.

The seasonal variation with a winter peak demonstrated in other areas was not found locally. The percentage of Drip Room admissions each month that were hypernatraemic remained fairly constant throughout the year (figure 5.26). In terms of absolute numbers most infants with hypernatraemic dehydration present during the hot summer months. This is also the time of peak incidence of infantile diarrhoeal disease and over 50 per cent of the annual admissions to the Drip Room regularly occur during the same four consecutive summer months.

6.7. Clinical features of hypernatraemic dehydration.

Early recognition of hypernatraemic dehydration by clinical means is difficult. Unlike the experience of Bruck et al the
condition was clinically diagnosed by the admitting medical officer in fewer than 5 per cent of cases in this series. Similar difficulty in recognising affected individuals has been reported on many occasions. 6, 10, 17, 67, 97 It is highly improbable that in circumstances where some 4000 infants with diarrhoea are admitted annually, the accuracy in clinical recognition claimed by Bruck et al could be achieved. However a higher index of suspicion would result in more cases being recognised before the serum sodium results become available. This would be important if early recognition is to result in modification of treatment.

Comparison of the two groups reveals that certain clinical features occur more frequently in infants with hypernatraemic dehydration. These should serve to arouse suspicion of the diagnosis in an infant with diarrhoeal disease.

The younger infant is particularly at risk and age appears to be an important differentiating feature between hypernatraemic and non hypernatraemic infants. The majority of hypernatraemic infants were under 6 months of age. This differed significantly from the findings in the non hypernatraemic group (table 5.7). Finberg also found most hypernatraemic infants to be less than 6 months old but in contradistinction to this series failed to show a difference in age between those with and without the
electrolyte disturbance. Bruck et al.\textsuperscript{12} and Weil and Wallace\textsuperscript{15} found a larger proportion of their hypernatraemic patients to be over 6 months of age. The reasons for the discrepancy in different series is not known but factors which lead to a decreased free water intake rendering infants susceptible to hypernatraemia undoutably occur more frequently in the very young infant.

An associated pneumonia is important and was present in a greater proportion of the hypernatraemic infants. The hyperpnoea accompanying pneumonia increases insensible water loss and may be a factor in the pathogenisis of hypernatraemia. The magnitude of the water loss by this route is considerable and with hyperpnoea may be two to three fold of normal.\textsuperscript{12, 30, 75}

The most useful clinical features distinguishing hyper- from non hypernatraemic infants are signs of central nervous system dysfunction including coma and convulsions. Such features were present in 38 per cent of hypernatraemic and only 4 per cent of non hypernatraemic infants. An altered level of consciousness, particularly a state of drowsiness, was the most common abnormal finding. The infants were easily rouseable, often then exhibiting a degree of irritability, but if left alone rapidly lapsed back to their former sleepy state. Such changes have
been noted before but in this series were not as common as previously reported.\textsuperscript{12, 35, 41, 69, 97, 135, 151} This is probably again due to the unselected nature of the patients in this study. Any selection based on the severity of clinical illness, as seems to be true of many studies, will undoubtably include those with central nervous system signs and few without such features. The presence of these features in any infant with dehydrating diarrhoea should strongly suggest the possibility of hypernatraemia.

Other features believed to be of value in diagnosing hypernatraemia in dehydrated infants were not found to be of value in this series as they frequently occurred in infants with non hypernatraemic dehydration. The sex of the infant was not a useful differentiating feature as has been suggested in previous reports where males predominated.\textsuperscript{12, 115, 136} A similar lack of sex differentiation was found by Macaulay and Blackhall.\textsuperscript{97}

A history of severe anorexia or of prior excessive salt or solute ingestion was more common in hypernatraemic infants but not significantly more so than in non hypernatraemic patients. Similarly a "doughy" feel to the skin was noted with certainty in so few cases as to be of little value as a clinical sign. This finding is similar to that of others\textsuperscript{6, 10, 41, 147, 151} but
unlike that of Bruck et al who reported it in 53 out of 59 cases studied. They felt it to be a useful clinical feature. Lack of subcutaneous fat due to malnutrition has been suggested as an explanation for the absence of this finding in some series. This is unlikely to account for its infrequency in this series as the majority of hypernatraemic infants were well nourished.

Nevertheless in marked contrast to previous reports, hypernatraemia was not uncommon in malnourished infants. Using a minimum of 80 per cent of expected weight for age (expected weight for age being the 50th Boston percentile) as indicative of adequate nutrition almost a third of the hypernatraemic group were malnourished. There was no significant difference in the nutritional status of hyper- and non hypernatraemic infants (table 5.9). The state of nutrition is also of no value in distinguishing hypernatraemic infants from the rest.

A finding of practical importance is the inability to clinically accurately estimate the degree of dehydration in hypernatraemic individuals. Dehydration was underestimated in almost 75 per cent of the cases. It was also underestimated in 36 per cent of the non hypernatraemic patients but as can be seen from table 5.12 the degree of underestimation was not as great as that of the hypernatraemic group.
The reason for this underestimation of the fluid losses in hypernatraemic infants is related to the relative preservation of the extracellular fluid volume at the expense of the intracellular fluid volume. This relative sparing of extracellular fluid volume depletion was adequately demonstrated in the first part of the study. The clinical signs of dehydration are directly related to the volume of water lost from the extracellular fluid compartment and thus may not be prominent despite a significant loss of total body water.

The inability to estimate fluid loss in these infants may well be to the patients advantage. By aiming to correct the estimated losses over 24 hours, as was done in this study, replacement of actual losses probably took place over a period of 48 hours or longer. Thus unhurried rehydration, which is emphasised as the optimal form of therapy,17, 20, 48, 49, 67, 69, 73, 74, 79, 80, 115, 151 will occur automatically using the routine fluid schedule.

6.8. **Coma and convulsions in hypernatraemia.**

Coma and convulsions prior to admission and the initiation of treatment appear to be poor prognostic features. Six of nine infants presenting in this way subsequently died (table 5.14).
These symptoms occurred only in hypernatraemic patients and their presence in an infant with dehydrating diarrhoea should alert one to the possibility of this diagnosis.

The association between coma and convulsions prior to treatment of hypernatraemic dehydration and a high death rate has been noted previously.45, 79, 98, 151 They are believed to be manifestations of structural brain damage due to intracranial haemorrhage115 which if severe enough will result in death. This is supported by post mortem studies of four of the infants in this series demonstrating extensive intracranial haemorrhage. Bleeding probably follows shrinkage of the brain within the rigid bony cranium with tearing of the bridging vessels.26, 43b, 64, 96, 138 Brain shrinkage occurs when there is a rapid rise in extracellular osmolality and osmotic equilibrium is maintained by movement of water from the cells to the extracellular fluid with subsequent loss of cell volume.40, 49, 138 Where the rise in extracellular fluid osmolality is more gradual cerebral cells have time to produce intracellular idiogenic osmoles.40, 108 These raise the osmolality in brain cells and prevent the loss of water and cell volume that would otherwise occur.

On this basis intracranial haemorrhage with coma and convulsions would be more likely to occur in an infant where
hypernatraemia develops rapidly.\textsuperscript{49} In five of the nine infants presenting with one or other of these features the duration of diarrhoea was less than twenty four hours prior to admission (table 5.14). This is in keeping with a fairly rapid development of hypernatraemic dehydration and supports the above hypothesis.

Convulsions occurring for the first time after starting intravenous fluid therapy do not have the same poor prognostic significance. Six infants, all hypernatraemic, were affected and none died.

Such seizures have previously been related to the volume and composition of fluids\textsuperscript{13, 22, 86, 151} and to their rate of administration.\textsuperscript{72, 73, 80, 135} Experimental work in animals shows these factors may produce cerebral edema with complex changes in ionic concentration in neurones.\textsuperscript{73, 112, 144} As far as could be ascertained none of the six infants were given more fluid than their calculated requirements. The treatment schedule was strictly adhered to and their management in no way differed from that of the hypernatraemic infants who did not convulse. It is difficult to relate the onset of seizures in these cases to the fluid therapy.

Three infants had a cerebrospinal fluid pleocytosis which, in view of the subsequent negative bacterial culture, suggested the
possibility of aseptic (viral) meningitis. This in itself might account for the convulsions in these cases.

An interesting finding was a low serum calcium concentration in all five of these cases in whom it was measured. This was significantly different from the serum calcium concentrations of the hypernatraemic infants who did not have convulsions (table 5.16). Hypocalcaemia is a well described feature among hypernatraemic individuals but little emphasis has been placed on it as a cause of convulsions.\textsuperscript{4, 12, 13, 17, 41, 42, 67, 74} As serum calcium concentrations were determined shortly after admission in these infants it is difficult to implicate the hypocalcaemia directly as a cause for the convulsions occurring up to thirty six hours after starting treatment. However, it is possible that it may be a precipitating factor in a situation where seizure threshold is declining as a consequence of a fall in the serum sodium concentration.\textsuperscript{112, 144, 145} Routine early administration of supplemental calcium to all infants with hypernatraemic dehydration during recovery might be of value in preventing convulsions. This possibility deserves further investigation.

It was not possible to relate the occurrence of convulsions to the initial serum sodium concentration nor to its rate of decline during recovery. This differs from the findings of Morris-Jones
et al.\textsuperscript{115} and Kahn et al.\textsuperscript{80} The former state that convulsions are more common when the initial serum sodium concentration exceeds 158 millimoles per litre. In this series there was no difference in initial serum sodium concentration between the infants who did and did not have convulsions during treatment. Kahn et al claim that the likelihood of convulsions is increased when the rate of decline of the serum sodium concentration exceeds 0.5 millimoles per litre per hour. Only two of the six infants in this study had a rate of decline exceeding this figure.

While the majority of infants who have convulsions only during treatment appear to recover completely, a small number may be left with residual central nervous system dysfunction and patient 102 (table 5.15) is an example. For this reason the convulsions should be terminated as rapidly as possible. In view of the finding of other possible etiologies in this study it is advisable that all other causes for seizures be excluded as far as possible.

6.9. Mortality and morbidity.

Mortality and morbidity is significantly greater in hypernatraemic than in non hypernatraemic dehydration. This emphasises the serious nature of hypernatraemia as a
complication of diarrhoeal disease. Both mortality (5.4 per cent) and morbidity (2 per cent) in this series were lower than those reported by others. 10, 20, 22, 35, 48, 79, 98, 115, 135 This is probably partly due to the unselected nature of the patients in the study but improved patient monitoring and management is also believed to have played a role.

All the morbidity in this series was related to residual damage to the central nervous system. It must be emphasised that the residual damage reported relates only to short term morbidity. In the long term this figure might be higher and more subtle damage in the form of learning difficulties, behavioural disorders and epilepsy could become apparent.

6.10 **Fluid therapy in hypernatraemic dehydration.**

The fluid therapy schedule used was shown to be satisfactory for treating infants with hypernatraemic dehydration. The vast majority treated in this way had an uncomplicated recovery. In many a slight rise in serum sodium above the initial level occurred during the first three to four hours of therapy. Thereafter a gradual decline occurred and was accompanied by a return of the acid base status to normal. A continuing or maintained elevation of the serum sodium concentration or persistence of acidosis beyond this time often indicated an
underestimation of ongoing losses. Increasing the rate of fluid administration was always successful in correcting this.

The findings in this study indicate that a large number of hypernatraemic infants will initially go undetected unless the serum sodium concentration is checked on all infants with dehydrating diarrhoea. This is not possible as a routine in all but the more sophisticated hospitals. Therefore it is imperative to have a fluid schedule satisfactory for the non hypernatraemic individual and with minimal risk of iatrogenic complications in the hypernatraemic infant.

The fluid schedule used in this unit has for many years been successful in the treatment of infants with non hypernatraemic dehydration. Its demonstrated efficacy for infants with hypernatraemic dehydration means that a standard fluid therapy regimen can be used for all infants with dehydrating diarrhoea regardless of their initial serum sodium concentrations. This is of practical value where large numbers of infants with dehydrating diarrhoea are treated annually as it obviates the urgent need to recognise the hypernatraemic individual early.

Because the degree of dehydration is so frequently underestimated in hypernatraemic infants full rehydration using this fluid regimen is delayed and occurs over a period of forty
eight hours or longer. The schedule thus meets the needs for unhurried rehydration so often emphasised in the management of hypernatraemic dehydration secondary to diarrhoeal disease. The scheme is simple to apply and associated with both a lower mortality and morbidity than reported from elsewhere in hypernatraemic infants. It can be safely recommended for treatment of all infants with dehydrating diarrhoea.
Summary and conclusions.

Although the incidence of hypernatraemia in Cape Town is lower than reported in other areas it still accounts for a significant number of the children who require admission for dehydrating diarrhoea each year. Hypernatraemia remains a serious complication of diarrhoeal disease and carries a higher mortality and morbidity than that of non hypernatraemic dehydration. Features of central nervous system dysfunction with coma and convulsions are the most striking and serious changes of the condition.

Coma and convulsions occurring prior to admission and the initiation of treatment are poor prognostic features and are associated with a high death rate. They are caused by structural brain damage due to intracranial bleeding which appears to occur with shrinkage of the brain during the development of hypernatraemia.

Convulsions occurring only after starting treatment do not have the same poor prognostic significance. However they may cause residual central nervous system dysfunction and should be terminated promptly. In some cases they may be caused by factors unrelated to hypernatraemia (eg meningitis) and in others could be precipitated by a low serum calcium...
concentration which frequently accompanies hypernatraemic dehydration. These potentially treatable causes should always be excluded in infants who have convulsions during recovery from this electrolyte disturbance.

The condition is difficult to diagnose clinically but certain features should arouse suspicion of the diagnosis. Very young infants, particularly those under six months of age, are most at risk and pneumonia (which may be important in the pathogenesis of the condition) is frequently present. The single most important clinical clue to the diagnosis is the presence of features of central nervous system dysfunction including coma and convulsions. Most often the infants are simply drowsy but if disturbed are very irritable. Other features are frequently found in infants with non hypernatraemic dehydration and are of little value in distinguishing the hypernatraemic individual.

Even with a high index of suspicion many hypernatraemic children would go undetected unless serum sodium concentrations were determined on all children with dehydrating diarrhoea. As a routine this is not always practically possible and it is imperative to have a fluid therapy schedule which is suitable for all infants with diarrhoea regardless of their serum sodium concentration. The fluid schedule used has been successful in treating non hypernatraemic infants in this hospital for many
years. The results now presented show it to be very satisfactory for use in infants with hypernatraemic dehydration. The scheme is simple to use and based initially on the rapid correction of shock with an intravenous plasma volume expander and of acidosis with intravenous sodium bicarbonate. Thereafter all intravenous fluids administered are half strength Darrow's solution in 5 per cent dextrose water. Fluid requirements are based on the clinical assessment of the degree of dehydration. The demonstrated tendency to underestimate dehydration in hypernatraemic infants is used to the patients advantage. By aiming to correct the estimated dehydration over a period of 24 hours the actual fluid losses are replaced over 48 hours or longer. The unhurried rehydration recommended by all is thereby achieved.

The schedule is associated with a lower mortality and morbidity in the management of infants with hypernatraemic dehydration than has been reported elsewhere. It is to be recommended in all cases of diarrhoeal dehydration in infants, particularly in those areas where large numbers have to be treated annually.
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Appendix.

Clinical, laboratory and statistical procedures performed by the author.

Blood, pH, pCO$_2$, base excess and standard bicarbonate.

Serum, urine and stool sodium concentration.

Determination of exchangeable sodium.

Blood volume measurement.

Extracellular fluid volume measurement.
Appendix.

Clinical, laboratory and statistical procedures performed by the author.

1. Clinical assessment, supervision of treatment and follow-up of the children admitted to the Drip Room.

2. Selection of patients, clinical management, treatment and follow-up of patients admitted to the metabolic unit.


4. Supervision of all stool and urine collections.

5. The measurement of all serum sodium concentrations and blood pH and determination of pCO₂, base excess and standard bicarbonate on the patients admitted to the metabolic unit. The corresponding measurements for the children in the Drip Room were performed by the staff of the chemical pathology laboratory at the Childrens Hospital.

6. The majority of the stool digest preparations for measurement of stool sodium concentration and
determination of the majority of the stool and urinary sodium concentrations. The remainder were performed by Mrs. P. Burns, Mrs. L. Moore and Miss G. Peat all senior technologists in the Institute of Child Health Research Laboratory.

7. The preparation and injection of the $^{99m}\text{Tc}$ labelled erythrocytes and the subsequent collection of blood samples and their counting for specific activity of $^{99m}\text{Tc}$.

8. The injection of sodium thiosulphate and subsequent collection of serum samples for determination of the thiosulphate space. A few of the titrations for serum thiosulphate concentration were performed by the author and the majority by Mrs. L. Moore.

9. The preparation and subsequent injection of the calculated dose of $^{24}\text{Na}$. The collection of blood samples and measurement of serum specific activity of $^{24}\text{Na}$ and the measurement of specific activity of $^{24}\text{Na}$ in all stool and urine samples.

10. All statistical analyses, calculations of blood and extracellular fluid volumes, sodium retention and total exchangeable sodium.
The laboratory methods used in this investigation but not detailed here are established methods that have been used in this unit for some time.
Blood pH, pCO₂, base excess and standard bicarbonate.

These were measured with an IL 213 pH/Blood Gas Analyser. Half a millilitre of venous blood, obtained by venipuncture from either the external jugular or a cubital fossa vein, was thoroughly mixed with a drop of heparin in a syringe. Tests were done immediately. The actual pH and pH at partial carbon dioxide pressures of approximately 30 and 60 mm Hg. were measured at 37°C. The actual pCO₂, base excess and standard bicarbonate were read off a standard acid base curve nomogram.

Reference.

Serum, urine and stool sodium concentration.

These were measured using an Instrumentation Laboratory digital flame photometer (Model IL 343) with internal standard of lithium nitrate. Standard solutions of sodium, prepared from suitably diluted commercial stock solutions, were used to calibrate the instrument. For serum sodium determinations the standard solutions used contained sodium in a concentration of 120, 140 and 160 millimoles per litre. For the stool and urinary sodium determinations the standard solutions contained sodium in a concentration ranging from 25 to 200 millimoles per litre with increments of 25 millimoles per litre. In determining stool or urinary sodium concentrations standards were selected so that the sodium concentration of the specimen fell between two that differed by no more than 25 millimoles per litre. Where the sodium concentration of a stool or urine specimen exceeded 200 millimoles per litre a suitable dilution of the specimen with distilled water was made to reduce the sodium concentration to below this value.

Serum for the sodium determination was separated by centrifugation at 2000g for 10 minutes within 20 minutes of the blood sample being obtained from the patient. The serum was stored at minus 20°C until analysis.
The volume of each urine specimen was recorded and an aliquot stored at minus 20°C until analysis.

The weight of each stool specimen was recorded. Stools consisting largely of a watery element with little solid matter were centrifuged at 2000g for 10 minutes. Approximately one millilitre of clear supernatant was removed and stored at minus 20°C until analysis. Where the specimen contained a lot of solid matter, or when it was not possible to get a clear supernatant following centrifugation, a stool extract was prepared using a modification of the method described by Wallace et al\textsuperscript{149} as follows:

**Preparation of stool extract.**

The entire stool specimen was thoroughly homogenised with an Ultra-Turex tissue homogeniser. One gram of the homogenate was boiled with 2.5 millilitres of concentrated AR nitric acid. The mixture was filtered into a 25 millilitre volumetric flask and the residue washed several times with distilled water. 12.5 millilitres of a solution of lithium nitrate containing 30 millimoles per litre of lithium were added and the volume made up to 25 millilitres with distilled water. The final mixture consisted of a 1 in 25 dilution of a stool extract with lithium nitrate now in a concentration of 15 millimoles per litre of
lithium. An aliquot of this mixture was stored at 4°C until analysis. Extracts from each stool were prepared in duplicate.

On the day the specimens were analysed a 1 in 200 dilution of each sample was made with lithium nitrate solution containing 15 millimoles per litre of lithium. Specimens and standards were determined alternately. All dilutions were done in duplicate and the concentration of each dilution measured twice. If the concentration of any duplicate differed by more than 5 per cent fresh dilutions were prepared. Sodium concentration of a specimen was recorded as the mean of the duplicate measurements.

To ensure the stool sodium measured by direct analysis of stool water was comparable to that measured following a preparation of an extract the following experiment was conducted.

Twenty different stool specimens containing varying proportions of solid matter were collected. Each was centrifuged at 2000g for 10 minutes and 0.5 millilitres of supernatant removed for measurement of sodium concentration. The remainder of the stool was thoroughly homogenised and a stool extract prepared as outlined above. Sodium concentration on both the stool extract and stool water was determined.
The results of the experiment are detailed in table A1 and confirm that the two methods of determining sodium concentration in stool are comparable.

Reference.

Table A1. Comparison of sodium concentration in stool as measured by direct analysis of stool water and following preparation of a stool extract.

<table>
<thead>
<tr>
<th>Stool no.</th>
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<td>24</td>
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</table>
Determination of exchangeable sodium.

Exchangeable sodium was measured by means of a dilution technique using radioactive sodium ($^{24}\text{Na}$). The $^{24}\text{Na}$ was supplied as sodium chloride by the S.A. Atomic Energy Board and the Radio Chemical Centre, Amersham.

A quantity calculated to deliver approximately 0.5 microcurie per kilogram body weight was drawn up into a syringe which was then accurately weighed (weight A). A drop was expelled into a test tube for use as a standard and the syringe reweighed (weight B). The $^{24}\text{Na}$ was injected intravenously into the patient and the empty syringe weighed (weight C). Thus the weight of the standard was obtained from wt. A - B and that injected into the patient from wt. B - C.

Blood samples were taken at 3 to 4 hourly intervals thereafter for 22 to 25 hours. The times of injection and sampling were recorded. The serum was separated by centrifugation and $^{24}\text{Na}$ content immediately determined on an accurately weighed aliquot. Sodium concentration of each serum sample was determined.
Each stool and urine specimen passed during this period was accurately weighed. The stools were thoroughly homogenised and $^{24}\text{Na}$ content determined on an accurately weighed aliquot of each stool and urine.

A Packard Modumatic II Auto Gamma counter (model 5120) set to measure the 1.37 MeV peak was used to determine the $^{24}\text{Na}$ content. The content of each sample and the standard was determined on at least three occasions with approximately an hour interval between measurements. Predetermined background activity was subtracted from each measurement.

Correction for decay was made for the standard and each specimen. The corrected count/minute/ml of the specimen was determined for the standard and each serum, stool and urine. The total counts/minute lost in each stool and urine specimen was determined as the product of the corrected count/minute/ml of specimen and the volume of the urine or weight of the stool specimen. The point of equilibration of $^{24}\text{Na}$ in the body was obtained by plotting the corrected count/minute/ml of serum against the time the specimen was obtained (figures A1 - A7). The $^{24}\text{Na}$ count/minute/ml of serum at the point of equilibration was used in calculating the exchangeable sodium.
Calculation of exchangeable sodium.

1. Counts/minute of $^{24}\text{Na}$ injected - $(C_i) = \frac{C_{\text{std}} \times \text{weight of } ^{24}\text{Na} \text{ injected}}{\text{weight } B - C}$

$(C_{\text{std}} = \text{corrected count/minute/ml standard } ^{24}\text{Na}).$

2. Counts/minute of $^{24}\text{Na}$ available for determination of exchangeable sodium - $(C_a) = C_i - \text{sum of counts/minute lost in stool and urine.}$

3. Therefore volume of distribution of $^{24}\text{Na}$ (millilitres) = $\frac{C_a}{C_{\text{ser}}}$

$(C_{\text{ser}} = \text{counts/minute/ml serum at equilibration}).$

The exchangeable sodium was then determined as the product of the volume of distribution of $^{24}\text{Na}$ in litres and the serum sodium concentration at the point of equilibration.

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Figure A.1: Patient 1. Serum Sodium-24 against Time
Figure A.2: Patient 2. Serum Sodium-24 against Time
Figure A.3: Patient 3. Serum Sodium-24 against Time
Figure A.4: Patient 4. Serum Sodium-24 against Time

Counts/min/ml

HOURS

0  5  10  15  20  25
Figure A.5: Patient 5. Serum Sodium-24 against Time
Figure A.6: Patient 6. Serum Sodium-24 against Time
Figure A.7: Patient 7 Serum Sodium-24 against Time
Blood volume measurement.

Blood volume was determined by means of a dilution technique using the patient's own erythrocytes which were labelled with technecium pertechnetate ($^{99m}$Tc). A commercial kit (CIS-Sorin) was used to label the erythrocytes.

Approximately 2 millilitres of whole blood was obtained by venipuncture shortly after the patient was admitted to the metabolic unit. The erythrocytes were immediately labelled according to the kit instructions. The labelled erythrocytes were then drawn up into a syringe which was accurately weighed (weight A). A small quantity was expelled into a 100 millilitre volumetric flask for use as a standard and the syringe reweighed (weight B). The remainder was injected intravenously into the patient and the empty syringe weighed (weight C).

The erythrocytes in the volumetric flask were diluted to 100 millilitres with 5% dextrose water. 0.1 millilitres of the diluted mixture was withdrawn and the $^{99m}$Tc content determined.

Samples of whole blood were obtained by venipuncture at 10, 20 and 40 minutes after injection. Each sample was accurately weighed and the $^{99m}$Tc content determined immediately thereafter.
A Packard Modumatic II Auto-Gamma counter (model 5120) set to measure the 140 keV peak was used to determine the $^{99mTc}$ content.

Calculation of blood volume.

Counts/minute/ml standard ($C_s$) =

Counts/minute of dilute solution $\times$ 1000

Weight of standard in grams ($A - B$)

Total counts/minute injected ($C_i$) =

$C_s \times$ weight in grams of injected erythrocytes ($B - C$).

Blood volume in millilitres = $\frac{C_i}{C_x}$

where $C_x$ represents the counts/minute/ml of the whole blood sample.

The blood volume for each of the three samples was determined and the mean of the three values calculated.
Extracellular fluid volume measurement.

The thiosulphate space was determined in a similar manner to that first described by Friis-Hansen.

A 7 per cent solution of sodium thiosulphate was prepared by the dispensary at the Children's Hospital and sealed in sterile ampoules. 1.5 millilitres per kilogram body weight of this solution was injected intravenously into the patient at a rate of 10 millilitres per minute. Four blood samples were taken. One immediately prior to the injection (for the serum blank determination) and a further three at 10, 20 and 40 minutes after infusion. The exact times of injection and sampling were recorded.

Reagents:

1. 0.67 N sulphuric acid.
2. 2 N hydrochloric acid.
3. 10% (W/V) sodium tungstate.
4. 0.1 N potassium iodate.
5. 0.1 N sodium thiosulphate (with 1 ml chloroform as preservative.)

On the day of the test the following solutions were prepared
potassium iodate and 1 millilitre hydrochloric acid. Seven minutes later 0.2 millilitres potassium iodide was added and the titration against sodium thiosulphate started immediately thereafter. Three drops of starch were added when the yellow colour had almost disappeared.

Calculation.

Serum concentration (mg/100 ml) =

\[
\frac{(\text{titration "serum blank"}) \text{ minus } (\text{titration "serum unknown"})}{\text{titration "reagent blank"}} \times 98.82
\]

Infusion mixture concentration − "I" (mg/100ml) =

\[
\frac{(\text{titration "reagent blank"}) \text{ minus } (\text{titration "dilute infusion mixture"})}{\text{titration "reagent blank"}} \times 98.82 \times 200
\]

The regression line for the \( \log_{10} \) serum concentration against time was calculated using the least squares technique. The intercept gave the serum concentration at time 0, ie. \( C_t \).
The corrected extracellular fluid volume was calculated from:

\[
\frac{V \times I \times (100 - P)}{100 \, C_t}
\]

where \( V \) = volume of thiosulphate infused

\( P \) = percentage serum solids.

References.

1. Friss-Hansen B.
   The extracellular fluid volume in infants and children.
   Acta Paediatrica (Uppsala) 1954;43:444.

2. Mann M.
   Potassium in young children.