MEASUREMENT OF THE FREQUENCY AND CLINICAL RELEVANCE OF MAGNESIUM DEFICIENCY IN ELDERLY HOSPITAL PATIENTS

Brendan Joseph Martin

M.B. Ch.B. (Glasgow) F.R.C.P. (Glasgow)

A thesis submitted to the University of Glasgow for the degree of Doctor of Medicine.

Department of Geriatric Medicine,

Lightburn Hospital, Glasgow G32 6ND.

Submitted September 1993

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

PREFACE

The work which forms the basis of this thesis was undertaken at the Department of Geriatric Medicine, Lightburn Hospital, Glasgow. Until July 1993, as part of the Royal Infirmary Hospital Group, Lightburn hospital served as the main geriatric assessment and rehabilitation centre for the elderly population of east Glasgow. Except where indicated, I personally carried out this work. I have enjoyed collaboration with a number of colleagues and this is formally acknowledged. The writing of this thesis is entirely my own work.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

FIGURE 13

Serum magnesium in elderly subjects receiving Bendrofluazide 5mg daily for treatment of hypertension page 140

ACKNOWLEDGEMENTS

I have received assistance from numerous individuals in the course of this work and I would like to acknowledge the following contributions:

Professor Francis Caird
University Department of Geriatric Medicine,
Southern General Hospital, Glasgow.
Professor Caird was the key person who suggested that my interest in the magnesium status of elderly patients might form the basis of a thesis. He acted as my adviser on the scope and scale of the thesis and assisted with financial support for biochemical analyses of magnesium in erythrocytes and mononuclear blood cells. He was a constant source of encouragement during the preparation of this manuscript.

The following members of staff at the Department of Clinical Biochemistry, Royal Infirmary, Glasgow.

Professor Gordon Fell who kindly provided laboratory resources for the analysis of magnesium in erythrocytes, mononuclear blood cells and autopsy tissue. He was also a helpful critic of my thoughts and ideas relating to measurement of magnesium status in the elderly.

David Lyon who was responsible for developing the methodology for laboratory measurement of magnesium in mononuclear blood cells and autopsy tissue. He also supervised laboratory analysis of erythrocyte magnesium.

Dr Alan McLelland who provided access to Department of Biochemistry Archives and helped retrieve "lost" data.

Dr Dennis O'Reilly who provided access to measurement of parathyroid hormone and blood lipids in hypomagnesaemic subjects receiving oral magnesium supplements.

Dr Mary Gilhooly
Department of Behavioural Sciences, University of Glasgow.
Dr. Gilhooly kindly provided expert advice on the measurement of patient wellbeing for the study of oral magnesium supplementation in hypomagnesaemic patients.

Dr Pamela McKay
Department of Haematology, Royal Infirmary, Glasgow.
Dr McKay kindly provided an expert opinion on the blood film characteristics of patients with skin breakdown in whom erythrocyte magnesium was measured.

The following members of staff at the Department of Geriatric Medicine, Lightburn Hospital, Glasgow.

Ms Karen Milligan, Dietitian, who conducted surveys of dietary magnesium intake in young and elderly patients.

Dr Jean Black, Medical Registrar, who assisted in the follow up of patients in the study of clinical outcome in hypomagnesaemia.

Ms Moreen Lovell, Hospital Pharmacist, who provided magnesium oxide and placebo capsules for the study of oral magnesium supplementation.

Dr Juan Santamaria, Medical Registrar, who carried out ECG analysis in the study of oral magnesium supplementation.

Sister Elizabeth Arbuckle who carried out measurements of blood pressure, grip strength and patient wellbeing in the study of oral magnesium supplementation.

Drs. George Chalmers, Brendan Devine and Paul Knight who referred cases of hypomagnesaemia to me.

Other members of medical and nursing staff at Lightburn Hospital who provided support at various times.

and special thanks to
Mrs Margaret Houldsworth, Secretary, who assisted in the preparation of this manuscript. Her patience and expert typing skills are much appreciated.

SUMMARY

Magnesium is the second most abundant intracellular cation in the human body and has an essential role in many biochemical and physiological processes. Magnesium deficiency has been implicated in the pathogenesis of various diseases such as diabetes mellitus, ischaemic cardiovascular disease and hypertension. Deficiency can potentiate other electrolyte abnormalities and may result in the development of overt neuromuscular and psychiatric symptoms. Symptoms may also be mild and non-specific even in apparently severe deficiency.

Dietary magnesium intake in the elderly tends to be lower than generally recommended and my own surveys indicate that intake amongst elderly subjects living in East Glasgow is even lower than reported elsewhere in the U.K. Principal dietary sources are from foods not rich in magnesium and there is little contribution from drinking water.

Although magnesium is located predominantly in bone, muscle and soft tissues, measurement of serum magnesium is the usual method of determining magnesium status in clinical practice. The mean serum magnesium level in elderly patients admitted to hospital was similar to that found in healthy elderly subjects living at home. However, the range in illness is wider and 5% of patients had a serum level less than 0.66 mmol/l. Severe hypomagnesaemia (serum magnesium less than 0.50 mmol/l) was present in approximately 0.5% of elderly patients admitted

to hospital. However magnesium in serum represents less than 1% of body content and is considered to be an unreliable indicator of body status, especially in illness. Measurements of magnesium in peripheral blood cells were therefore evaluated.

Mean erythrocyte magnesium was 2.30 mmol/l in out-patients and 2.35 mmol/l in in-patients, similar to levels reported elsewhere. However, the distribution of in-patient values was quite skewed with high levels found in patients suffering from skin breakdown and infection. Erythrocyte magnesium concentration reflects body magnesium status at the time of erythropoiesis and can be distorted by changes in red cell turnover that may occur during illness. The raised levels found in patients with skin breakdown and infection almost certainly reflected a change in cell characteristics rather than enhanced magnesium status, thus reducing the value of the measurement in these and possibly other conditions.

Mononuclear blood cell (MBC) magnesium is considered a better indicator of general intracellular magnesium status. Two frames of reference were measured. Healthy subjects had a mean value of 3.5 fmol/cell, similar to other reports, but the same subjects had a mean value of 0.049 umol/mg protein, lower than reported elsewhere. Values for in-patients were higher using fmol/cell measurements ($P = 0.028$) and much lower using umol/mg protein measurements ($P < 0.001$). There was no correlation beween the two methods of measurement. Biological variability and analytical

imprecision limit the use of a single MBC measurement and, as with erythrocytes, alterations in MBC magnesium values during illness could reflect altered cell characteristics rather than true magnesium status.

Magnesium balance is regulated by the kidneys and, except in renal magnesium wasting disorders, urine magnesium falls during deficiency. Mean values for 24 hour urine magnesium excretion were 2.60 mmol for healthy elderly subjects, 1.85 mmol for normomagnesaemic in-patients and 0.96 mmol for hypomagnesaemic in-patients. Normal values for younger healthy adults are reported at 4 - 8 mmol. Accurate urine collections are difficult to obtain and lower excretion in the elderly may reflect impaired renal function rather than magnesium deficit.

Percentage retention of a parenterally adminstered magnesium load has been advocated as a reliable method for assessment of magnesium status in clinical practice. According to test criteria, all healthy elderly subjects studied had some degree of magnesium deficit as did most in-patients in whom deficit was suspected. However it is difficult to relate percentage magnesium retention to the degree of deficit. The prolonged nature of the test, the influence of declining renal function and difficulties with accurate urine collection limit the value of this procedure in elderly patients.

Magnesium levels in autopsy samples of skeletal and cardiac muscle were significantly lower in elderly patients than in young accident victims. No such difference was found for

liver or kidney samples. There was close correlation between magnesium and potassium levels in muscle and heart.

A prevalence study of diuretic therapy in 570 elderly patients revealed a significant reduction in serum magnesium in those taking thiazide diuretics. In a subsequent prospective study of thiazide treatment in 20 elderly hypertensive subjects, serum magnesium fell significantly within 2 months of starting treatment but remained stable thereafter; there was no change in erythrocyte magnesium. A separate analysis of autopsy samples failed to reveal a significant reduction in tissue magnesium in association with diuretic treatment. Diuretics cause mild hypomagnesaemia but evidence of clinically important tissue depletion is inconclusive.

No significant differences were detected in six month survival, duration of hospital stay or proportion of patients discharged home when outcome in hypomagnesaemic elderly patients (serum Mg < 0.65 mmol/l) and normomagnesaemic patients (serum Mg 0.80-0.82 mmol/l) was compared. Furthermore, severe hypomagnesaemia (serum Mg < 0.50 mmol/l), although often associated with severe illness, was not associated with significant increase in six month mortality. Hypomagnesaemia was often associated with hypokalaemia and, in more severe cases, with hyponatraemia.

In a single blind study of oral magnesium supplementation in elderly hypomagnesaemic out-patients, effects of

magnesium oxide (600mg daily for eight weeks) were compared with placebo. There was a significant rise in serum magnesium and serum potassium in the nineteen subjects (initial serum magnesium < 0.70 mmol/l) who received magnesium. No statistically significant changes were noted in other biochemical indices and supplements had no apparent effects on blood pressure, electrocardiogram, grip strength or patient wellbeing. Routine administration of oral magnesium treatment to asymptomatic elderly subjects is of dubious value but further study is required to evaluate the merits of such therapy during illness.

There is no single test in routine clinical use which unequivocally reveals magnesium deficiency. Advanced techniques for measurement of free ionised magnesium hold promise for the future but, for the time being, clinicians must continue to rely on simple laboratory measurements and clinical judgement when considering the implications of possible magnesium deficit in an ill elderly patient.

PART 1

CHAPTERS 1 - 3

BACKGROUND. MAGNESIUM IN CLINICAL PRACTICE

CHAPTER 1

MY INTEREST IN MAGNESIUM

MY INTEREST IN MAGNESIUM

1.1 Introduction

I have had a special interest in the magnesium status of elderly patients since 1980 when, as a senior house officer, I uncovered hypomagnesaemia in a 78 year old man who had presented with ataxia, tremor, and a seizure of uncertain aetiology. The request for a serum magnesium estimation was "unusual" and, having found the level to be low, I am told that my subsequent request for urine magnesium measurement was "the laboratory's first such request on a geriatric patient". The patient's clinical condition improved in association with magnesium supplementation and he eventually returned home.

1.2 A case of hypomagnesaemia

I have since encountered numerous cases of hypomagnesaemia amongst elderly patients and give the following case summary as an example.

An 80 year old woman was admitted to hospital on account of poor mobility, balance impairment, falls and general weakness. Her known medical history included congestive cardiac failure, osteoarthritis and unconfirmed alcohol abuse. Medications comprised frusemide 40mg daily, digoxin 0.125mg daily and potassium supplements, all taken on a regular long-term basis. The principal features on clinical examination were atrial fibrillation at a rate of 110-120/min (ECG) and right heart failure (raised JVP,

peripheral oedema and hepatomegaly).

Despite increasing doses of digoxin and diuretics there was little change in the patient's condition during the first week following admission. Table 1 summarises electrolyte results during this time.
Other results were as follows: aspartate transaminase (AsT) 97 U/l, alanine transaminase (AlT) 45 U/l, total bilirubin 20 umol/l, albumin 31 g/l, haemoglobin 10.9 g/dl, mean corpuscular volume 98 fl. Indices of thyroid function and results of blood glucose, vitamin B12 and folate estimations were within the normal laboratory range.

The patient was treated with magnesium sulphate infusion, 0.25mmol magnesium/kg, followed by a magnesium fortified diet. Her clinical condition gradually improved thereafter; she regained independence within the ward environment and she was able to be discharged home two weeks later. Serum electrolytes had almost returned to normal by the time of discharge.

The same patient was readmitted to hospital 5 months later with similar presenting symptoms of atrial fibrillation poorly controlled with digoxin and moderate heart failure. Biochemical results again indicated magnesium depletion (Serum Mg 0.40mmol/l, urine Mg 0.2mmol/24hrs). Alcohol consumption was confirmed as a contributing predisposing factor on this occasion.

Treatment was similar to the first admission but during this second occasion more emphasis was given to improved

TABLE 1

Serum electrolytes in a hypomagnesaemic patient

		Before magnesium treatment		After treatment
		Day 4	**Day 8**	**Day 21**
Serum:	Na^+	132	132	139 mmol/l
	K^+	3.6	2.6	4.3 mmol/l
	Cl^-	87	96	100 mmol/l
	HCO_3-	30	35	25 mmol/l
	Urea	5.5	5.6	5.6 mmol/l
	Creat.	100	85	85 umol/l
	Ca++(corr)	1.90	1.90	2.10 mmol/l
	PO_4-	1.0	0.95	0.95 mmol/l
	Mg^{++}	0.38	0.39	0.89 mmol/l
Urine magnesium (mmol/24 hours)		0.9	0.7	2.8

diet and limitation of alcohol intake on recovery. The patient was discharged and has since remained relatively well living on her own at home. A urine magnesium at follow up one year later was 2.7 mmol/24hrs and recent serum magnesium levels have been 0.76 and 0.79 mmol/l (four years later).

The hypomagnesaemia noted on both admissions was probably multifactorial and due to diuretics, digoxin, aldosteronism of heart failure, and possibly alcohol and poor diet as contributing factors (see Chapters 2 and 3). The low urine magnesium excretion values were consistent with renal conservation (see Chapter 7).

1.3 Questions raised during clinical practice

Despite being the fourth most abundant cation in the human body magnesium tends not to be measured routinely on serum electolyte requests. Yet, in clinical geriatric practice, as my interest in magnesium has developed and I have sought serum magnesium estimations more often in ill patients, I have regularly encountered mild hypomagnesaemia. I have also uncovered encountered cases of more profound hypomagnesaemia both in severely ill patients and in those who were not so ill. With each case I have become ever more curious and I have come to ask myself a number of questions about magnesium in old age:

1. How common is hypomagnesaemia in the elderly and what are the predisposing factors?

2. To what extent does serum magnesium reflect whole body magnesium status in health and illness?

3. In clinical geriatric practice, how useful and reliable are other methods for determination of body magnesium status?

4. Does hypomagnesaemia contribute significantly to morbidity and does it influence the clinical outcome?

5. Would treatment of hypomagnesaemia benefit affected elderly subjects?

The following chapters describe my attempts to satisfy my own curiosity and, in doing so, to answer these questions.

Chapter 2 is a brief review of magnesium metabolism, the causes, symptoms and signs of magnesium deficiency, the significance of such deficiency in ischaemic heart disease and the emerging therapeutic role for magnesium in myocardial ischaemia.

Chapter 3 considers the uncertainty about dietary magnesium requirements and, within this context, the evidence, including some of my own, pointing to suboptimal dietary intake in the elderly.

Chapters 4 to 8 consider the assessment of magnesium status in the elderly in clinical practice. My own studies of magnesium measurements in serum, erythrocytes, mononuclear blood cells, and urine as well as experience of the magnesium load procedure are outlined. The advantages and drawbacks of each technique are discussed and, where

applicable, the literature pertaining to the elderly is reviewed.

Chapter 9 describes my study of magnesium levels in autopsy tissue from elderly subjects and compares results with those obtained from younger subjects.

Chapter 10 considers the evidence for diuretic-induced magnesium deficiency and describes my own cross-sectional and longitudinal studies in the elderly.

Chapter 11 describes my study observing the influence of hypomagnesaemia on the outcome of illness in elderly patients.

Chapter 12 describes my attempt to examine the clinical and biochemical effects of giving oral magnesium supplements to elderly subjects with mild hypomagnesaemia.

Chapter 13 summarises my observations and suggests some areas worthy of further research.

The literature contains several units of measurement for magnesium in the various body tissues: for uniformity all values in this text are expressed in S.I. units (1 millimol = 2 milliequivalents = 24.3 milligrams).

The following abbreviations have been used:
CI = confidence interval
sd = standard deviation

CHAPTER 2

THE METABOLISM AND CLINICAL IMPORTANCE OF MAGNESIUM

2.1 Summary of biochemical and physiological roles

Magnesium is essential for plant and animal life. Chlorophyll, the green pigment of plants, could not be synthesized without magnesium. In the human body it is the second most abundant intracellular cation and fourth most abundant cation overall. The biochemical and physiological importance of magnesium has been reviewed in detail elsewhere [1,2,3,4]. It is essential in reactions involving adenosine triphosphate and it is responsible for catalysing approximately 300 separate enzyme systems within the body. Its role is that of a co-factor in biochemical reactions involved in cellular energy production and storage, protein synthesis, DNA synthesis, maintenance of cellular electrolyte composition, and glucose metabolism. The physiological properties of magnesium include control of neuronal activity, neuromuscular transmission, myocardial and vascular smooth muscle contractility, and skeletal muscle contraction. It has a role in temperature regulation, normal growth, wound healing, coagulation, thrombogenesis and in immunocompetence.

2.2 Distribution in the human body

The adult body content of magnesium is between 820 and 1150 mmols (20 and 28 grams). About 60% of the total is in bone, 20% is located in skeletal muscle, and the remaining 20% is distributed fairly evenly to other organs including

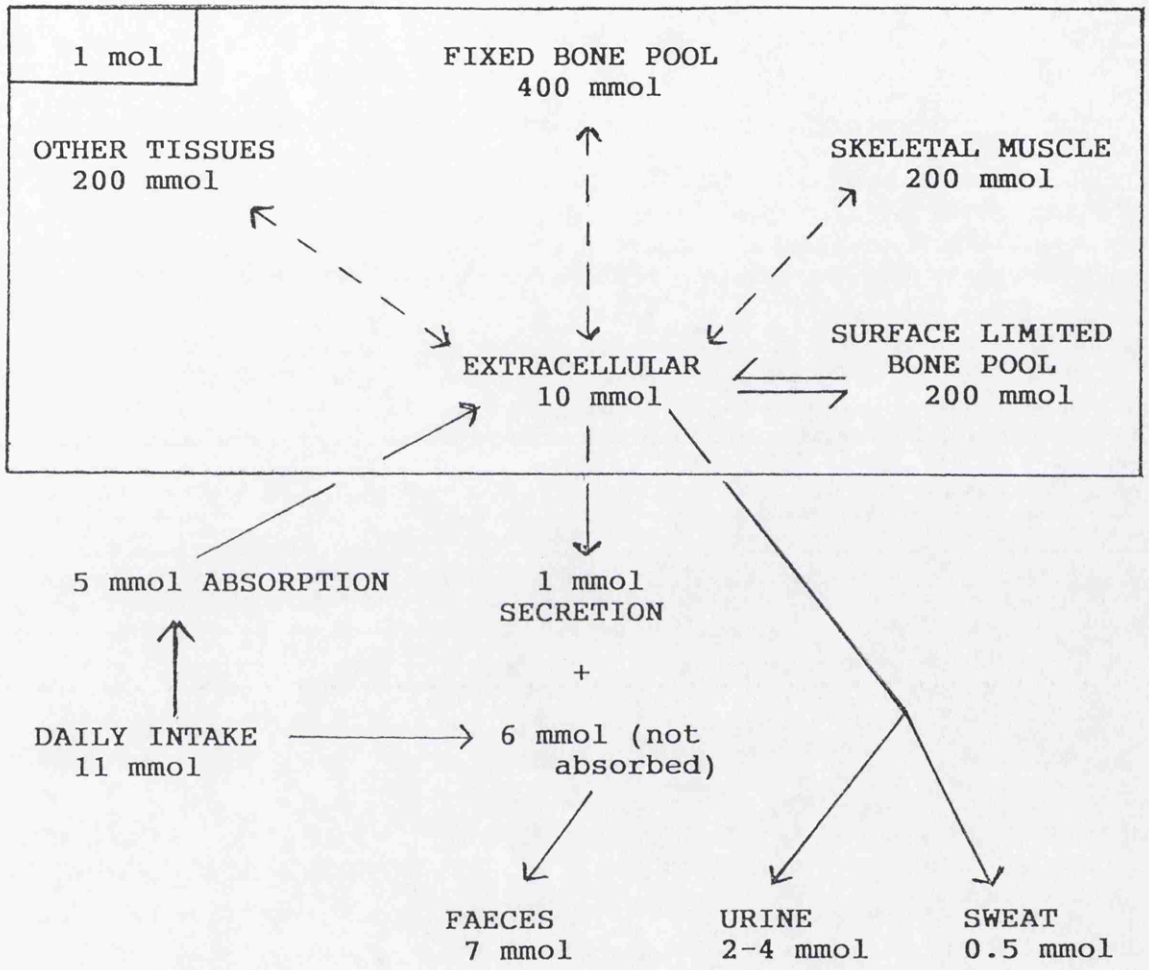
the kidney, liver, pancreas, and heart. Less than 1% is extracellular and approximately one third of the extracellular magnesium is protein bound (Figure 1). Within bone there are two distinct pools of magnesium [5,6]. The crystal mineral lattice portion is fairly stable and release of magnesium from this portion is dependent on bone absorption and formation. It is not influenced by acute changes in serum magnesium. In contrast the surface pool is rapidly exchangeable and is the body's main reservoir for endogenous magnesium. The surface pool is difficult to evaluate clinically, but it is thought to be about 30% of total bone magnesium and appears to correlate well with plasma magnesium concentrations [7].

2.3 Magnesium absorption

The dietary intake of magnesium varies considerably but is generally between 8 and 12 mmol per day, lower than the dietary intake recommended by some (see Chapter 3). Most absorption of magnesium occurs in the mid-ileum [8]. Absorption appears to be influenced by the amount of magnesium in the diet, the smaller the load the greater the percentage of absorption [9]. Drastic dietary reduction is needed to induce negative balance because of extremely effective renal conservation and increasing proportional intestinal absorption with reduced dietary intake. Efficiency of absorption increases from about 25% of ingested magnesium on high magnesium diets to about 75% on magnesium restricted diets [10]. The exact mechanism of magnesium absorption is uncertain but there appears to be a

FIGURE 1

Magnesium Balance



mixture of carrier mediated transport and simple diffusion [11]. The recognition of familial hypomagnesaemia is evidence for a specific magnesium transport mechanism [12,13]. Growth hormone and parathyroid hormone increase absorption [14] and phytates and cellular phosphate reduce absorption. The evidence linking Vitamin D to magnesium absorption is conflicting [15,16,17] Calcium appears to influence magnesium absorption perhaps by sharing a common transport pathway across the intestinal wall, although the evidence is more convincing in animals than in man. A high calcium intake appears to reduce intestinal absorption of magnesium and also increases renal loss [18]. There is little or no absorption of magnesium from the large bowel. There is an obligatory loss of approximately 1 mmol/day from intestinal secretions.

2.4 Renal Handling and Magnesium Excretion

The kidney acts as the main regulator of serum concentration and body magnesium content. It is only the non-protein bound circulating magnesium that is filtered. Once filtered 20 - 30% is reabsorbed in the proximal tubule and a further 50 - 60% is reabsorbed at the level of the thick ascending loop of Henle. A further 1 - 5 % is reabsorbed at the distal convoluted tubule. These latter two steps appear to be under the influence of parathyroid hormone [19,20]. On average 3 - 8% of the filtered load is excreted in the urine. The renal tubule maximum capacity for reabsorption (T max) of magnesium occurs at serum levels around 0.9 mmol/l at the upper end of the normal

range. Hypermagnesaemia is therefore difficult to sustain in the presence of normal renal function. Urine magnesium reflects the amount of magnesium absorbed from the gastrointestinal tract and is therefore closely related to dietary intake under normal circumstances [21]. Reabsorption increases greatly in response to deficiency [22]. Increased urine calcium competitively inhibits renal tubular reabsorption of magnesium in the ascending loop of Henle [23,24]. Hypomagnesaemia can occur with hypercalcaemia of any cause. Hyperaldosteronism, by inducing sodium retention and modest extracellular fluid volume expansion, causes reduced reabsorption of magnesium in the proximal tubule and loop of Henle [25].

2.5 Magnesium lost through perspiration

Magnesium lost through perspiration is usually negligible in temperate climates at around 0.6 mmol/day, but can be higher during work in high temperature environments [18,26].

2.6 Clinical manifestatons of magnesium deficiency

Until the development of atomic absorption spectrophotometry (AAS) in the mid-1960's, techniques for measurement of magnesium in body tissues and fluids were technically complex and unreliable and, as a result, relatively little attention was paid to the role of magnesium in clinical medicine. The availability of AAS provided a simple accurate and reliable method for the

routine measurement of magnesium in small amounts of serum, urine and tissues [27,28]. As measurement techniques became more widely available much was learned about magnesium metabolism and its relevance to clinical medicine. In the early 1980s several reviews were published describing the clinical importance of hypomagnesaemia and magnesium deficiency [29,30,31,32].

The signs and symptoms of magnesium deficiency in humans have been well described by Shils who produced experimental magnesium deficiency in humans by severe dietary restriction (< 0.4 mmol/ kg/day) [22]. His principal biochemical findings were hypocalcaemia and hypokalaemia which occurred in 6 of 7 subjects despite normal intakes of both calcium and potassium. Clinical symptoms of anorexia and apathy preceded neurological signs such as the Trousseau sign and tremors which occurred between 25 and 110 days. Electrocardiographic changes such as prolonged QT intervals were observed in 4 of 7 subjects and electromyographic abnormalities were observed in all 5 subjects monitored. None of the 7 had positive electroencephalographic changes. Magnesium depletion was associated with negative potassium balance and positive sodium and calcium balances. All of the abnormalities reverted to normal with magnesium replacement. Shils was unable to identify any specific symptoms associated with magnesium deficiency per se. All of the clinical manifestations were consistent with hypokalaemia or hypocalcaemia which had occurred secondary to magnesium deficiency.

Flink [29] has classified the clinical manifestations of magnesium deficiency into four categories viz: neuromuscular hyperactivity, psychiatric disturbances, cardiac effects, and potassium and calcium effects (Table 2).

2.7 Causes of magnesium deficiency

The causes of magnesium deficiency are numerous. Table 3, adapted from Flink [29], lists the most commonly found causes. Chernow et al [31] list a few additional causes which might be encountered in the critical care setting e.g. burns, hypothermia, and severe sepsis. Juan [30] lists causes of hypomagnesaemia rather than causes of magnesium deficiency. The two are not synonymous as hypomagnesaemia can be due to intracellular shift of the ion during stress.

Loss of magnesium from skeletal muscle during protein-calorie malnutrition exceeds the loss expected from a simple reduction in protein content and hence the magnesium/nitrogen ratio is reduced. During recovery whole body retention of magnesium is greater than that of nitrogen [33].

Malabsorption and increased intestinal loss are major causes of magnesium deficiency. Hypomagnesaemia can occur in various intestinal mucosal diseases and may also complicate pancreatic insufficiency [34]. The mechanisms leading to magnesium deficiency include reduced mucosal surface area, increased intestinal secretion of magnesium and the formation of insoluble magnesium soaps.

TABLE 2

Clinical manifestations of magnesium deficiency

(adapted from Flink [29])

A. Neuromuscular hyperactivity

1. Tremor of extremities and tongue and grimace of facial muscles
2. Myoclonic jerks
3. Convulsions
4. Chvostek sign (commonly)
5. Trousseau sign (rarely)
6. Spontaneous carpopedal spasm - classical tetany (rarely)
7. Ataxia
8. Nystagmus - both lateral and vertical
9. Dysphagia and gut hypomotility

B. Pyschiatric Disturbances

1. Apathy
2. Some or all facets of delirium
3. Coma

C. Calcium and potassium effects

1. Refractory hypocalcaemia responsive only to magnesium therapy
2. Refractory hypokalaemia with metabolic alkalosis completely responsive only to magnesium therapy

D. Effects on myocardium

1. Ventricular arrhythmias - premature ventricular contractions and ventricular tachycardia
2. Ventricular fibrillation
3. Sudden death

TABLE 3

Causes of magnesium deficiency in adults

(adapted from Flink [29])

A. Nutritional Causes

1. Prolonged parenteral fluid administration, including "total parenteral nutrition" without magnesium
2. Starvation with attendant metabolic acidosis
3. Protein calorie malnutrition and kwashiorkor
4. Alcoholism

B. Intestinal Causes

1. Chronic diarrhoea from any cause
2. Intestinal malabsorption disorders

C. Renal Causes

1. Disease related
   a. Renal tubular acidosis
   b. Diuretic phase of acute tubular necrosis
   c. Chronic glomerulonephritis and pyelonephritis
   d. Familial and sporadic renal magnesium loss
2. Drug-related renal losses
   a. Diuretics - loop and thiazide
   b. Antibiotic-induced tubular dysfunction - gentamicin, ticarcillin, carbenicillin, amphotericin B
   c. Antineoplastic drugs - cisplatin particularly, but also combinations of gentamicin, carbenicillin and a cytotoxic agent

D. Endocrine and Metabolic Causes

1. Primary and secondary aldosteronism
2. Hyperthyroidism
3. Excessive lactation
4. Pregnancy in last trimester
5. Hypercalcaemia due to malignant diseases
6. Primary hyperparathyroidism
7. Diabetic ketoacidosis

Magnesium deficiency secondary to renal magnesium wasting states can be subdivided into those caused by intrinsic tubular disorders and those produced by extrarenal factors. In congenital renal magnesium wasting there is a selective defect in renal magnesium reabsorption leading to hypomagnesaemia. There may be associated loss of calcium and potassium with metabolic alkalosis [35]

Drug induced renal losses are often accompanied by renal potassium loss and hypokalaemia. Digoxin [36] and alcohol [37,38] can increase urine magnesium excretion. Chronic alcoholism is a common cause of magnesium deficiency, being associated with reduced dietary intake, malabsorption secondary to renal and pancreatic disease, increased intestinal loss because of vomiting and diarrhoea, and increased renal excretion.

About 7% of patients presenting with severe diabetic ketoacidosis have hypomagnesaemia. Insulin deficiency leads to release of magnesium from cells and excretion in the urine. Excretion is enhanced by the acidosis and the osmotic diuresis induced by glucose. Ironically insulin treatment drives magnesium into cells and can temporarily worsen hypomagnesaemia [39].

2.8 Magnesium deficiency and the cardiovascular system

Recent reviews have focussed on the links between magnesium deficiency and cardiovascular problems such as hypertension, digitalis toxicity, cardiac arrhythmias and ischaemic heart disease [40,41,42]. Higher death rates from

ischaemic heart disease have been linked to low levels of magnesium in soil and drinking water [43]. Elwood [44] compared autopsy material from subjects who had died from ischaemic heart disease with subjects who had died from other causes and found magnesium to be 20% lower and calcium 10% higher in myocardial tissue of the ischaemic heart disease group. Transient hypomagnesaemia sometimes occurs during the first 24 hours following acute myocardial infarction due to migration of magnesium from the extracellular to the intracellular space. This flux is thought to be secondary to a fall in intracellular ionised magnesium caused by catecholamine induced lipolysis and the formation of insoluble magnesium soaps [45]. Hypomagnesaemia in patients with acute myocardial infarction or congestive cardiac failure increases the risk of ventricular arrhythmias [46].

2.9 The therapeutic role of magnesium

Observations such as these as well as extensive evidence from animal experiments have inspired the recent interest in the possible therapeutic role for magnesium in acute myocardial infarction. Recent randomised studies in which intravenous magnesium has been given to patients with suspected acute myocardial infarction, indicate that such treatment could possibly reduce mortality during the first few weeks by as much as 50% [47]. However, in these studies intravenous magnesium has been administered irrespective of magnesium status and doses have generally been far in excess of normal daily requirements. In all cases mean

serum magnesium post-infusion has been raised above the normal reference range indicating a pharmacological rather than a physiological effect. The problem of distinguishing pharmacological and physiological properties of magnesium has been highlighted [48]. Iseri et al [49] reviewed the early reports of successful magnesium treatment of refractory arrhythmias, some related to digoxin toxicity, in patients considered to be magnesium deficient. It now seems likely that in some cases at least, success was due to pharmacological effects of large doses of parenteral magnesium rather than simply physiological correction of deficiency. The mode of action of magnesium in these clinical situations is unknown and too large a dose could have adverse consequences. Until now treatment has been empirical and further investigations are required to identify optimum dose regimens [50].

2.10 Magnesium in Old Age

In 1983 Seelig drew attention to the mechanisms through which magnesium deficiency might contribute to ill health in old age [51]. She highlighted the need for accurate methods of determining body magnesium status and the requirement for intervention studies in cases of suspected deficiency in the elderly. Subsequent chapters describe my attempts to meet Seelig's challenge.

CHAPTER 3

MAGNESIUM AND DIET

3.1 Availability in food

The nutritional intake of magnesium has diminished since the early 1900's in Western countries with a progressively higher intake of foods which are poor in magnesium. Selective fertilising practice has reduced the magnesium content of agricultural soil and the use of certain pesticides inhibits plant absorption of magnesium. However magnesium remains widely available in food. It is found most abundantly in beans, bananas, cocoa, nuts, whole grain products, cereals, some dark green vegetables such as spinach, and in shell fish [48,52] [Appendix 1].

Some dietary macronutrients such as calcium, phytates, inorganic phosphates, and fat can hinder magnesium absorption [53]. The magnesium content of the diet can be reduced during preparation of food, e.g some magnesium is lost into water when vegetables are boiled [54].

3.2 Dietary magnesium requirements

In considering dietary requirements one must try to distinguish between the average minimum intake necessary to prevent nutritional disease and the optimum intake required for good health. It is generally accepted that the amount of magnesium required to maintain the serum magnesium level within the normal reference range is more than is required to maintain magnesium balance. In circumstances of reduced dietary intake the serum magnesium level may fall as the

body establishes "balance" at a new lower serum level. The new lower level is maintained by increased renal tubular reabsorption and by increased uptake from the gastrointestinal tract. However, the optimum daily requirements for magnesium remain uncertain and results of studies to determine the minimum intake required to maintain health have been conflicting.

Based on balance studies on 102 miscellaneous subjects Nordin concluded that 6 mmol (approximately 0.1 mmol/kg) magnesium daily should be sufficient to maintain serum magnesium levels within the normal range in the healthy adult, whilst the minimum requirement is likely to be in the order of 0.04 mmol/kg per day or less. Nordin was convinced that magnesium deficiency could not result from dietary deficiency in normal people on ordinary diets [21]. Jones and colleagues found that less than 0.12 mmol/kg per day induced negative balance in healthy adults and that at least 0.17 mmol/kg per day is needed to ensure positive balance. However, obese subjects managed positive balance on 0.08 mmol/kg per day [55].

On the other hand Seelig carried out extensive reviews to present evidence of a dietary requirement of at least 0.21 mmol/kg per day in health. She has pointed out that most of the metabolic balance data are derived from studies of young adults on controlled dietary intakes and do not reflect altered needs during growth and illness. Since magnesium plays an important role in protein and nucleic acid synthesis, Seelig has recommended safe dietary levels

of 0.25 mmol/kg per day for women and 0.29 - 0.42 mg/kg per day for men [53,56].

She also believes that the elderly have higher dietary requirements and this view is shared by others. Intakes of up to 30 mmol magnesium per day have been suggested for the elderly [57,58].

3.3 United Kingdom recommended dietary allowance for magnesium

Until recently there was no specific United Kingdom recommended dietary allowance (RDA) for magnesium and investigators usually referred to the United States Food and Nutrition Board RDA of 12.5 - 14.5 mmol per day (0.21 mmol/kg) [59]. However, the recent report of the Panel on Dietary Reference Values has produced a dietary recommendation for the UK which is more conservative [60] and reflects the calculated national average daily intake of magnesium amongst adults [61,62]. The report estimates the average daily dietary requirement to be 10.3 mmol for adult men and 8.2 mmol for adult women with lower safety limits of 7.8 mmol and 6.2 mmol respectively. Expressed in terms of body weight, the average daily requirement is estimated to be 0.14 mmol/kg per day for all adults, including the elderly.

3.4 Dietary magnesium intake of the elderly

A 1977/78 Nationwide Food Consumption survey in the U.S.A. revealed that 75% elderly men had magnesium intakes below

the RDA of 14.5 mmol and almost 1 in 6 elderly women consumed less than 6 mmol (RDA for women 12.5 mmol) [63]. A more recent survey of 270 free living elderly (less than 75 years) in Adelaide, Australia, revealed 42% of males and 36% of females had a magnesium intake below the Australian RDA (13.5 mmol for men and 11.25 mmol for women) [64].

3.5 Dietary magnesium intake of the elderly in Glasgow

A survey of 264 elderly subjects living at home in north Glasgow between 1969 and 1972 revealed a wide scatter of dietary magnesium intake with an average daily intake of 13.5 mmol in 77 men and 9.5 mmol in 187 women [65]. However two more recent studies from elsewhere in the UK suggest that the Glasgow study may have overestimated magnesium intake in the elderly [66,67].

In view of this discrepancy and as part of a study to assess the effects of diuretic therapy on magnesium status at the time of hospital admission [68], I asked my colleague Karen Milligan (senior hospital dietitian) to estimate and compare the daily dietary magnesium intakes of 50 frail elderly subjects and 50 younger subjects in relatively good health living in east Glasgow.

a) Subject selection and method of estimation

The elderly subjects were selected from hospital in-patients within one week of their admission to Lightburn Hospital. Patients were selected for interview only if deemed able to give a reliable dietary history. The

assessments were of home diet prior to hospital admission and were based on patient recall, each patient being interviewed on two or three occasions to determine normal food habits. When possible, corroborative information was obtained from carers.

The 50 younger subjects, selected at random from patients attending a hospital contact dermatitis clinic, were interviewed on one occasion only and magnesium intake was based on 24 hour dietary recall.
For both groups the magnesium content of various foodstuffs was derived using standard food tables [69].

b) Results

The findings of the two surveys are summarised in Table 4. In 14% of elderly patients magnesium intake was estimated to be less than 4.11 mmol (100 mg) per day. Expressed in relation to body weight the average intakes were 0.11 mmol/kg per day (sd 0.04) for both men and women. Expressed similarly, the daily intakes of the younger subjects were 0.11 mmol/kg (sd 0.05) for females and 0.12 mmol/kg (sd 0.06) for males. The younger subjects therefore had higher total daily intakes than elderly subjects but intakes were broadly similar when expressed in terms of body weight.

c) Comment

The calculated dietary magnesium intake is lower than found elsewhere but, as the surveys were retrospective and relied on recall without direct analysis of food consumed, the consumption of both groups may have been underestimated.

TABLE 4

Estimated dietary magnesium intake in east Glasgow

Subjects	Number and sex	Mean age (years)	Estimated intake mmol/day mean (sd)
Elderly (recent hospital admissions)	13 male	79	6.8 (2.4)
	37 female	81	6.0 (2.0)
Younger adults (out-patient attenders)	19 male	51	8.5 (3.0)
	31 female	42	7.6 (3.2)

The results of the other surveys of magnesium intake of elderly subjects in the United Kingdom [65,66,67] are summarised in Table 5. The most accurate study to date is that carried out by Bunker and Lawson who used duplicate biochemical analysis techniques [67]. The housebound subjects described in their study and those in hospital and at home in Belfast (66) had an intake approximately 25% greater than the estimated intake in our east Glasgow survey. Duplicate biochemical analysis techniques provide an accurate record of intake whereas even the best dietary record/history can only be an approximation. However weighing of actual diet components as in the Belfast study provides a more accurate record than history alone.

Although the magnesium intake of the subjects in our survey was perhaps underestimated there is other evidence to support low intake. The serum magnesium levels of 0.87 mmol/l for healthy elderly subjects and 0.86 mmol/l for housebound subjects described by Bunker and Lawson [67] are higher than those of elderly living in Glasgow who have mean values of 0.81 mmol/l (see Chapter 4). Similarly the urine excretion values of 2.6 mmol/day (housebound) and 3.2 mmol/day (healthy) reported by Bunker and Lawson are also slightly higher than found in the elderly population of east Glasgow (see Chapter 7).

Within the United Kingdom there is considerable geographical variation in dietary pattern with lower consumption of fruit and fresh green vegetables in Scotland contributing to a lower magnesium intake [70]. Compared

TABLE 5 - Dietary magnesium intake in the elderly - Other UK studies

Authors Year [Ref]	Site Category	Measurement Method	Number & Sex of Subjects	Mean Age (Years)	Magnesium Intake (mmol)
Macleod et al 1969 - 72 [65]	Glasgow North	7 Day Dietary Record	Males 77	73	13.5
			Females 187	75	9.5
	Living at Home	Food Tables			
Vir & Love 1974 - 76 [66]	Belfast Hospital (Long Term)	Weighed Diet Food Tables	Males 24	80	8.1
			Females 73		6.9
	Living At Home		Males 15	77	8.75
			Females 38		8.0
Bunker et al 1985 - 86 [67]	Southampton Healthy At Home	5 Day Metabolic Balance + Duplicate Biochemical Analysis	Males 11	76	
			Females 13		10.7
	Housebound		Males 7	78	
			Females 13		8.1

with the U.K. average intakes for men aged 16 - 64, men in Scotland have a significantly lower intake of magnesium. Magnesium intake of Scottish women aged 16 - 64 is also lower than in other regions, although the difference is less than in men [62]. Magnesium intake is also affected by socioeconomic status, being lower in low income families. Similar regional differences in nutrient consumption have previously been reported in the elderly population [71]. However, differences may be offset by relative energy consumption when magnesium intake is expressed as a ratio of energy intake [62]. East Glasgow has a high proportion of low income families and unemployment rates are high. The diet, especially that consumed by older generations, is not plentiful in magnesium rich food and most magnesium is derived from the large quantities of bread and milk consumed. Another factor often overlooked in dietary surveys is the contribution from drinking water. Glasgow water has relatively little magnesium, the value for east Glasgow being 0.02 - 0.04 mmol/l [72]. By contrast in certain areas of England, borehole water has a magnesium concentration of approximately 2 mmol/l.

Amongst the elderly in hospital there is evidence to suggest that, even when the magnesium content of the available diet is relatively low, the effect of patient selection lowers still further the actual magnesium intake [73]. The same effect is likely to be seen in the frail elderly at home, many of whom are reliant on home help and meals-on-wheels services for meal provision.

3.6 Summary

The recommended dietary intake for magnesium has tended to be higher than the actual intake of magnesium amongst elderly subjects. The recent United Kingdom RDA is more conservative than previous United States and Australian recommendations for magnesium intake and more accurately reflects actual intake in this country. However it is likely that elderly subjects living in east Glasgow continue to have a lower intake than elsewhere. Principal dietary sources are from foods not rich in magnesium (e.g bread and milk) and there is relatively little contribution to dietary magnesium from drinking water. Our evidence suggests that the elderly subjects of east Glasgow establish magnesium balance at lower serum levels as a consequence of reduced intake and this is reflected in lower urinary output of magnesium. Nordin has observed that magnesium output in urine is closely related to dietary intake [21].

PART 2

CHAPTERS 4 - 9

ASSESSMENT OF MAGNESIUM STATUS IN CLINICAL GERIATRIC PRACTICE

CHAPTER 4

SERUM MAGNESIUM

4.1 Introduction

Serum magnesium comprises less than 1% of the total body magnesium pool but, being the most readily available specimen, it is the usual method of determining magnesium status in clinical practice. Magnesium in serum exists in three fractions; an ultrafilterable fraction consisting of free ionised magnesium (60 - 62%), magnesium complexed to citrate, bicarbonate and phosphate (5%), and a protein-bound non-ultrafilterable fraction (33 - 34%) [74]. Approximately 25% of the total serum magnesium is bound to albumin and 8% to globulins. The ionised fraction is believed to be the physiological active fraction. Patients frequently have alterations in serum proteins and changes in acid-base status which alters protein binding, and so in illness serum total magnesium correlates poorly with the ionised fraction. Ultrafilterable magnesium comprises mainly the ionised fraction, and Zaloga et al [75] have demonstrated that serum total magnesium has 100% sensitivity and 73% specificity for detecting ultrafilterable hypomagnesaemia.

4.2 Technical Considerations

Atomic absorption spectrophotometry (AAS) is the current method of choice for measurement of serum magnesium. It has advantages over other methods in terms of precision, sensitivity, accuracy, and specificity [76,77]. Dye

binding methods recover less magnesium than atomic absorption at low serum levels, whereas at high serum levels this situation is reversed. Thus reference ranges tend to be wider with dye binding methods of measurement. In terms of precision, sensitivity and accuracy the titan yellow method is the least desirable of the dye binding methods [76,77].

It is important that blood is taken without undue stasis to avoid artificial elevation of serum levels caused by a combination of egress of cellular magnesium and raised serum proteins [78,79]. I have demonstrated the importance of separation of serum from erythrocytes as soon as possible after blood is drawn and certainly with four hours [80].

Serum magnesium has a circadian rhythm and for accuracy, when making intra-individual comparisons, the sample should be taken at the same time each day. The peak phase for serum magnesium is late forenoon for both elderly males and females [81].

4.3 Serum magnesium in Healthy Populations (using AAS)

The normal range for serum magnesium in healthy adults in the United States has been well defined by Lowenstein and Stanton [82]. Samples from over 15,000 persons revealed a mean serum level for the age range 18 - 74 years of 0.85 mmol/l. 95% of samples fell within the range 0.75 - 0.96 mmol/l. Levels were slightly higher for both sexes in infancy and childhood but fell during adult years and

remained relatively stable thereafter.

The same authors reviewed the world literature on serum magnesium in healthy adult populations. They considered 18 studies in nine difference countries in which serum magnesium had been measured using atomic absorption spectrophotometry. The mean population values for studies carried out in European countries (Germany, France, Denmark, and England) ranged from 0.74 - 0.85 mmol/l. Most studies showed slightly higher levels for adult men compared with women.

4.4 Serum magnesium (by AAS) in adults living in Glasgow

The mean serum level in the healthy adult population of the Greater Glasgow area is lower than that reported for the United States. Seventy-one healthy volunteers, mean age 38.5 years (range 19 - 65), participating in the Good Hearted Glasgow Project [83], were found to have a mean serum level of 0.79 mmol/l (sd 0.06) and range of 0.65 to 0.98 mmol/l. The samples were measured at the Department of Clinical Chemistry, Glasgow Royal Infirmary, using atomic absorption spectometry. The analytical error for the laboratory is very small* and intra-subject sampling has revealed a biological variation of less than 5% for samples taken one week apart.

* (The laboratory within-assay and between-assay standard deviations, for serum magnesium in the range 0.4 - 1.10 mmol/l, are 0.005 and 0.01 respectively.)

4.5 Serum magnesium (by AAS) in hospital and clinic patients

It was pointed out by Lowenstein and Stanton (82) that clinical ranges for serum magnesium tend to be greater as they include a greater percentage of abnormally low and high values. Mean values from clinical groups tend to be the same as in the healthy populations from which the samples are taken. Jackson and Mair [84] in 1968 suggested that routine serum magnesium measurement might be worthwhile in clinic patients after they demonstrated the association between hypomagnesaemia and certain clinical conditions. In a study of 5,100 patients they found a mean serum magnesium level of 0.89 mmol/l (sd 0.08). They found that up to 20% of hypomagnesaemic patients had diabetes mellitus compared to only 3.8% with normal serum levels. Similarly 13% of patients on diuretic therapy were hypomagnesaemic compared to only 4.8% with normal serum levels.

Whang and colleagues [85] recommended routine measurement of serum magnesium with urea and electrolytes in all hospital patients after finding that 6.9% were hypomagnesaemic (less than 0.63 mmol/l) and that the condition was associated with alcohol related disease, diabetes mellitus, chronic airways disease, hypertension, and anaemia. The same authors [86] reiterated this recommendation several years later by demonstrating that hypomagnesaemia was associated with hypokalaemia, hypophosphataemia, hyponatraemia, and hypocalcaemia.

Wong and colleagues [87] supported routine serum magnesium estimation after finding that 11% of hospitalised patients had low serum magnesium levels (< 0.6 mmol/l) and that, after correction for protein binding, hypocalcaemic patients had double the rate of hypomagnesaemia of other hospital patients.

4.6 Serum magnesium (by AAS) in intensive care patients

Ryzen et al [88] in a study of 94 severely ill patients in intensive care found that 65% of those with normal renal function were hypomagnesaemic (< 0.53 mmol/l) and 50% of patients so affected had alcohol related disease. In a study of 193 patients admitted to post-operative intensive care units Chernow et al [89] found 117 (61%) were hypomagnesaemic. Higher mortality and more hypokalaemia were found in severely hypomagnesaemic patients (< 0.5 mmol/l) than in similarly ill patients with normal serum magnesium levels. Several authors have shown reduced serum magnesium associated with acute myocardial infarction [90,91].

4.7 Serum magnesium in Hospital Patients using a dye binding method

Reference intervals for serum magnesium have also been determined for hospital patients using a dye based colorimetric method of measurement [92]. The mean value for 800 patients was 0.82 mmol/l with 95% of samples falling between 0.63 and 1.05 mmol/l. Exclusion of samples

with co-existent abnormalities of calcium, albumin or alkaline phosphatase produced little change in reference intervals for serum magnesium. The mean value for the 473 remaining patients was 0.81 mmol/l with 95% of values between 0.64 and 1.03 mmol/l. These authors again found the serum concentration of magnesium in men to be slightly higher than in women and the mean value for each sex increased with age significantly between the third and ninth decades. The authors attributed this rise to progressive impairment of renal function.

4.8 Serum magnesium in the elderly

There have been relatively few studies of serum magnesium in exclusively elderly populations. Table 6 summarises the findings of investigators other than myself where subjects taking diuretic therapy have been excluded and atomic absorption spectrophotometry was the method of measurement [93,94,95,96,97]. Mean values range from 0.79 mmol/l in elderly Day Hospital attenders in Ireland, to 0.89 mmol/l in healthy elderly women in Sweden.

In 1973 Leask et al [98] used a dye binding technique [99] to measure serum magnesium in 41 elderly subjects (65 and over) living at home either in North Glasgow or Kilsyth. They found a normal distribution of results with 95% between 0.62 and 1.02 mmol/l. The mean value overall was 0.82 mmol/l but was slightly higher in men (0.84 mmol/l compared with 0.81 mmol/l for women).

TABLE 6

Serum magnesium in the elderly - other investigators' results

(Using Atomic Absorption Spectrophotometry)

Author Country	Population type	Number of subjects	Mean age	Serum mmol/l mean (sd)
Petersen Denmark 1977 [93]	Healthy	43 Men	60*	0.82 (0.05)
		30 Women	60*	0.81 (0.07)
Landahl Sweden 1980 [94]	Healthy	55 Men	70*	0.85 (0.06)
		55 Women	70*	0.89 (0.08)
Hayes Ireland 1989 [95]	Day Hospital Attenders	25 Men	77 (M + F)	0.79 (0.09)
Sherwood England 1986 [96]	Geriatric Admissions	17 Men	83	0.84 (0.14)
		27 Women	(M + F)	
	Geriatric Admissions	14 Men	80	0.80 (0.09)
		39 Women	(M + F)	
Touitou France 1987 [97]	Long Term Care	198	80 (M + F)	0.83 (0.07)

* = all subjects

4.9 Personal Studies of serum magnesium in the Elderly

a) Introduction

Over the years I have requested estimation of serum magnesium on many occasions in the course of my clinical practice. The estimation is now performed on my patients whenever magnesium depletion could be a factor in illness and is therefore currently measured at least once on the majority of my in-patient cases.

b) Blood sampling

Initial samples were taken by me as part of my research interest [100], but in recent years most in-patient samples have been taken by members of junior medical staff under my supervision. These staff are instructed on the problems posed by excessive stasis and delayed analysis of samples. Most samples from out-patients and all samples taken from healthy elderly volunteers for research purposes continue to be drawn by me. Except in acute illness, almost all samples are taken between 0800 and 1100 hours.

c) Laboratory analysis

Atomic absorption spectrophotometry has been used for all serum magnesium estimations. Initial samples were measured in the Department of Biochemistry, Victoria Infirmary, Glasgow [100]. Since 1985 all serum estimations have been performed at the department of Clinical Chemistry, Royal Infirmary, Glasgow. The standard deviation for

within-assay comparisons in the latter laboratory, for serum magnesium in the range 0.4 - 1.10 mmol/l, is 0.005. By agreement with the laboratory, serum not separated from cells by centrifugation within 4 hours of sampling time is not analysed for magnesium [80].

d) Results

Table 7 is a summary of serum magnesium results extracted from my studies of magnesium status in the elderly. Analysis of my in-patient results reveals a slight rise in serum magnesium with age from 65 years upwards and the trend is just significant at the 5% level (Figure 2). Comparison of serum magnesium with serum creatinine reveals a significant positive relationship between the two even within the range of serum magnesium 0.70 - 0.92 mmol/l (mean + sd for the in-patient population) (Figure 3). Data from these studies will be presented in more detail in subsequent chapters.

e) General observations

Serum levels in the elderly do not differ significantly from those of younger adults. As is the case with younger adults, ranges in illness tend to be wider than those in health although mean values usually coincide with those of the healthy population. The slight rise in serum magnesium with age is consistent with studies of younger subjects which have shown a rise in serum magnesium from the age of 20 onwards [82,92].

TABLE 7

Serum magnesium in the elderly - Personal studies

Date Population [reference]	Number of Subjects	Age (Mean)	Serum mmol/l mean (sd)
1981 Hospital admissions [100]	107 (M+F)	80	0.80 (0.11)
1987 Hospital admissions* [66]	250 (M+F)	81	0.82 (0.10)
1988 Outpatients (Unpublished)	41 M 105 F	74 78	0.78 (0.08) 0.76 (0.08)
1988 Healthy elderly at home ** (unpublished)	11 M 27 F	71 75	0.81 (0.06) 0.81 (0.06)
1991 Hospital admissions [101]	1576 (M+F)	81.5	0.81 (median)

* None taking diuretic treatment

** Attenders at a lunch and dance club

FIGURE 2 Relationship between serum magnesium and age in in elderly subjects admitted to hospital

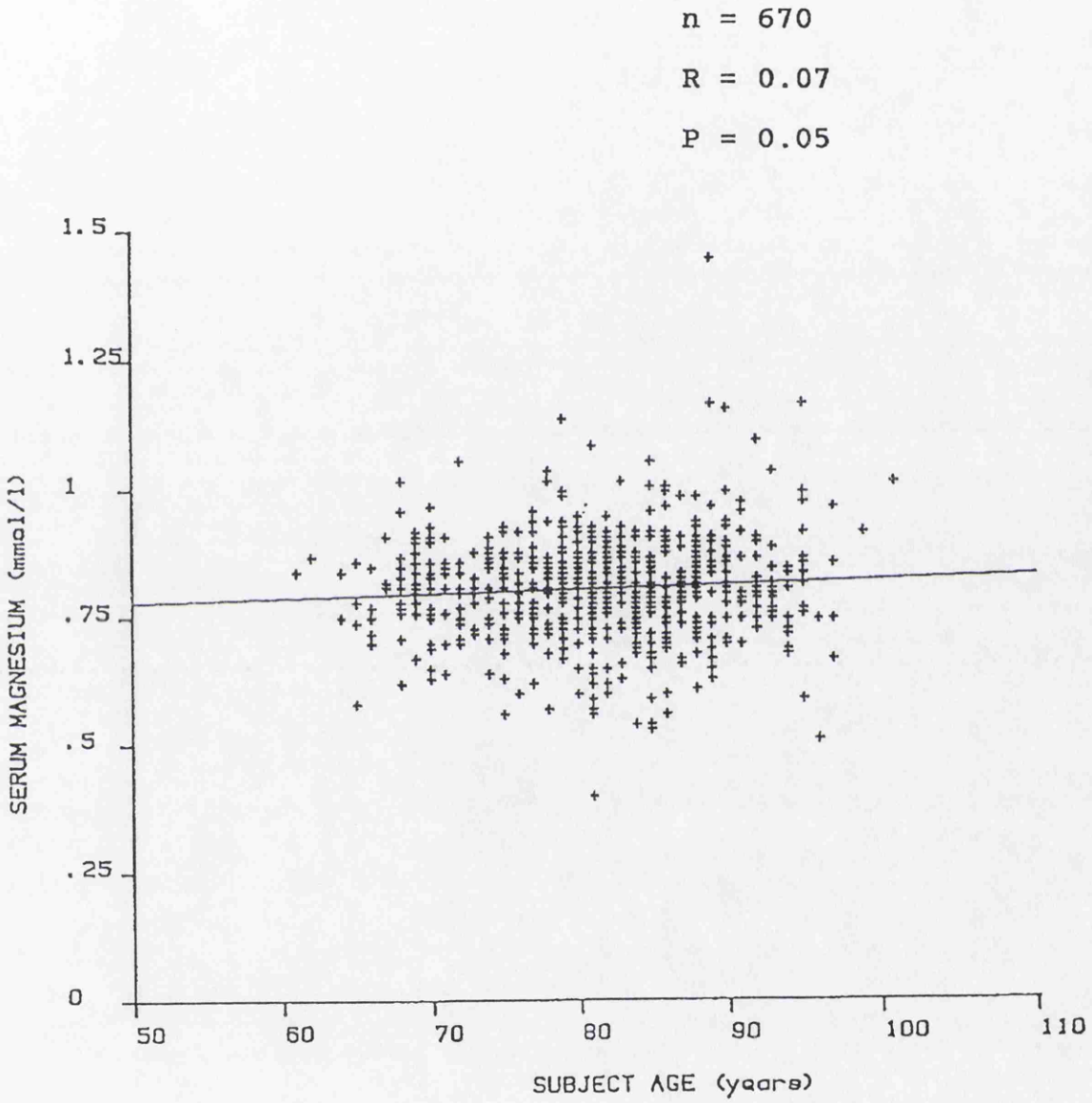
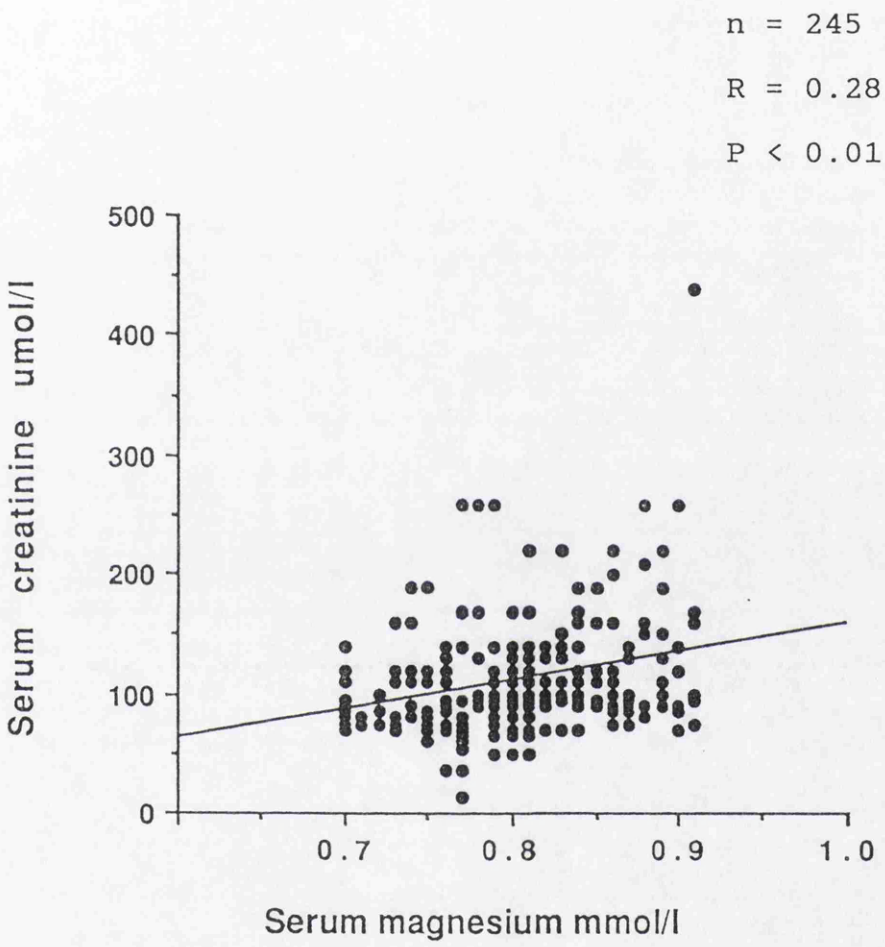


FIGURE 3 Relationship between magnesium and creatinine in serum in elderly subjects admitted to hospital

(serum magnesium range 0.70 - 0.92 mmol/l)



4.10 Drawbacks of serum magnesium as an indicator of body magnesium status

Although easily measured serum magnesium represents less than 1% of total body stores. It is the ionised (free) portion which is important but most clinical data are based on measurement of total serum magnesium. The ionised portion, which is affected by protein binding and acid-base status, is difficult to measure. Alkalosis increases protein binding whereas acidosis decreases it [102]. Cellular depletion can exist with normal serum levels and hypomagnesaemia per se does not mean unequivocal magnesium depletion. During total starvation serum levels may be maintained despite tissue depletion because of catabolic release of intracellular magnesium [33]. Serum levels may be lowered during the stress of severe illness especially if there is significant pain [103]. This is likely to be related to adrenalin release which lowers serum magnesium by causing a shift into cells [104,105]. Adrenocorticotrophic hormone and insulin have a similar effect [39,106]. Many of the cases of hypomagnesaemia reported in medical and surgical intensive care may not have had tissue magnesium depletion. When such cases were followed up serum magnesium returned to normal within a short time [107].

The clinical significance of hypomagnesaemia in severe illness is uncertain. Many patients remain asymptomatic whilst others seem to be at risk of serious neurological and cardiological complications. Routine measurement of

serum magnesium continues to be recommended [108] but difficulty with measurement of the free ionised component restricts our knowledge of the significance of magnesium changes in illness. One approach might be to measure ultrafilterable magnesium more often [102].

CHAPTER 5

ERYTHROCYTE MAGNESIUM

5.1 Introduction

Erythrocyte magnesium has been advocated as one of the two basic measurements of magnesium status in clinical pratice, the other being serum magnesium, and a mean value of 2.30 mmol/l (sd 0.24) for erythrocyte magnesium in healthy adults has been derived from several population studies [109]. The measurement has been used in a variety of clinical situations on the basis that it provides a reasonably good and simple guide to body stores [90,110,111,112,113,].

5.2 Erythrocyte magnesium in elderly patients

This study was performed to compare erythrocyte magnesium levels in elderly out-patient attenders with levels in ill elderly patients on hospital admission and to assess the effects of illness, if any, on erythrocyte magnesium measurement.

a) Subjects

Serum and erythrocytes were assayed for magnesium in 150 consecutive out-patient attenders, mean age 77 years (sd 6.2), and in 100 in-patients, mean age 80 years (sd 7.4), during the first week of hospital admission. Each patient was allocated to one or more of 25 diagnostic subgroups based on known history, presenting clinical features and current medications.

b) Blood sampling and laboratory analysis

All samples were obtained between 0900 and 1100 hours. Blood was drawn into 4ml potassium EDTA glass bottles without undue stasis. The whole blood samples were mixed on a rotary mixer and an aliquot taken and diluted 1 + 80 with lanthanum chloride. Samples were then spun at 2,500 rpm for 5 minutes using a Mistral 2000 centrifuge; serum samples were obtained and likewise diluted 1 + 80 with 0.5% lanthanum chloride. The magnesium content of both sample types was measured by flame atomic absorption using a Perkin Elmer 3030 atomic absorption spectrophotometer. The erythrocyte magnesium concentration was calculated by subtraction of the serum value from the value for whole blood magnesium with correction for the haematocrit:

$$R = S + (100\ [W - S] / H)$$

where R = erythrocyte magnesium, S = serum magnesium, W = whole blood magnesium and H = haematocrit (%).

The precision of both whole blood and serum assays was better than 2%. Intrasubject temporal variation for erythrocyte magnesium was assessed by performing 2 measurements 8 weeks apart on 16 healthy subjects. There was little change with time, the coefficient of variation being 4.2%.

c) Statistical methods

Kruskal-Wallis non-parametric test for independent groups and one way analysis of variance were used to compare erythrocyte magnesium levels of the diagnostic subgroups.

d) Results.

(i) Comparison with other studies

Table 8 shows the erythrocyte magnesium results for the in-patient and out-patient study groups. The findings are compared with the results of three previous studies of erythrocyte magnesium in elderly subjects also summarised within the table. In-patient values appear to be higher but differences were not significant for either sex. In fact the values for in-patients were considerably skewed with the median value being 2.28 mmol/l, 95% CI 1.76 - 3.24 (skew 0.82). Out-patient results on the other hand followed a near normal distribution, median value 2.32 (skew 0.16).

Serum magnesium levels were normally distributed and mean values were similar for both in-patients and out-patients, 0.79 mmol/l (sd 0.08) and 0.77 mmol/l (sd 0.07) respectively, with no significant sex difference within either group. There was a significant correlation between erythrocyte and serum values for out-patient samples, $R = 0.29$; $P < 0.001$, but not for for in-patients, $R = 0.14$.

(ii) Effects of illness

There were no significant differences between out-patient diagnostic subgroups. However, amongst in-patients, those with infections had slightly higher erythrocyte magnesium levels and the subgroup admitted with infected pressure sores had much higher values. Table 9 shows the values for the 6 largest in-patient diagnostic subgroups listed

TABLE 8

Erythrocyte magnesium in elderly subjects

Authors	Subjects	Number	Age (years) mean (sd)	Eryth. mg. mmol/l mean (sd)
Personal study	Geriatric out-patients	46 male	75 (5.6)	2.33 (0.32)
		104 female	79 (6.0)	2.29 (0.29)
Personal study	Geriatric hospital admissions	35 male	78 (6.5)	2.35 (0.38)
		65 female	81 (7.8)	2.35 (0.38)
Sherwood et al. [96]	Geriatric hospital admissions	104 (31 male)	81 (6.4)	2.48 (0.34)
Touitou et al. [97]	Geriatric long-term care	90 male	80 (9.5)	2.30 (0.30)
		291 female		2.32 (0.30)
Petersen et al. [93]	Healthy at home *	43 male	60 (all)	1.95 (0.18)
		30 female		2.03 (0.21)

* no diuretics or magnesium containing medications

TABLE 9

Erythrocyte magnesium: In-patient diagnostic groupings

Diagnosis	number	erythrocyte magnesium mmol/l mean (sd)	95% confidence interval
Alcohol related disease	8	1.98 (0.15)	1.85 - 2.11
Degenerative joint disease	11	2.24 (0.23)	2.04 - 2.44
Congestive cardiac failure	10	2.28 (0.23)	2.11 - 2.45
Cerebrovascular disease	20	2.32 (0.34)	2.16 - 2.48
Respiratory infection	10 *	2.59 (0.48)	2.19 - 3.00
Pressure sore(s)	9 **	2.85 (0.47)	2.48 - 3.21

* significant at 0.05 level

** chi square = 22.6, P = 0.0009

according to rank. Despite having elevated erythrocyte magnesium levels, the nine patients admitted with pressure sores had a mean serum magnesium level of 0.78 mmol/l (sd 0.08), marginally lower than the in-patient group as a whole. Five of these patients made a complete recovery and had repeat erythrocyte magnesium measurements. Values fell in all five from a mean of 3.06 (mmol/l (sd 0.28) to 2.38 mmol/l (sd 0.48) over an average interval of six weeks. Retrospective analysis of available haematological data on patients with infections and/or pressure sores did not reveal any relationships between raised erythrocyte magnesium and other indices such as haemoglobin, mean corpuscular volume, leucocyte count or platelet count.

5.3 Further study of erythrocyte magnesium in patients with pressure sores

In view of the above results suggesting an association between skin breakdown and infection and elevation of erythrocyte magnesium the following additional study was performed.

a) Patients and methods

During a six month period patients admitted to hospital with pressure sores were identified. Serum and erythrocyte magnesium, full blood count and reticulocyte count were measured in the standard manner but the blood films from each patient were selected for special study by a trained

haematologist. When possible the laboratory measurements were repeated after an interval of 8 weeks irrespective of skin condition.

b) Results

Of the patients identified during the study period, repeat samples at eight weeks were obtained in six of them. Results are shown in Table 10. All six patients had an elevated erythrocyte magnesium in at least one sample, usually associated with a moderately high reticulocyte count (normal laboratory range = 30 - 100 x 10^9/l). There was considerable variation in erythrocyte magnesium level between samples. Serum magnesium levels were low or normal in five patients and varied little between samples. No other abnormalities which could explain elevated erythrocyte magnesium were noted on examination of the blood films.

5.4 Discussion

The erythrocyte is not a typical cell. It has no nucleus and no mitochondria and the magnesium content is low compared with other cells. Most erythrocyte magnesium is in the haemoglobin. Magnesium enters the cells at erythropoeisis and tends to leak out exponentially as the cell ages [114,115]. The half period for red cell magnesium has been estimated at 22.4 days [116]. There is virtually no "exchange" of magnesium between plasma and red cells and the amount of magnesium in erythrocytes is largely a function of two variables; the age of the cells and the

TABLE 10

Erythrocyte magnesium and haematological indices in six patients with pressure sores: two measurements taken 8 weeks apart

Sample	Erythrocyte magnesium mmol/l	Serum magnesium mmol/l	Mean corpuscular volume fl	Reticulocyte count x 10^9/l
1	3.38	0.80	101	115
2	2.38	0.82	95	79
1	3.46	0.81	84	132
2	2.00	0.70	81	49
1	2.69	0.91	88	82
2	3.20	0.83	104	144
1	2.76	0.66	87	108
2	2.67	0.74	87	118
1	2.60	1.08	92	68
2	3.11	1.04	98	137
1	2.37	0.87	85	121
2	3.20	0.84	87	91

amount of magnesium in bone at the time of erythropoiesis. Changes in red cell magnesium occur relatively slowly and tend to be more moderate than those seen in serum. However in situations of accelerated red cell turnover a raised erythrocyte magnesium can occur but this does not necessarily imply a whole body excess of magnesium. More likely, it is an indication of relative youth of cells [117].

There are two recognised methods of erythrocyte magnesium measurement and both methods yield comparable results [118]. The indirect method used in this study derived the erythrocyte magnesium concentration from serum and whole blood measurements. The direct method involves measurement of magnesium in separated saline washed erythrocytes. Washing does not cause significant loss of cellular magnesium but it is important that a representative sample of cells is studied. Reticulocytes and young erythrocytes tend to remain at the top of a centrifuged column of red cells and older cells settle to the bottom [119]. Therefore either the entire column should be studied or only samples at the lowest level should be analysed. Seelig, in a review of 20 studies comparing both methods, found a wide range of mean values (1.9 - 3.1 mmol/l) with an even wider "normal" ranges in some individual studies. Numerous sources of technical error were documented and doubt was cast on the reliability of erythrocyte magnesium as a guide to magnesium status [118].

It has been pointed out that the wide reference range for

erythrocyte magnesium limits the value of a single measurement in an individual because the result obtained may be very unusual for the individual yet still be within the normal reference range [120]. There is evidence that erythrocyte magnesium levels are genetically determined and that they may be low or high in some subjects irrespective of magnesium status [121].

Several authors have commented on the lack of correlation between serum and erythrocyte magnesium levels [109,122,123]. In this study there was a relationship for magnesium between serum and erythrocytes in the relatively stable outpatient population. The lack of correlation between the two measurements in in-patients was almost entirely due to the high values values obtained in patients with infection and/or skin breakdown. These high values fell towards the group mean in association with healing. It would appear therefore that such conditions can distort values for erythrocyte magnesium in the same way as has been observed in high red cell turnover states such as thalassaemia and sickle cell disease [114,117]. The evidence suggests that increased marrow production of young erythrocytes can cause the high erythrocyte magnesium values found in most patients with skin breakdown and this would probably also explain the moderately raised levels observed in some patients with infection. More detailed studies of erythrocyte production and survival in these circumstances would be required to confirm this.

Touitou et al [97] have previously investigated the effects

of different illnesses on erythrocyte magnesium in geriatric patients in long term care. Hypertension was associated with lowered erythrocyte magnesium levels but no illness category was associated with elevated levels. However, infection does not seem to have been considered as a separate diagnostic grouping.

In this study alcohol related disease accounted for the lowest erythrocyte magnesium levels amongst in-patients but differences did not reach significance at the 5% level. There were 18 non-insulin dependent diabetic outpatient attenders whose erythrocyte magnesium levels were no different from the group as a whole. Similarly erythrocyte magnesium levels in 28 hypertensive out-patients taking thiazide diuretic therapy were not significantly different. The effect of diuretic therapy on erythrocyte magnesium in elderly out-patients was investigated in more detail as described in Chapter 10.

In summary, erythrocyte magnesium levels found in these two groups of elderly patients are similar to those reported elsewhere. However the presence of skin breakdown and/or infection was associated with higher levels than normal in some cases. Such high levels are likely to be due to alterations in characteristics of the erythrocytes themselves with a higher proportion of younger cells rather than an indication of body magnesium excess.

CHAPTER 6

MONONUCLEAR BLOOD CELL MAGNESIUM

6.1 Introduction

Determination of magnesium in mononuclear blood cells [MBC] has been used as an indicator of magnesium status. There is some evidence of correlation for magnesium between MBC and muscle in human subjects and agreement is evolving for reference intervals using several units of measurment [122,124,125,126,127]. Some workers have used MBC magnesium to evaluate magnesium status in specific clinical conditions [112,128,129]. MBC magnesium has been suggested as a possible candidate to fulfil the requirement of a simple reproducible test which could be widely used to give meaningful information on overall intracellular magnesium status [130].

6.2 MBC magnesium in the elderly

It seemed appropriate to evaluate MBC magnesium measurement in the elderly, and the following study was performed to compare two frames of reference for MBC magnesium in both health and illness.

a) Subjects

Blood samples were obtained from 24 healthy elderly subjects living at home in the community and from 21 ill elderly subjects from the same community, but recently admitted to hospital with a variety of medical problems. The community subjects comprised 9 males and 15 females,

average age 76 years (range 67 - 93), and those in hospital comprised 7 males and 14 females with an average age of 79 years (range 65 - 90).

b) Blood sampling and laboratory analysis

Blood samples were taken between 0900 and 1000 hours without undue stasis and measurements of magnesium in serum and MBCs were made as follows:

After dilution of the serum sample 1 + 70 with lanthanum chloride (0.5%) the magnesium content was determined by flame atomic absorption spectrometry [28]. The procedure for separation of cells was based on Boyum's methods [131,132]. Pellets of MBC were obtained, after a minimum period of storage of no more than four hours, by layering 8 ml of heparinized blood on to 12 ml of Ficoll-Paque (1.077 g/ml). The density gradient was centrifuged at 300g for 40 minutes and the MBC layer which forms at the Ficoll - serum boundary was collected and washed twice with phosphate buffer saline (PBS) to avoid platelet contamination. The pellet was re-suspended in 1.5 ml of PBS and 50 ul taken for cell counting using a Neubauer haemocytometer. The cells were re-pelleted (300g, 10 minutes) and lysed with 1.5 ml of sodium dodecyl sulphate (SDS). The magnesium concentration was determined on 1 ml of the lysate diluted 1 + 1 with lanthanum chloride solution (0.5%) and analysed by atomic absorption spectrometry. The remaining 0.5 ml of the lysate was assayed for protein using the Lowry method [133].

c) Precision of laboratory assays

Duplicate analysis of the samples from the 24 community subjects revealed coefficients of variation for MBC magnesium measurements to be 8.8% expressed as fmol/cell and 12% expressed as umol/mg protein. The equivalent analytical errors for magnesium, protein and cell count were less than 2%, 3.4% and 5 - 10% respectively.

d) Results

The characteristics of the in-patient group and the results obtained from them are shown in Table 11. Excessive alcohol consumption was a factor in two patients and 10 patients were receiving either loop or thiazide diuretic therapy. No patients were receiving theophylline derivitive medications.

Table 12 compares results obtained for inpatients with those of community subjects. Inpatient MBC magnesium levels, expressed umol/mg protein, were significantly lower than those for community subjects ($P < 0.001$, Student's t test: $t = 4.59$). The difference between the means of the two groups was 0.014 umol/mg protein, 95% confidence interval 0.008 to 0.02. However, expressed as fmol/cell, in-patients had higher MBC magnesium levels ($P = 0.028$).

There was no significant correlation between the two methods of MBC magnesium measurement for either patient population (Figure 4). Neither form of MBC measurement showed a correlation with serum values.

TABLE 11 - Serum and MBC Magnesium in Ill Elderly Patients

Age (years)	Sex	Serum Mg mmol/l	Magnesium fmol/cell	Magnesium umol/mg prot	Diuretics*	Medical Conditions*
76	M	0.79	4.5	0.037	L	IHD, CCF
69	F	0.89	1.9	0.031	-	CVI, Pneumonia, Pressure Sore
90	F	1.03	3.1	0.062	-	IHD, Angina
74	F	0.54	3.6	0.042	T	MI, Femoral Embolus, Alcoholism
73	F	0.81	6.1	0.035	-	Diverticulitis
83	F	0.82	4.3	0.026	L	Diverticular disease, CCF, Leg Ulcers, Hypothyroidism
84	M	0.71	5.4	0.021	-	Anaemia, Pneumonia
83	M	0.86	5.2	0.029	-	Parkinson's Disease, Pneumonia
84	F	0.82	5.5	0.021	T	MI, CCF
69	M	0.86	3.3	0.033	-	CVI, Alcoholism
77	F	0.64	3.9	0.050	L	CCF, Henoch Schonlein Purpura
88	F	0.76	5.4	0.043	T	PVD, Foot Ulcer
80	F	0.76	5.7	0.042	-	CVI
68	M	0.66	2.3	0.048	-	CVI, Peptic Ulcer
87	F	0.84	3.3	0.031	L	CCF, Femoral Embolism
79	F	1.00	6.2	0.038	L	Acute Rheumatoid Arthritis Pleural effusion
79	F	0.81	4.9	0.033	-	MI, Pneumonia
78	M	0.78	3.3	0.040	L	IHD, CCF
90	F	0.72	3.9	0.031	L	CCF, Osteoarthritis
65	M	0.90	4.3	0.021	-	CVI
78	F	0.71	4.1	0.029	-	Carcinoma of Vagina, CRF

* Abbreviation Key

CRF - Chronic Renal Failure
CVI - Cerebral Vascular Incident
IHD - Ischaemic Heart Disease
PVD - Peripheral Vascular Disease
MI - Myocardial Infarction
CCF - Congestive Cardiac Failure
L - Loop Diuretic
T - Thiazide Diuretic

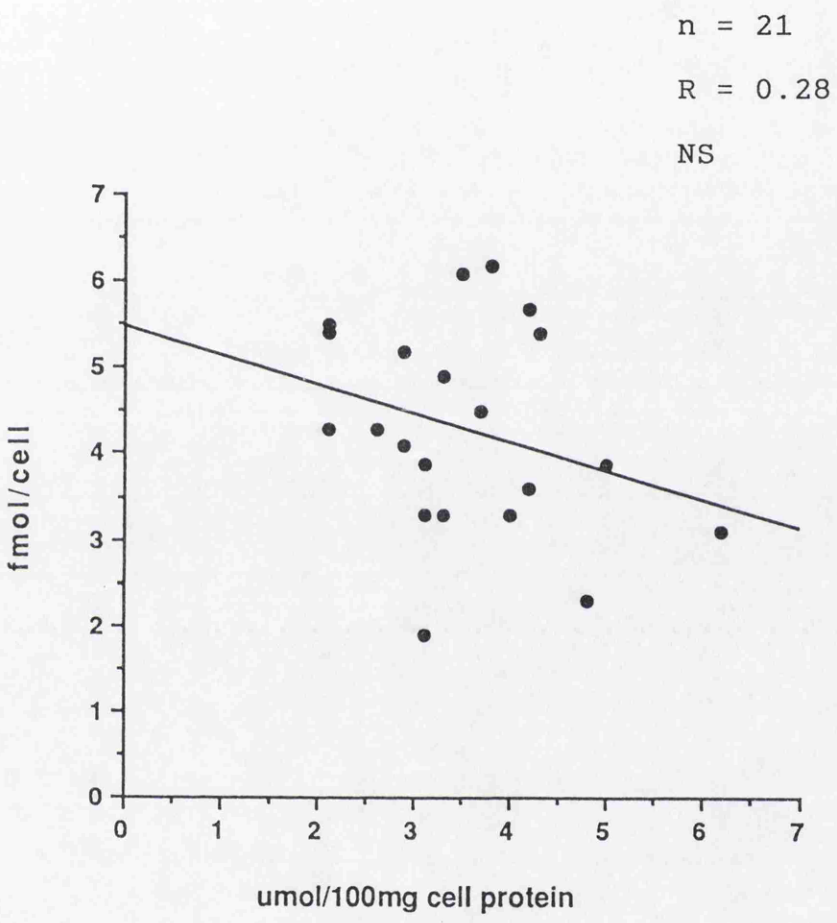
TABLE 12

Serum and Mononuclear Blood Cell Magnesium in the Elderly

	Serum mmol/l	MBC fmol/cell	MBC umol/mg prot
Community subjects (N = 24)	0.75 (0.07)	3.5 (1.14)	0.049 (0.01)
In-patients (N = 21)	0.80 (0.11)	4.3 (1.20)	0.035 (0.01)

results shown as mean (sd)

FIGURE 4 Magnesium in Mononuclear Blood Cells from elderly hospital patients: relationship between measurements of fmol/cell and umol/100mg cell protein



e) Biological variation

Biological change was assessed by drawing further samples from 10 community subjects later on the same day and again after an interval of seven days. The coefficient of variation for same day intrasubject analysis for fmol/cell measurements was 12% and at one week was 22%. The equivalent intrasubject values for serum were 2.8% and 4% respectively.

6.3 Discussion

The values of MBC magnesium for elderly subjects in the community, expressed as fmol/cell, are broadly in line with those found in normal controls of all ages in previous studies [127,134,135,136,137,138] whereas the values expressed as umol/mg protein are lower than in other studies of adults [122,128,135], but not children [136]. For both frames of reference the scatter of results is wide in this elderly population sample. The lack of correlation between the fmol/cell and umol/mg protein measurements has previously been observed [136] and the lack of correlation of either with serum has been reported by several authors.

The comparative results for ill in-patients, who had slightly higher values for fmol/cell and serum and much lower values expressed as umol/mg protein, seem at first to be quite bizarre. However, these conflicting results could reflect the effects of illness on the size and protein content of cells in the lysate. The magnitude of these illness effects on cell characteristics may

over-shadow the effects of illness on magnesium status per se.

With the methodology used in this study, it has been shown that in normal individuals MBCs account for 97% of cells harvested from a Ficoll-Paque gradient with more than 80% being lymphocytes [139]. However, changes in relative proportions of cells harvested as well as variations in cell age and size can lead to spurious results for MBC magnesium [140,141].

There are several different populations of circulating lymphocytes. They vary in size as well as function and have widely varying circulating life spans [142,143,144,145]. Larger lymphocytes tend to be those which have been activated by antigen and, for a fixed cellular concentration of magnesium, these larger cells will have a higher magnesium content [141,146]. Some cells exist for a few days whilst others survive for several years. Furthermore, there is evidence that the magnesium content of a lymphocyte gradually declines as the cell ages [140]. Therefore a greater proportion of larger newly produced cells within the lymphocyte population, as might be expected in response to illness, could result in a higher than expected value for cell magnesium content expressed as fmol/cell.

Monocytes usually account for less than 10% of the total white blood cell population and less than 20% of "harvested" MBC cells. However, the volume of a monocyte is much greater than that of a lymphocyte and, as is the

case with larger lymphocytes, for any given concentration of cellular magnesium, an increase in the relative proportion of monocytes will result in a corresponding increase in the value of magnesium content/cell. An increased proportion of monocytes is present during the recovery phase of most infections, in malignant disease, inflammatory disorders, and in collagen-vascular diseases. These clinical disorders, which result in monocytosis, are often contributors to illness in elderly hospitalised patients.

Conversely these same in-patients who had slightly higher values expressed as cell content had low values for MBC magnesium expressed as umol/mg protein. A possible explanation for this discrepancy is that the protein content of cells varies greatly according to physiological and pathological conditions [147,148]. Protein synthesis is greater in cells activated during infection and inflammation. For a fixed amount of cellular magnesium the resultant increase in cell protein content will lead to an overall lower concentration value for magnesium when protein is used as the denominator. In other words the lower value for MBC magnesium expressed as umol/mg protein in these hospitalised subjects may reflect more cellular protein rather than less cellular magnesium.

Whilst the analytical error using these methods of measurement was modest and comparable with errors reported by others, and could account for the same day biological variation, there was considerable biological variability in

measurements one week apart. It is possible that factors such as residual platelet contamination, despite the repeated washings with phosphate buffers to remove platelets, contributed to the analytical error.

6.4 Conclusions

There continues to be debate as to the clinical usefulness of MBC magnesium measurement as well as the most appropriate frame of reference [135,136,149]. The results obtained here indicate that MBC magnesium can perhaps act as a guide to the magnesium status of a stable population group and could be used to assess trends within that group as well as to permit comparison with other similar groups. However, the biologic variability and analytical imprecision not only preclude use of a single MBC magnesium measurement as an accurate guide to an individual's magnesium status but probably also preclude reliability of multiple measurements from a single individual.

Care should be taken in interpretation of values obtained in groups of individuals during the course of illness when the cell population is likely to differ from normal either as a result of the illness itself or even as a result of treatment [150]. Observed alterations in magnesium MBC content or concentration could reflect to a far greater extent the effects of illness on cell characteristics compared with the effects on magnesium status per se. Detailed analysis of the differential cell type and the size of cells in the lysate would be necessary

to put magnesium values, expressed as content/cell, into context in each clinical situation thus adding yet another step to the already complicated procedure. Similarly when expressing the results in terms of protein the effects of illness and cell protein content would have to be considered. The technical procedures required for this measurement, as well as its biological variability and analytical imprecision would appear to limit its usefulness.

CHAPTER 7

URINE MAGNESIUM

7.1 Introduction

The kidney is the organ principally responsible for regulating the total body content of magnesium and conserves magnesium very effectively in circumstances of magnesium deficit [22]. Figure 5 shows how urine magnesium measurements can aid diagnosis in hypomagnesaemia.

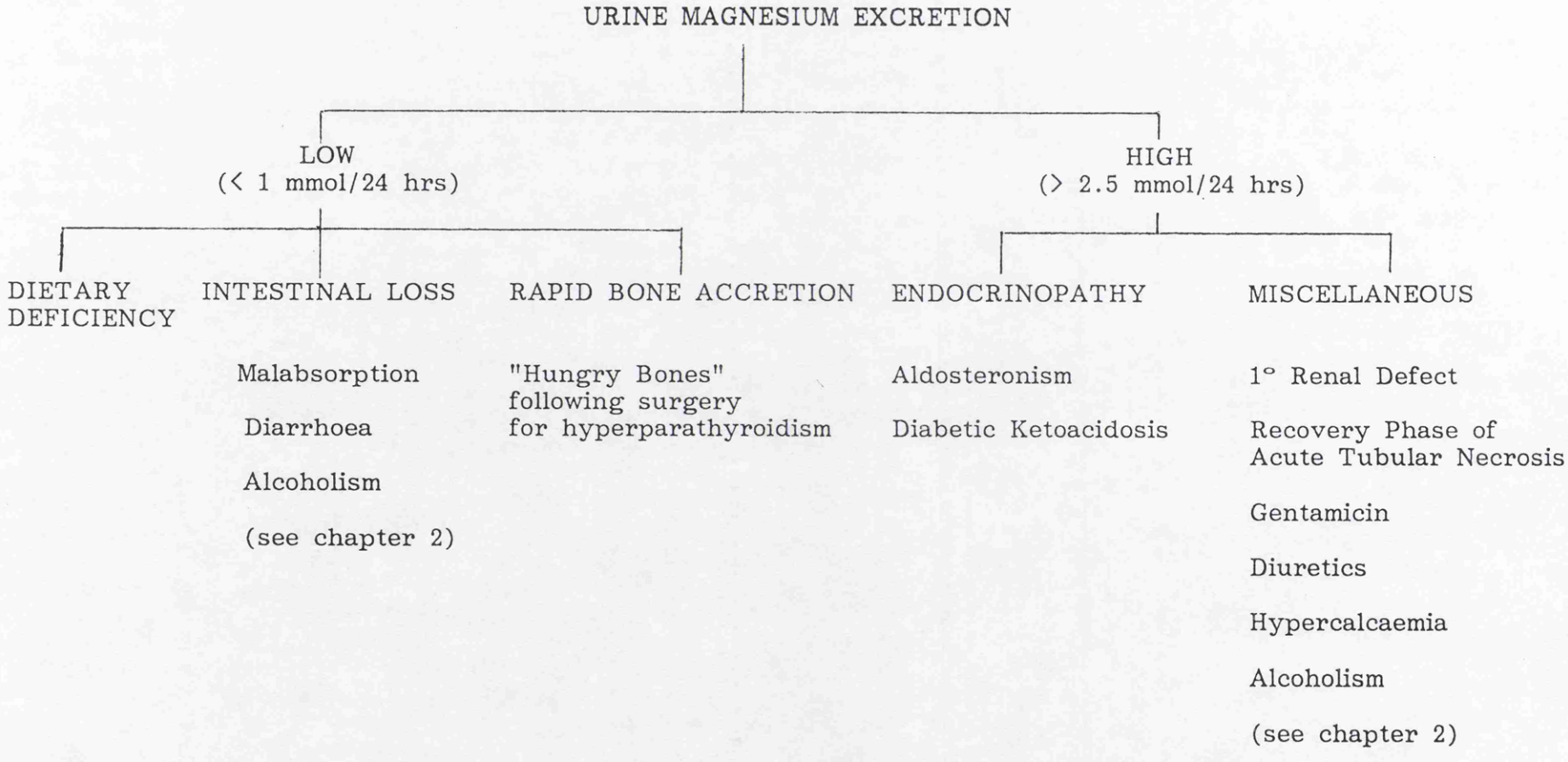
7.2 Urine magnesium in the elderly

It seemed reasonable to consider the contribution of urine magnesium measurement to the assessment of magnesium status of elderly subjects. There is a circadian rhythm to the excretion of magnesium by the kidney and it is therefore preferable to collect a 24 hour urine specimen to assess magnesium excretion accurately [9]. Unfortunately accurate 24 hour urine collections are not easily obtained in elderly subjects, especially in the geriatric ward setting, and a large number of collections had to be abandoned in the process of collecting the data presented here.

a) Subjects

Renal magnesium excretion was studied in 3 groups of elderly subjects. Group A comprised elderly individuals living at home and enjoying active retirement, most being recruited from local lunch and dancing clubs. The patients in Group B and C were recently admitted to the geriatric assessment ward and were undergoing medical investigations

FIGURE 5 - Urine magnesium as a guide to cause of hypomagnesaemia



and/or rehabilitation. Group B patients had serum magnesium levels within the normal range whereas all patients in group C were hypomagnesaemic (serum magnesium less than 0.7 mmol/l). Data exclude subjects/patients taking diuretics, the effects of which were assessed separately and will be discussed in Chapter 10.

b) Methods

The purpose of the 24 hour urine collection was explained to each volunteer subject and an appropriate receptacle was provided with instructions on how to ensure accurate urine collection at home. In-patient urine collections were closely supervised by trained nursing staff who were aware of the purpose of the study and the need for full and accurate collections. A few patients had a bladder catheter in situ which made accurate collection more easily attainable. Despite precautions, many collections were abandoned because of contamination or being considered incomplete. Once complete, a 10 ml aliquot of urine was analysed for concentration of magnesium and creatinine and the 24 hour excretion of both was then calculated from the known total volume of the collection. The ratio of magnesium to creatinine excretion (Mg/Cr) was also calculated.

c) Results

Table 13 shows the results of complete 24 hour urine collections in the three groups of elderly subjects.

TABLE 13 - 24 hour urine magnesium in the elderly

	Age	Serum Mg mmol/l	Urine Mg mmol/24 hrs	Mg/Creatinine Ratio
Elderly at Home N = 20	76 (6.5)	0.76 (0.09)	2.6 (1.42)	0.37 (0.17)
Normomagnesaemic Patients N = 43 (Serum mg > 0.70 mmol/l)	81 (6.4)	0.81 (0.08)	1.85 (1.01)	0.37 (0.26)
Hypomagnesaemic Patients N = 21	80 (6.7)	0.66 (0.08)	0.96 (0.72)	0.24 (0.16)

All values are shown as mean (sd)

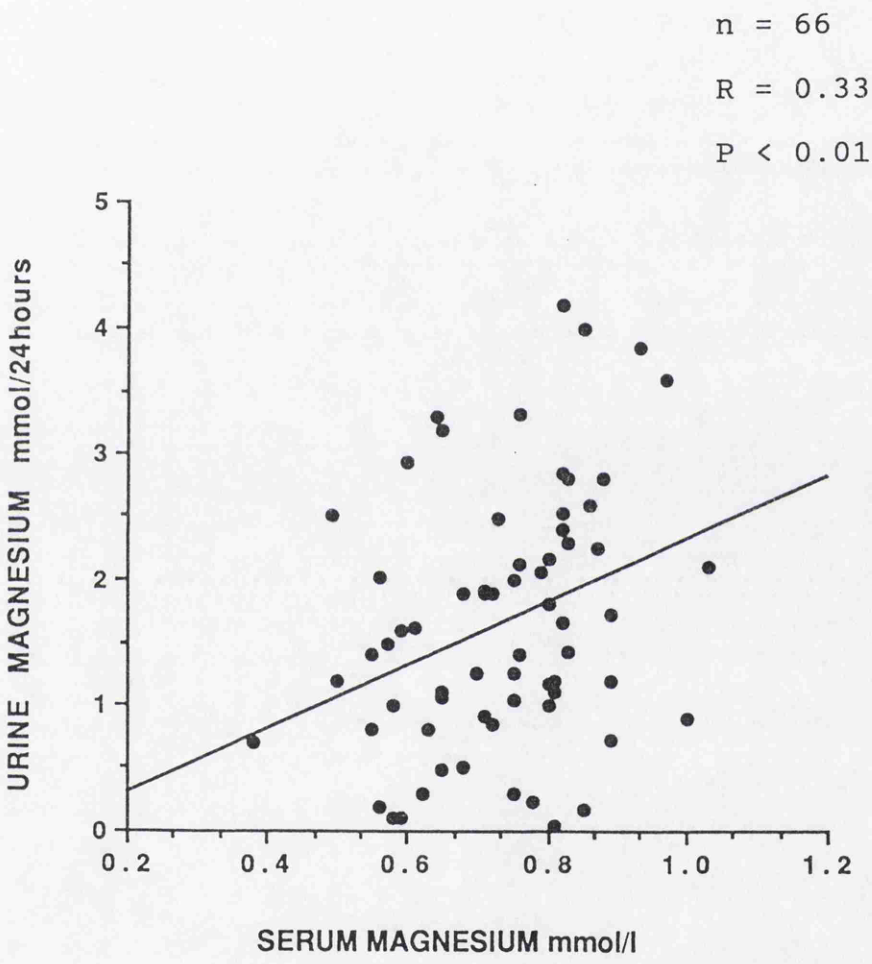
Despite a wide scatter of results there was a significant correlation between serum magnesium and 24 hour urine magnesium excretion (Figure 6).

7.3 Discussion

The renal excretion of magnesium is generally reported as 4 - 6 mmol/24 hrs for an adult taking a normal diet [151,152,153,154,155,156]. The results obtained here indicate a much lower magnesium excretion in both healthy and hospitalised elderly subjects. The hypomagnesaemic patients in Group C have an even lower urine magnesium excretion than the two normomagnesaemic groups and this would be consistent with increased compensatory renal conservation of magnesium in most patients within Group C. The values obtained are also slightly lower than those found in a previous study of elderly living at home (3.2 mmol/24 hours for healthy subjects and 2.6 mmol/24 hours for housebound subjects), although the groups of individuals in that study also had higher serum magnesium levels than found here [67].

It is likely that several factors contribute to the relatively low urine magnesium values obtained for all three groups. Renal function deteriorates with age. The glomerular filtration rate (GFR) and renal plasma blood flow show a linear reduction with increasing age. At age 65 there is a reduction of approximately 30% in the GFR compared with young adults [157]. The healthy subjects of Group A had a mean creatinine clearance of 61 $\pm$ 25.6

FIGURE 6 Relationship between serum magnesium and 24 hour urine magnesium excretion in elderly subjects admitted to hospital



mls/min/1.73 m^2. Magnesium excretion declines with GFR, but magnesium clearance falls proportionately less than the GFR in renal failure indicating less reabsorption of magnesium per functioning nephron. This effect may be due to increased sodium or increased osmotic load per functioning nephron [158]. Reduced dietary intake (see Chapter 3) and reduced gastrointestinal absorption may also contribute to lower renal magnesium excretion in the elderly. For these reasons serum magnesium does not increase significantly in the elderly until GFR falls below 15 mls/min.

A value for 24 hour urine magnesium considered to be very low in a young adult indicating renal conservation in the context of depleted body stores, could be normal for an elderly individual with renal impairment. Conversely an elderly subject with magnesium depletion secondary to renal magnesium wasting might have a urine magnesium well within the normal adult range. Results of urine magnesium must therefore be interpreted with caution and accurate knowledge of renal function is required. Despite declining renal function serum urea and creatinine are generally normal in the elderly individual and can be misleading. Normal values may reflect a state of lower protein intake and reduced production secondary to reduced body mass rather than the normal elimination of urea and creatinine.

The Mg/Cr ratio is a measure of the renal effort to conserve magnesium and has been suggested as an indicator of total body magnesium stores [159]. The low Mg/Cr ratio

in Group C hypomagnesaemic subjects is in keeping with this hypothesis. It would therefore seem to be a potentially useful index in the elderly, compensating for declining renal function, since both GFR and urine magnesium tend to be lower in old age. The mean 24 hour urine creatinine in Group A subjects was 7.3 $\pm$ 2.4 mmols (range 2.1 - 14.4) compared with a normal adult range of 9 - 18 mmols/day. However individual results for Mg/Cr ratio would have to be interpreted with caution as the ratio could be high in circumstances of renal magnesium wasting despite total body magnesium depletion.

7.4 Summary

Renal magnesium excretion is lower in the elderly primarily reflecting a decline in renal function. Results must therefore be interpreted with caution and knowledge of renal function is required. 24 hour magnesium/creatinine excretion ratio is a useful measure which helps to compensate for declining renal function but values are high in renal magnesium wasting disorders. When taken together with serum measurements urine magnesium can be a useful guide to body magnesium status but declining renal function can hinder accurate interpretation of results in the elderly.

CHAPTER 8

THE MAGNESIUM LOAD TEST

THE MAGNESIUM LOAD TEST

8.1 Introduction

Despite their drawbacks serum and urine magnesium measurements, taken together, generally give a reasonable indication of body magnesium status for most clinical situations. However, when doubt exists as to the true magnesium status of a patient the parenteral magnesium load test is currently widely reckoned to be the most clinically practical and reliable physiological method of assessment [160,161,162]. The procedure involves a 24 hour collection of urine for magnesium followed by an intravenous infusion of magnesium over several hours. A second 24 hour urine collection is commenced at the start of the infusion and the percentage excretion of infused magnesium is the difference between pre-load and post-load urine magnesium excretion divided by the infused load. Normal individuals in magnesium balance excrete essentially all of the injected magnesium within 24 hours.

This method of assessment of magnesium status has been in clinical use since the early 1960's [163,164,165] but there are still considerable variations in the accepted protocol. In most cases a 30 mmol magnesium load is administered over 8 - 12 hours with excretion of more than 60% within 24 hours being accepted as a normal result [160,161,166]. With this protocol, retention of more than 50% is considered to indicate depleted magnesium stores.

However, lower doses of infused magnesium, around 16 mmol,

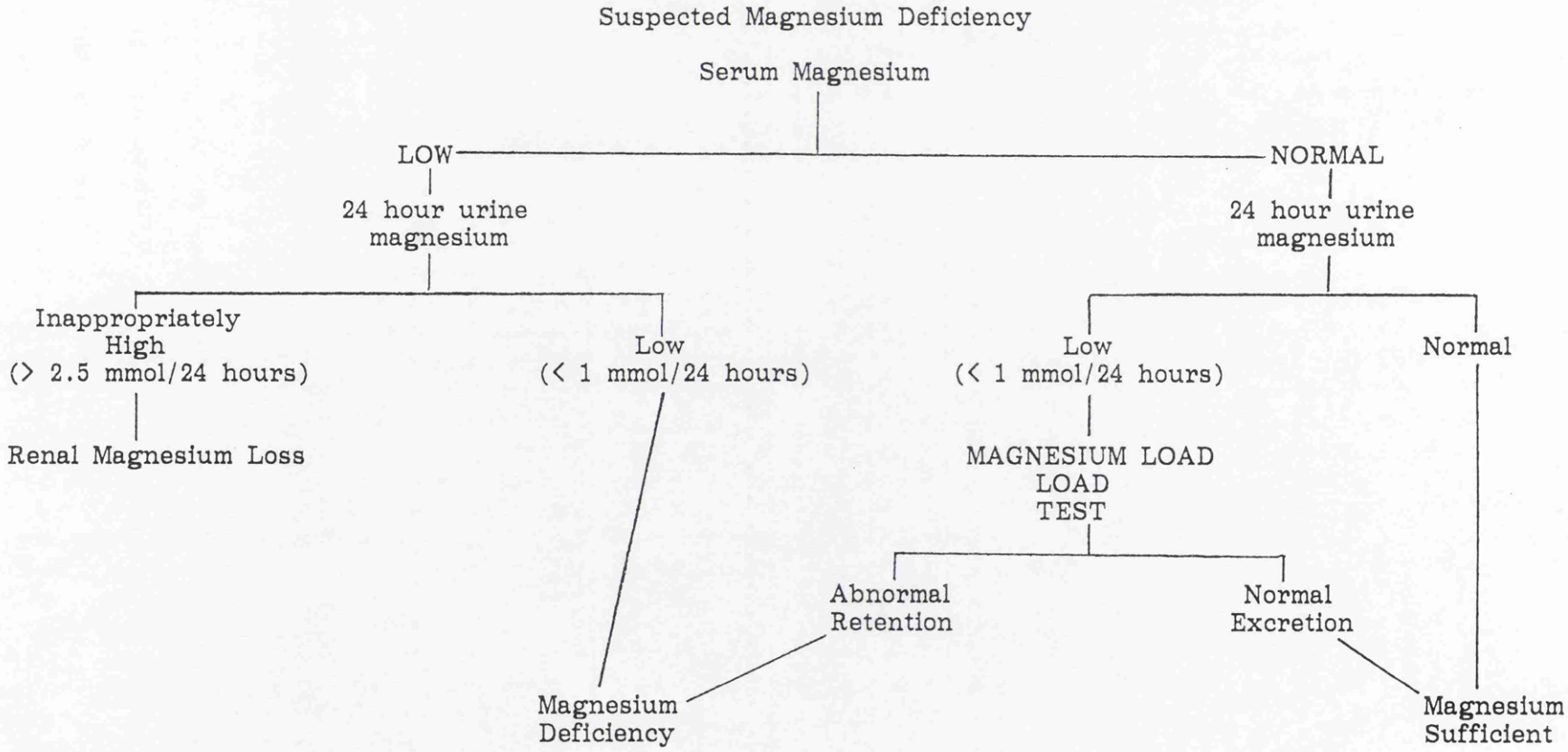
have been considered to be just as effective in discriminating between normal and depleted patients. Retention of more than 20% of a 16 mmol dose is considered by some to be abnormal [163,167,168] whilst others accept retention of more than 40% to be abnormal [169]. The duration of magnesium infusion using this dosage has not been uniformly defined, varying from 1 - 6 hours.

A lower dose administered over a longer period will minimise "renal spillage" caused by exceeding the renal tubular maximum for magnesium reabsorption during infusion. On this basis very low doses of 0.1 mmol/kg, given over 4 hours, have been used recently. Using this regimen more than 20% retention at 24 hours is highly suggestive of magnesium deficiency and more than 50% retention is considered to be diagnostic [159,170].

8.2 Experience of the magnesium load test in elderly in-patients with suspected magnesium depletion.

The procedure is indicated when there is doubt about magnesium status in circumstances where magnesium deficiency could exacerbate pre-existing clinical problems (Figure 7). It is now clear that even a low serum magnesium level does not necessarily imply tissue deficit in illness (see Chapter 4). The combination of mild hypomagnesaemia and low urine magnesium excretion are relatively common in ill elderly patients and, in these circumstances, the magnesium loading test would seem to be a useful means of

FIGURE 7 - Diagnostic approach to magnesium deficiency



Adapted from Berkelhammer and Bear (1985) [60].

both starting magnesium supplementation and, at the same time, identifying those patients who require longer term magnesium treatment.

However experience in such clinical situations has led me to doubt its usefulness in the elderly. A review of results in 23 consecutive patients, mean age 82 years, revealed that all but one had a positive result according to the test criteria. Using a modified 16 mmol load protocol (0.25mmol/kg body weight), 22 patients retained more than 20% of the infused magnesium load and 19 retained more than 50%. If the test criteria are valid, these results suggest a high level of magnesium deficit in this elderly patient population. The procedure had to be abandoned in at least 15 patients because of incomplete urine collections.

There was a significant relationship between the level of serum magnesium pre infusion and the degree of magnesium retention as illustrated in Figure 8. However, there was a similar relationship between magnesium retention and creatinine clearance (ml/min/1.73m^2):- $R = -0.59$, $P < 0.01$.

8.3 The magnesium load test in healthy elderly subjects

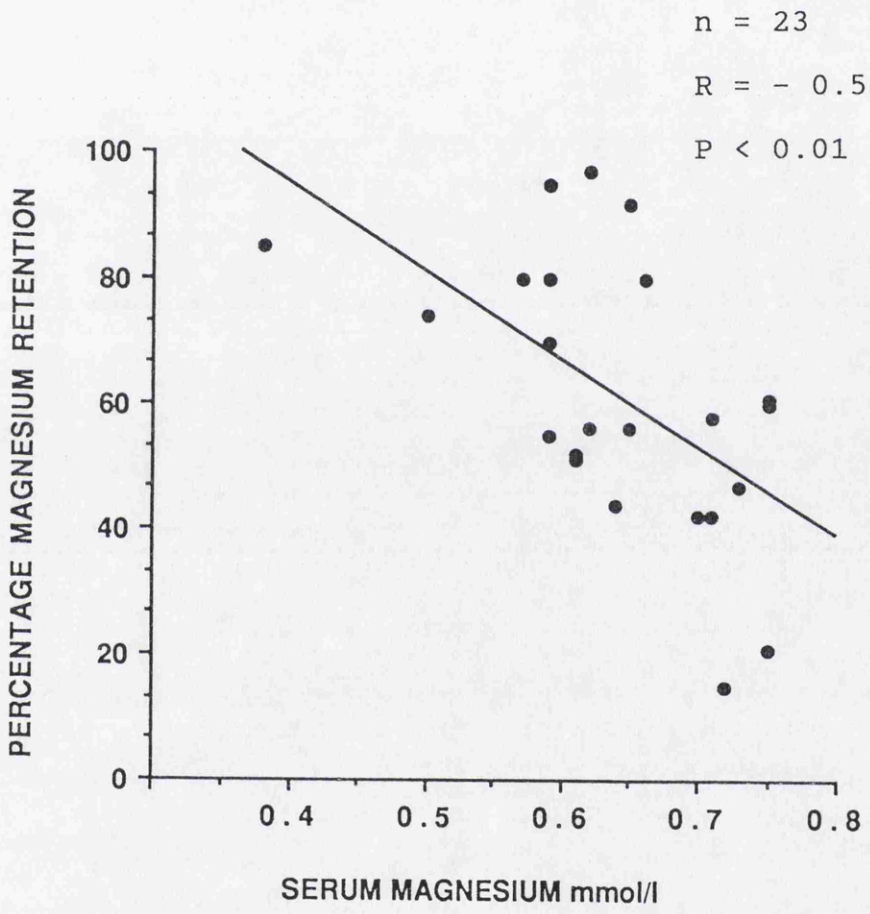
a) Aims

In view of the observations above, the following study was carried out with three aims.

1. To determine a reference range of results for healthy elderly individuals living in Glasgow to permit more

FIGURE 8 Magnesium load test in elderly patients with suspected magnesium deficiency: relationship between pre-load serum magnesium and percentage magnesium load retention

(magnesium loading dose = 0.25 mmol/kg body wt.)



enlightened interpretation of results in clinical practice.

2. To assess whether the decline in renal function with age significantly impairs the value of the procedure in elderly patients.

3. To compare results with other measures of magnesium status.

b) Subjects

It was hoped that at least 25 subjects would complete the study protocol. Volunteers were recruited from local lunch and dancing clubs for retired senior citizens. Subjects taking diuretic therapy and those with known significant medical conditions were excluded. The study received Hospital Ethical approval and all subjects gave informed consent.

c) Methods

Blood was drawn for routine electrolytes and levels of magnesium in serum, erythrocytes and mononuclear cells. Two consecutive 24 hour urine collections were performed to determine baseline magnesium excretion and creatinine clearance corrected for body surface area. Results from the two urine collections were averaged and the procedure was abandoned when there was more than a 30% variation in baseline magnesium excretion. Subjects with a creatinine clearance less than 30 ml/min/1.73m^2 were excluded from further study. Remaining subjects were given magnesium

sulphate by intravenous infusion in a dose of 0.25 mmol magnesium/kg body weight at a rate of 2.5 mmol/hour. A second 24 hour urine collection was commenced at the start of the magnesium infusion.

Magnesium retention (% ret) was calculated as follows:-

$$\% \text{ ret} = 100 \times \left[1 - \frac{(\text{post infusion urine} - \text{baseline urine})}{\text{infused magnesium load}}\right]$$

Blood pressure and heart rate were measured at hourly intervals during the infusion and for six hours thereafter. A standard ECG run at 50 mm/second was perfomed at the start and end of the magnesium infusion. Magnesium and other serum electrolytes were measured again at the end of the infusion.

d) Results

Eleven healthy subjects (5 males + 6 females), mean age 74 years completed the protocol. One female subject, aged 76 years, and one male subject, aged 71 years, were found to be hypomagnesaemic with serum magnesium levels of 0.58 mmol/l and 0.66 mmol/l respectively. The mean serum magnesium level for the 9 normomagnesaemic subjects, pre-load, was 0.77 (sd 0.03) mmol/l.

The 9 normomagnesaemic subjects retained an average of 44% of infused magnesium. All retained more than 20% and four retained at least 50% of the infused dose (range 23 - 68). The hypomagnesaemic subjects retained 98% and 43% respectively (Table 14).

TABLE 14 - Magnesium Loading Test in Healthy Elderly. Loading Dose 0.25 mg Magnesium/kg

Sex	Age Years	Serum Mg. mmol/l	Urine Mg. mmol/24 hrs	Serum urea mmol/l	Serum Creatinine umol/l	Creatinine Clearance ml/min/1.73m²	Magnesium/ Creatinine Excretion ratio	% Retention
F	80	0.81	1.2	11.6	150	50	0.16	23
F	78	0.75	1.55	5.7	70	54	0.44	36
F	69	0.74	3.9	7.2	80	63	0.51	33
F	71	0.74	2.6	5.7	85	78	0.48	50
F	74	0.78	2.0	6.8	110	38	0.38	68
F	76	0.73	1.8	5.7	90	47	0.26	56
M	65	0.81	2.7	4.8	100	63	0.55	39
M	76	0.82	4.3	5.4	85	98	0.39	38
M	80	0.77	1.6	3.6	90	40	0.31	57
F*	76	0.58	2.8	9.1	120	54	0.36	98
M*	71	0.66	1.4	6.8	95	34	0.27	43

* Hypomagnesaemic

There were no significant changes in blood pressure or heart rate during magnesium infusion. Similarly, there were no significant changes in serum calcium or serum potassium and there were no changes in PR or QT intervals on standard ECG run at 50 mm/second.

The data for the 9 normomagnesaemic subjects were examined for relationships between percentage magnesium retention and pre-load serum magnesium and creatinine clearance respectively with the following results:-

Pre-load serum magnesium: R = - 0.33, NS

Creat. clearance ml/min/1.73m^2: R = 0.39, NS

Neither mononuclear blood cell magnesium (fmol/cell) or red cell magnesium (mmol/l), measured prior to magnesium loading, showed any relationship with percentage magnesium retention.

e) <u>Comment</u>

Depending on the criteria chosen to interpret results from the 16 mmol magnesium load test possibly all of these apparently healthy elderly subjects or as few as six of them could be classified as magnesium depleted. Although not quite statistically significant at 5%, the data also suggest that the result of the magnesium load test in an elderly individual could perhaps be influenced as much by renal function as by underlying magnesium status. A larger number of subjects would have helped draw more firm conclusions from statistical analysis but recruitment of suitable volunteers proved to be difficult.

8.4 Discussion

Cohen and Kitzes have recently performed magnesium load tests on 20 apparently healthy elderly men aged between 70 and 80 years. Using criteria based on a 1 mmol magnesium load they categorised 7 subjects as having definite magnesium deficiency and a further 10 as probably deficient in magnesium. However they did not consider the effect of age related decline in renal function [171].

It has been shown that endogenous creatinine clearance corrected to a body surface area of $1.73m^2$ falls by approximately 10 ml/min for each decade from age 20 years onwards [172,173]. It is therefore unlikely that loading test criteria used to interpret results in young adults will be equally valid in old age.

The magnesium load test has not been precisely defined and the procedure has recently been criticised on the basis that it is difficult to relate the percentage retention to the total body deficit of magnesium [152]. It is not clear from published reports that all investigators have accounted for baseline urine magnesium excretion; failure to do so could result in an error of 10 - 20% for magnesium retention.

8.5 Conclusion

The prolonged nature of the test, the influence of declining renal function, and the difficulties in obtaining accurate urine samples, as well as lack of correlation with

cellular indices, would appear to limit the role of the magnesium loading procedure in the assessment of magnesium status of ill elderly subjects.

CHAPTER 9

MAGNESIUM IN MUSCLE AND OTHER TISSUES

A STUDY OF AUTOPSY TISSUE

9.1 Introduction

Magnesium contained in skeletal muscle and soft tissues accounts for approximately 40% of total body stores. Low levels of skeletal muscle magnesium have been found in situations of chronic magnesium loss such as alcoholism [38,168], prolonged diarrhoeal illness [174], long term diuretic therapy [175,176], starvation [33], and diabetes mellitus [125]. In view of the evidence pointing to suboptimal dietary magnesium intake in the elderly (see Chapter 3) and the high number of positive magnesium retention tests (see Chapter 8), it seemed appropriate to assess whether this was reflected in the muscle tissue of elderly patients.

9.2. A study of magnesium in autopsy tissue from elderly subjects

As patient discomfort precluded analysis of tissue magnesium levels in a clinical setting, the opportunity was taken to measure levels of magnesium in samples of tissue from elderly patients obtained at autopsy. Furthermore, it was possible to compare results with those previously obtained in young accident victims [177].

a) Subjects

Autopsy tissue samples were taken from 33 aged subjects who had been admitted to the Glasgow Eastern District Geriatric

Service based at Lightburn Hospital. The study group comprised 14 males and 19 females with an average age of 80 years (range 69 - 94). All subjects had been resident within the Eastern District of Glsgow prior to hospital admission.

b) Tissue sampling and analysis

The procedures adopted were identical to those described in the previous report [177]. Samples of kidney, liver, skeletal muscle and heart (25-50 grams wet wt.) were removed within 48 hours of death. Samples taken at the mortuary with stainless steel scalpels were put into plastic containers and frozen. Prior to analysis the samples were thawed, the exterior together with gross fatty and connective tissue trimmed off with a titanium knife and the sample freeze-dried. The samples (approx. 0.5 grams dry wt.) were digested with 5ml nitric acid in acid washed pyrex tubes and made up to 25 ml with deionised water. A sample of NIST1577a bovine liver was included with each batch. The values found for bovine liver were in good agreement with the certified values. Magnesium was measured by atomic absorption spectrophotometry.

c) Statistical methods

Student's t test was used to compare tissue magnesium levels found in these elderly subjects with those previously reported in young adults.

d) Results

The principal cause(s) of death for each elderly subject based on clinical and post mortem findings are recorded in Appendix 2. The duration of illness prior to death was arbitrarily defined as "sudden" if less than 48 hours and "short" if between 48 hours and one week. Subjects who were clinicaly unwell for more than one week prior to death have been classified as having "chronic" illness.

The findings for the elderly subjects are summarised in Table 15 and compared with those previously reported in healthy accident victims [177]. The range of values for young and elderly are illustrated in Figure 9. Magnesium was found to be significantly lower in the muscle and heart of elderly subjects. No difference was found in kidney levels. For liver the group variances were different ($P < 0.001$, $F = 6$). Some elderly subjects had much lower magnesium levels whereas others had higher levels. Expression of results per unit of nitrogen did not contribute additional useful information. There was no relationship between duration of illness and tissue magnesium concentrations amongst elderly subjects.

Potassium was also measured (flame photometry). It was found to be significantly lower in the muscle ($P < 0.001$: $t = 5.2$: CI 2.8 - 6.4) and heart ($P < 0.001$: $t = 5.9$: CI 2.2 - 4.6) of elderly subjects. It was also lower in the kidney tissue of elderly subjects ($P < 0.05$). No difference was found in liver potassium content between young and

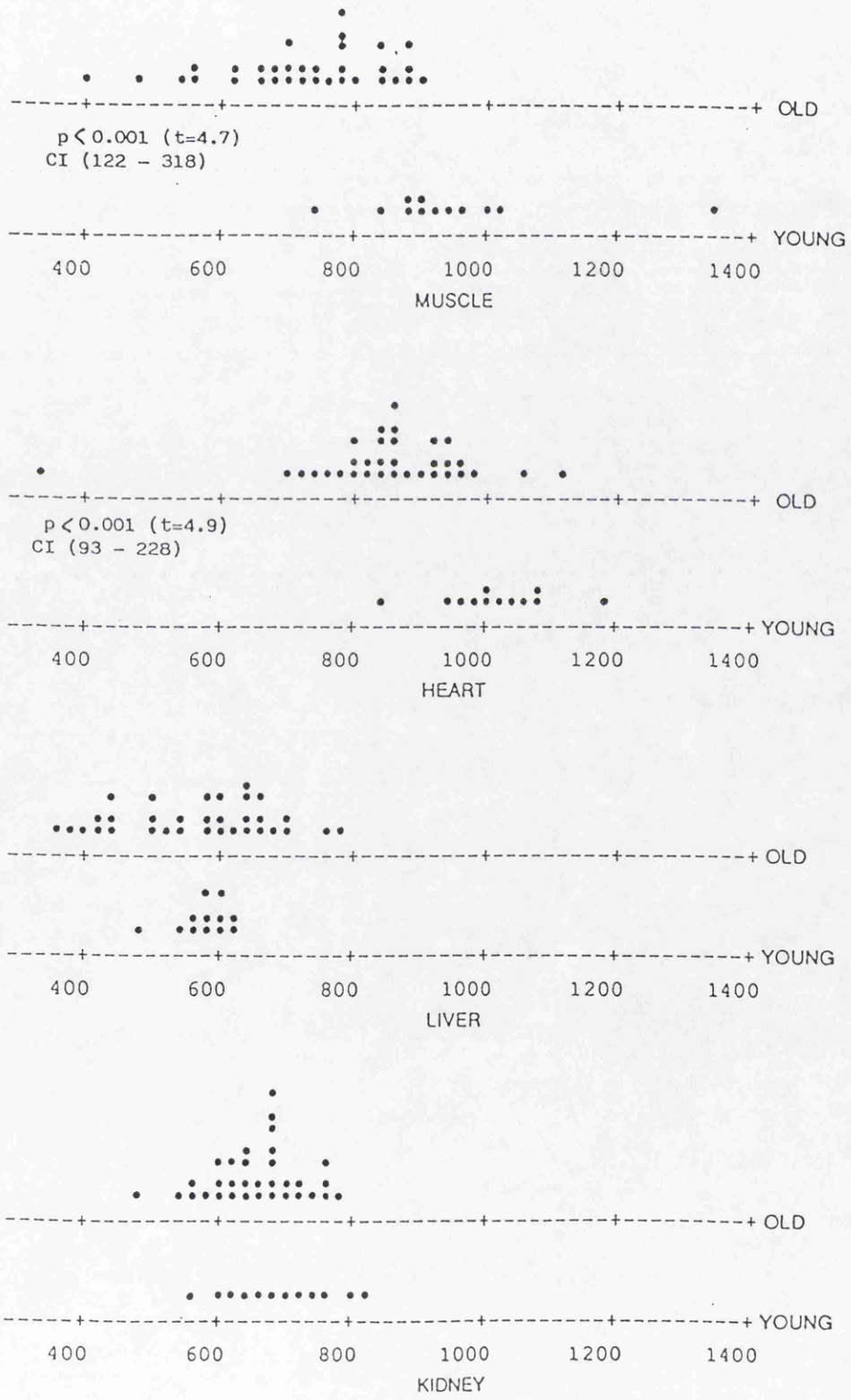
TABLE 15

Magnesium in autopsy tissue (mg/kg dry weight)

	mean age (years)	Muscle	Heart	Liver	Kidney
Elderly subjects n = 33	80	724(123)	853(128)	565(112)	655(68)
Young accident victims n = 12	29	943(143)	981(147)	578(41)	691(78)
		P<0.001 t = 4.7	P<0.001 t = 4.9		

tissue values expressed as mean(sd)

FIGURE 9 Magnesium in autopsy tissue from young accident victims and elderly hospital patients (ug/kg dry weight)



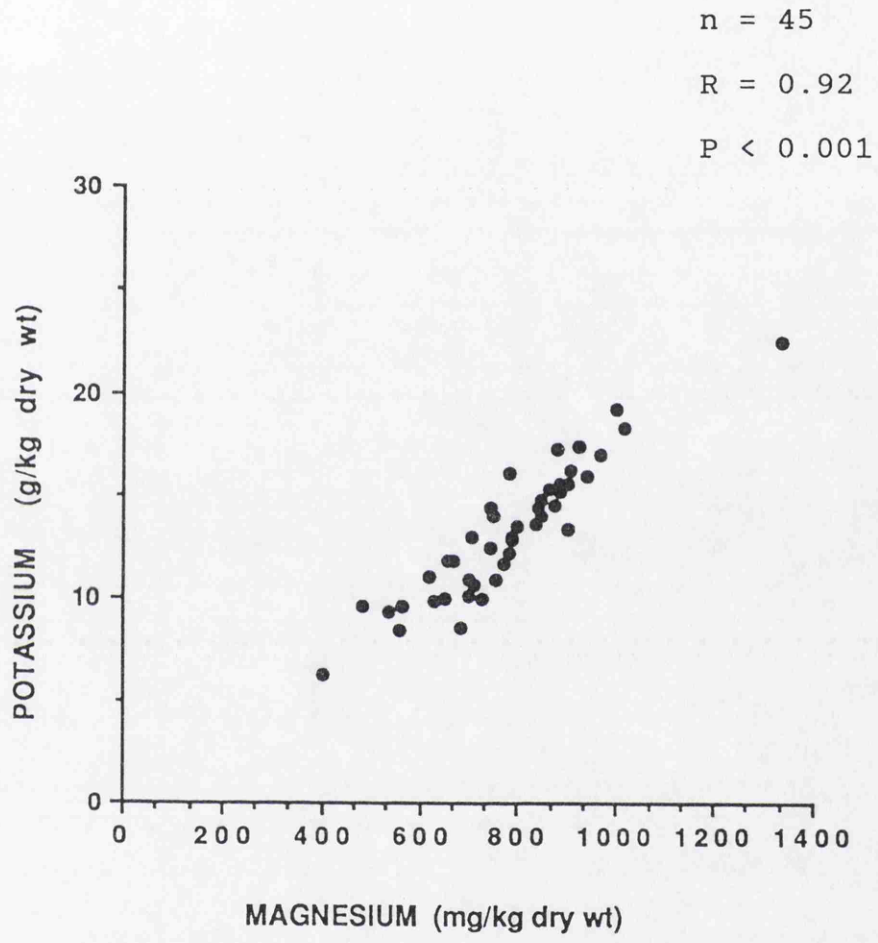
elderly. When the values for young subjects and elderly subjects were considered as one group there was a highly significant correlation between concentrations of potassium and magnesium in both heart, $R = 0.88$; $P < 0.001$, and muscle, $R = 0.92$; $P < 0.001$, (Figure 10).

9.3 Discussion

A progressive fall in levels of magnesium with age has been noted in myocardial tissue of rats [178]. A previous study failed to detect any influence of age on the magnesium content of human autopsy tissue [179]. However in that study less than 1 in 10 of the study population were aged over 65 years at the time of death, only liver was examined, wet weight was used as the frame of reference, and all subjects were accident victims. In this study dry weight has been used as the frame of reference and the aged subjects died as a result of illnesses of varying complexity and duration.

It is probable that several factors such as disease, drug therapy, the magnesium content of diet and drinking water [180], as well as the ageing process itself have contributed to varying extent to the lower levels of magnesium in heart and muscle of these elderly subjects. The observed effects of diuretics are considered in more detail in Chapter 10. The values for muscle magnesium obtained in young accident victims are similar to those obtained in previous studies of autopsy tissue from accident victims where dry weight was used as the frame of

FIGURE 10 Relationship between magnesium and potassium in skeletal muscle obtained at autopsy from young accident victims and elderly hospital patients



reference [6,180]. The values are also in line with results obtained in biopsy samples from healthy volunteers [175,176].

The clinical significance of lower magnesium in muscle and heart of elderly subjects is uncertain. The close relationship between magnesium and potassium in muscle tissue has been observed by others [6,176,181]. Most investigators agree that muscle magnesium content does not contribute greatly to the readily exchangeable body magnesium pool but low levels probably reflect prolonged magnesium depletion. Furthermore, muscle magnesium depletion can lead to loss of potassium from muscle with eventual potassium depletion. Such potassium depletion proves refractory to treatment unless magnesium status is also corrected [181,182,183]. However, since muscle magnesium relates poorly to magnesium content of serum and bone but is so closely related to muscle potassium content, it has been argued that muscle magnesium depletion is likely to be a reflection of low body potassium stores rather than low magnesium stores [6].

9.4. Summary

This study of autopsy tissue has revealed significantly lower muscle stores of magnesium in elderly patients compared with younger subjects. There is no single test in routine clinical practice which unequivocally reveals magnesium deficiency and the drawbacks of the those

utilised in previous chapters have been discussed. Nevertheless, the cummulative evidence from dietary surveys, urine measurements, loading tests and autopsy tissue analysis tends to support a degree of magnesium deficit in the elderly patient population studied.

PART 3

CHAPTER 10

DIURETICS AS A CAUSE OF MAGNESIUM DEPLETION

10.1. Introduction

Diuretics are listed among the various causes of hypomagnesaemia outlined in Chapter 2. This chapter investigates more fully the relationship between these commonly prescribed drugs and magnesium depletion in elderly subjects.

Increased urinary excretion of magnesium with diuretic therapy is well documented and diuretics are a recognised cause of magnesium depletion [184,185,186]. Diuretics are frequently prescribed for the elderly [187] but, in contrast to diuretic induced potassium losses, the potential problem of diuretic induced magnesium depletion has not been widely recognised. The relationship between diuretics and magnesium in the elderly has therefore been investigated in three studies.

10.2. Study 1: Prevalence of diuretic associated hypomagnesaemia in the elderly

a) Introduction

This study was designed to assess the prevalence of hypomagnesaemia in ill elderly patients following hospital admission with particular reference to the effects of different types of diuretic therapy.

b) Patients and Methods

Serum total magnesium concentration was measured in 320 consecutive elderly patients who were known to be taking diuretic therapy at the time of hospital admission. During the same period serum magnesium concentration was also measured in 250 consecutive patients who had not been receiving diuretics. All serum samples were obtained as part of a standard biochemistry admission profile, the majority being taken within 24 hours of hospital admission. Laboratory analysis for magnesium by atomic absorption spectrophotometry [28] was performed within four hours of venepuncture.

24 hour urine magnesium output and creatinine clearance were measured in selected patients who were either normomagnesaemic (serum magnesium 0.70 - 1.0 mmol/l) and not receiving diuretics, or were hypomagnesaemic. The hypomagnesaemic patients were divided into representative sub-groups receiving either thiazide diuretics, loop diuretics, or potassium conserving combinations, and a group not receiving diuretics.

Prior to initiating a 24 hour urine collection, a second serum sample was obtained to verify serum magnesium status. All patients received a standard hospital diet containing an average of 8 mmol magnesium daily for at least three days prior to the urine collection. Urine collections were closely supervised by trained nursing staff who recorded each episode of micturition. When urine incontinence was recorded or daytime micturition intervals exceeded 4 hours

the urine collection was repeated or the procedure was abandoned. Diuretic therapy and dosage remained unchanged until the completion of urine collections.

Percentage renal excretion of magnesium was calculated by the formula -

$$\% \text{ Ex. Mg.} = \frac{\text{Urine Mg (mmol/24 hrs) x 100}}{\text{Serum Mg x creatinine clearance}}$$

To compensate for the effect which varying renal function might have on urine magnesium excretion between groups, the ratio of magnesium concentration (mmol/l) to creatinine concentration (umol/l) was calculated on each 24 hour urine collection.

Most patients receiving loop diuretics and potassium sparing combinations were being treated for cardiac failure, whereas the majority of patients taking thiazide diuretics were hypertensive with approximately 50% having suffered a cerebrovascular incident. Respiratory infection and gastrointestinal disorders were the most common diagnostic categories in patients not receiving diuretics.

c) Statistical methods

One-way analysis of variance and independent t tests were used to compare means of normally distributed data and the Kruskal-Wallis test was used for comparisons of skewed data.

d) Results

During the study period approximately 36% of patients were receiving diuretic treatment at the time of admission in the proportions 50% loop diuretics, 30% thiazides, 20% combinations which included potassium conserving agents. The results of serum magnesium analysis on 570 patients comprising 320 consecutive patients receiving diuretics, subdivided according to class, and 250 patients, not receiving diuretics, are shown in Table 16.

Mean serum magnesium was significantly lower in those patients receiving thiazide diuretics compared with those not taking diuratics. Serum magnesium levels tended to be inversely related to the dose of bendrofluazide, the most commonly prescribed thiazide diuretic, but the effect was not statistically significant. There were no significant differences in serum magnesium levels among patients taking the various types of potassium sparing diuretics.

Twenty-four hour urine collections were obtained in 84 patients. Urine magnesium excretion in 30 normomagnesaemic patients (mean serum magnesium 0.83 mmol/l (sd 0.06)) was 1.46 mmol/24 hours (sd 0.66) with a range of 0.18 to 3.16 mmol. The overall magnesium/creatinine excretion ratio for these patients was 0.35 (sd 0.28). The results of urine magnesium excretion for the four hypomagnesaemic sub-groups are shown in Table 17 and illustrated in Figures 11 and 12. All four groups had a wide range of urine magnesium excretion values with no significant differences between groups (Kruskal-Wallis one-way ANOVA).

TABLE 16

Serum magnesium and diuretic therapy in elderly patients

Type of Diuretic	No.of patients	Serum mg mmol/l mean (sd) (95% C.I.)	% below 0.70mmol/l	% below 0.67mmol/l
Loop	160	0.80 (0.12) (0.78-0.82)	10	7
Thiazide	94	0.77 (0.11) * (0.75-0.79)	27	14
Potassium conserving combinations	66	0.80 (0.11) (0.77-0.83)	12	9
No diuretic	250	0.82 (0.10) (0.81-0.83)	8	4

one-way ANOVA for all four groups; $F = 5.07$, $P < 0.005$

* Thiazide Vs No diuretic; $P < 0.001$; Student's t test

99% confidence interval for the difference = 0.02 to 0.08

TABLE 17 - Renal Handling of Magnesium in Elderly Hypomagnesaemic Subjects

	Serum Mg mmol/l	Urine Mg mmol/24hr	Percentage renal excretion	Magnesium/ Creatinine ratio	Serum Urea mmol/l	Serum creatinine umol/l
Loop diuretics	0.66 (0.07)	1.32 (0.75)	7.1 (4.7)	0.35 (0.12)	8.3 (3.4)	109 (48)
N = 14						
Thiazide diuretics	0.67 (0.6)	1.75 (1.03)	5.5 (2.4)	0.32 (0.10)	7.5 (4.3)	98 (44)
N = 14						
Potassium sparing combinations	0.65 (0.05)	1.09 (0.62)	5.3 (2.8)	0.29 (0.14)	9.8 (2.7)	108 (19)
N = 8						
No diuretic	0.66 (0.08)	0.97 (0.75)	4.5 (3.5)	0.24 (0.16)	7.0 (4.1)	95 (55)
N = 18						

Values shown as mean (s.d)

FIGURE 11 Urine magnesium excretion in elderly hypomagnesaemic subjects: effect of different classes of diuretics

(serum magnesium less than 0.70 mmol/l)

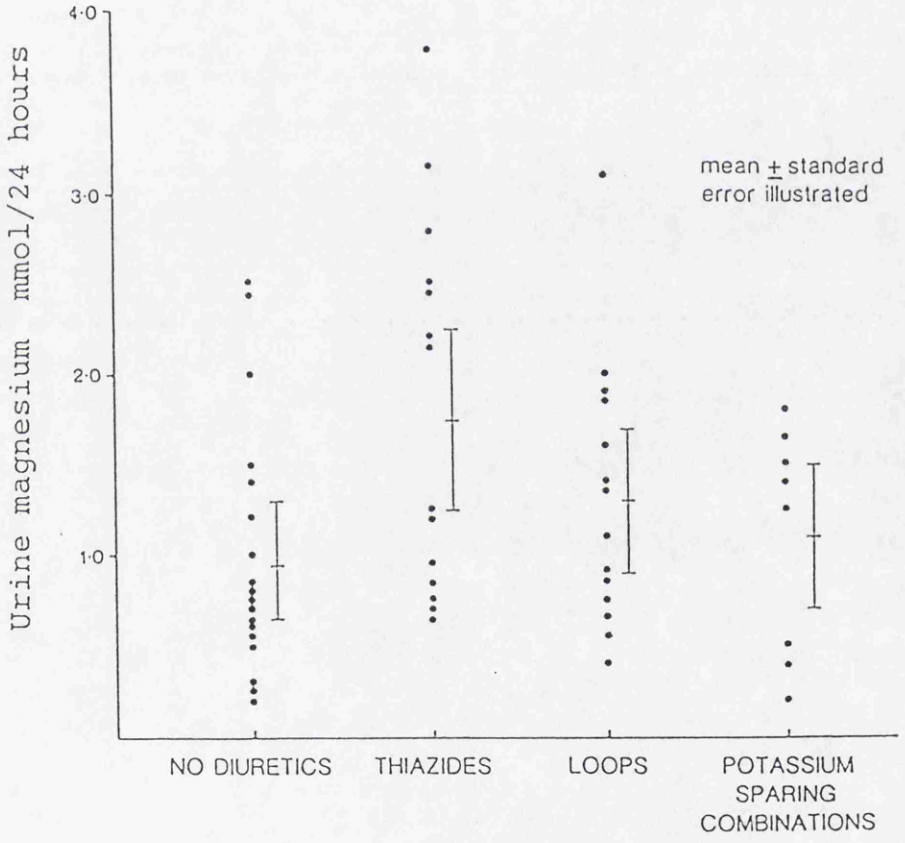
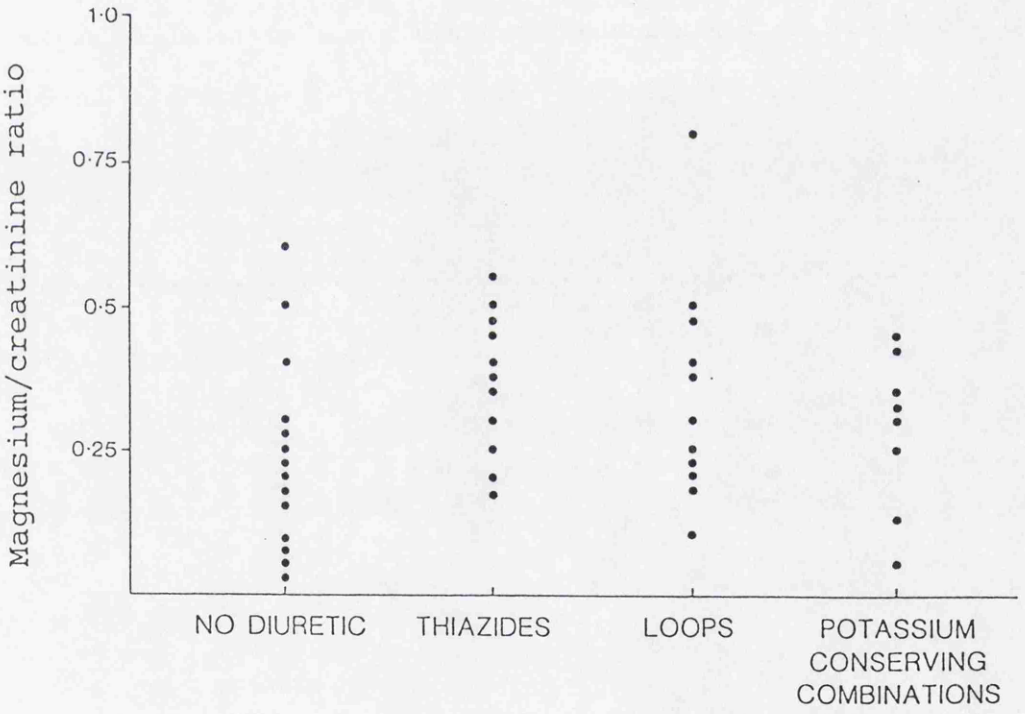


FIGURE 12 Ratio of magnesium/creatinine excretion in 24 hour urine collections from elderly hypomagnesaemic subjects: effect of different classes of diuretics



e) Discussion

Loop diuretics have been most commonly implicated in magnesium depletion [112,175,188,189,190] although studies have often tended to be on subjects in heart failure where the effects of digoxin [25] and secondary aldosteronism [36,191] may have contributed to magnesium losses.

By exerting their main action in the ascending part of the loop of Henle, where most of the filtered magnesium is reabsorbed, it is not surprising that the loop diuretics are liable to produce magnesium deficiency. However, the increase in urine magnesium excretion induced by loop diuretics may be partly due to mechanisms other than direct blockade of magnesium reabsorption [192].

The results of this study indicate that, when compared with loop diuretics in ill elderly patients, thiazide diuretics are just as likely to be associated with hypomagnesaemia. It has long been known that thiazide diuretics cause an increase in urine magnesium excretion [193]. Thiazides are active at the proximal part of the distal convoluted tubule where only about 5% of filtered magnesium is reabsorbed. Most magnesium loss is therefore likely to be due to an indirect effect of thiazide treatment. Thiazides also cause changes in calcium reabsorption and chronic administration can cause hypocalciuria, elevated serum calcium and a reduction in serum parathyroid hormone. This in turn results in reduced magnesium reabsorption at the loop of Henle and increased urine magnesium excretion

[192,194]. Thiazide-induced alteration in the renin-angiotensin-aldosterone system may add to increased urine magnesium excretion [185,191].

Thiazides are commonly prescribed for treatment of hypertension and most studies of younger patients have revealed some lowering of serum magnesium associated with such treatment. However there is no clear consensus as to whether such changes are clinically significant [195,196,197,198].

The reported magnesium-conserving abilities of potassium sparing diuretics [190,199] are supported by results of this study. Neither serum levels nor urine magnesium output differed significantly from those of patients not receiving diuretics.

The results of this study show that whilst increased urine magnesium losses are induced by diuretic therapy, the wide range of urine excretions found in all groups studied make attempts to relate urine magnesium excretion to serum levels of limited value in the individual subject.

10.3. Study 2: Thiazide diuretic therapy : a prospective analysis of serum magnesium in hypertensive patients

a) Introduction

Lowered serum magnesium levels and hypomagnesaemia in association with thiazide diuretic treatment in the elderly has been observed in studies by others following hospital admission [21,22] and in hypertensive patients in the community [201]. Like Study 1 described above these studies were cross sectional surveys, the exact duration of thiazide therapy was either unknown or approximated, doses varied, and factors other than thiazide therapy which could influence magnesium status were likely to be present especially in ill hospitalized patients.

The following prospective study was therefore performed to assess more precisely the timing and magnitude of changes in magnesium status in elderly patients induced by thiazide treatment.

b) Subjects and Methods

Elderly out-patients with untreated hypertension were considered for selection and 20 subjects aged between 65 and 80 years (mean age 72 years) were recruited over a two year period. Prior to treatment all 8 men and 12 women had systolic blood pressure above 160 mm mercury and diastolic pressure above 90 mm mercury on three consecutive occasions one month apart and none of the patients had previously received treatment for hypertension. All subjects were

living at home and were free from other significant medical disorders. All had normal biochemical and haematological profiles at commencement of the study. Subjects were prescribed bendrofluazide 5 mg daily and were reviewed at 1 month, 2 months, 4 months, 6 months, 12 months, 18 months and 24 months after commencement of treatment. At each review biochemical indices including serum magnesium were checked between 0900 and 1000 hours following an overnight fast.

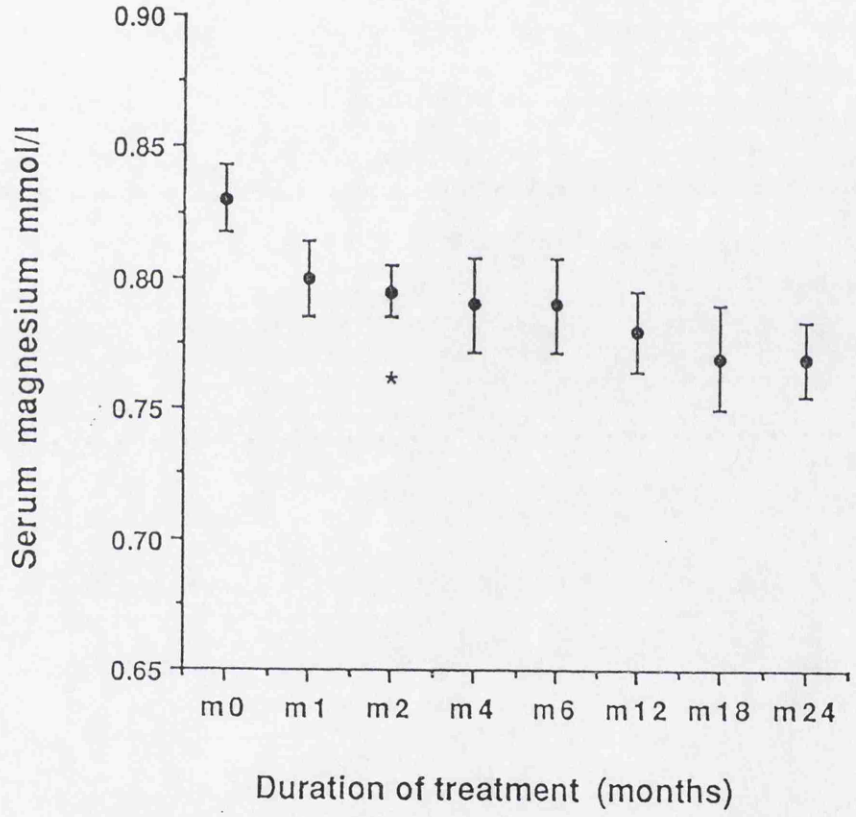
The study received hospital ethical committee permission and all participants gave informed consent.

c) Results

Follow up was completed in 15 patients to one year and in 12 patients to two years. There was a significant fall in serum magnesium between month 0 and month 2 (P = 0.039, paired t test) and thereafter the serum magnesium level remained relatively constant (Figure 13). During the first 2 months there was also a rise in mean serum calcium concentration, corrected for albumin binding, from 2.44 mmol/l (sd 0.09) to 2.49 mmol/l (sd 0.08) (P = 0.009, paired t test). The mean serum calcium remained at between 2.47 and 2.49 mmol/l thereafter. There was a gradual fall in mean serum potassium concentration from 4.32 mmol/l (sd 0.35) before treatment to 4.17 mmol/l (sd 0.42) at 12 months and it remained at this level thereafter. This change did not reach significance at the 5% level.

FIGURE 13 Serum magnesium in elderly subjects receiving Bendrofluazide 5mg daily for treatment of hypertension

mean and standard error illustrated



* m0 versus m2

p = 0.039 paired t test

Erythrocyte magnesium was measured in 14 subjects during this study. There was no significant change in mean erythrocyte magnesium concentration analysed at various intervals between month 0 and month 24 (Table 18).

d) Discussion.

Animal studies and some clinical studies have failed to show a significant change in serum magnesium as a consequence of short term thiazide treatment [185]. However most prospective studies of thiazide treatment lasting 4 months or more have shown a significant reduction in serum magnesium and this has been dose related [192,196,197]. A study by Cocco et al [202] of younger hypertensive patients used serum measurements and magnesium loading tests performed at 0, 6 and 12 months to determine changes in magnesium status from commencement of thiazide treatment. Results of that study indicated that magnesium losses are already maximal at 6 months and persist thereafter. Recent work by Siegal et al [203] randomised 233 hypertensive men, average age 61 years, to 6 forms of treatment each lasting 2 months. Subjects had received supplementation with magnesium and potassium for 1 month prior to randomisation and treatment. At 2 months there were small reductions in mean serum magnesium in 60 subjects given hydrochlorothiazide and in 30 given chlorthalidone. These reductions did not reach significance at the 5% level but in both groups the number of subjects with hypomagnesaemia (<0.70 mmol/l) more than doubled. The authors pointed out

TABLE 18

Erythrocyte magnesium and bendrofluazide treatment in elderly subjects with hypertension

Duration of treatment (months)	Number of subjects	Erythrocyte Mg mmol/l mean (sd)	95% confidence interval
0	14	2.29 (0.41)	2.06 - 2.53
2	14	2.30 (0.41)	2.07 - 2.56
6	14	2.37 (0.37)	2.17 - 2.56
12	12	2.26 (0.29)	2.08 - 2.45
18	12	2.17 (0.34)	1.96 - 2.39
24	12	2.24 (0.27)	2.11 - 2.37

that prolonged treatment might result in greater reduction in serum magnesium especially in older subjects in whom additional risk factors for magnesium loss are more likely to be present.

The fall in serum magnesium in the elderly subjects in this study is more pronounced than has been observed in younger subjects. Lower body magnesium stores and/or altered homeostatic responses to thiazide-induced magnesium loss are possible contributing factors. The rise in serum calcium which also occurred within the first 2 months of treatment supports the evidence that thiazide-induced changes in serum concentrations of both elements are linked [192]. Serum levels of neither element changed significantly after 2 months. The plateau in serum magnesium may be due to increased intestinal absorption compensating for thiazide-induced renal losses with re-adjustment of magnesium balance at a lower serum level [21]. However it is possible that some magnesium is mobilised from body stores and, therefore, tissue magnesium depletion could arise over a prolonged period especially in circumstances of poor dietary intake or malabsorption co-existed.

Some previous studies have shown a reduced concentration of magnesium in erythrocytes in association with long-term thiazide treatment [112,201] whilst another failed to do so [167]. The erythrocyte is not a typical cell and magnesium concentration may not accurately reflect the situation in the intracellular environment elsewhere.

Some workers have measured mononuclear cell magnesium to determine the intracellular effects of diuretic treatment [112,167,203]. Such measurements were commenced in this study but soon abandoned because of the excessive intra-subject variation evident in a control group.

10.4. Study 3: Effect of diuretics on magnesium levels in autopsy tissue of elderly subjects

a) Introduction

Studies have indicated risk of significant magnesium depletion in skeletal muscle resulting from long term treatment with loop diuretics [175,199] but studies of thiazides have produced conflicting results [167,199]. There has been little information relating to the situation in old age and the following analysis was therefore performed.

b) Methods

Magnesium concentrations in autopsy skeletal muscle and heart tissue from the 33 elderly subjects described in chapter 9 were grouped according to diuretic use prior to death (Appendix 2). Data from 15 subjects who had not received any form of diuretic therapy during the 3 months before death were compared with those from 14 subjects who had been taking one or more diuretics daily for at least 1 year (5 loop diuretics, 5 thiazides and 4 potassium conserving combinations). The remaining 4 subjects did not

fit into either category and were excluded from the analysis.

c) Results

There was a trend for subjects taking both loop and thiazide diuretics to have lower levels of magnesium in skeletal muscle but confidence intervals were wide and differences were not significant at the 5% level in either skeletal muscle or heart (Table 19) (Kruskal-Wallis one way analysis of variance). Furthermore, the mean skeletal muscle magnesium concentration of 682 mg/kg (sd 145) for the combined loop and thiazide diuretic groups was not significantly different from those not taking diuretics, ($P = 0.086$, Mann-Whitney).

10.5 Discussion

The balance of evidence from my own studies and the literature points to a small but significant reduction in serum magnesium as a consequence of both loop and thiazide diuretic treatment. However intracellular losses probably only occur to a significant degree in a small minority of susceptible individuals after prolonged treatment. High diuretic dosage, poor dietary magnesium intake and co-existent disease such as heart failure, alcoholism and diabetes mellitus increase risk of magnesium depletion. Do diuretic-induced magnesium losses matter? Are there clinical circumstances when magnesium supplements should be given with diuretic treatment? The rationale for magnesium

TABLE 19

Effect of diuretics on magnesium in autopsy tissue from elderly subjects

Diuretic type	No.	Skeletal muscle tissue Magnesium concentration (mg/kg dry wt.) mean (sd)	95% confidence interval
Loop diuretic	5	711 (194)	469 - 952
Thiazide	5	657 (80)	556 - 957
Potassium conserving	4	732 (146)	498 - 966
No diuretic	15	770 (146)	713 - 826

Diuretic type	No.	Heart tissue Magnesium concentration (mg/kg dry wt.) mean (sd)	95% confidence interval
Loop diuretic	5	886 (68)	802 - 791
Thiazide	5	851 (157)	656 - 1047
Potassium conserving	4	688 (234)	315 - 1068
No diuretic	15	895 (69)	856 - 933

supplementation mirrors the situation with potassium since both elements are closely interrelated at a cellular level [185,186,190,204]. However after 20 years of debate there is still controversy as to the clinical indications or even need for potassium supplementation with diuretic treatment [205,206,207,208,209,210,211].

Hollowfield [186] has advocated use of potassium/magnesium conserving diuretics as first line treatment in appropriate patients. He cited the close cellular interrelationship between magnesium and potassium, the evidence of increased ventricular ectopic activity associated with magnesium and potassium depletion with the risk of sudden death, and the concern that tissue depletion of both elements may arise with normal serum levels.

Ryan [185] has followed a similar line of reasoning and, in addition, argued that magnesium supplementation may be beneficial in the treatment of hypertension.
More recently Whang et al [204] have gone further and recommended provision of magnesium supplements to all patients with low serum potassium even when the serum level of magnesium is unknown. However Siegal et al [203] failed to find any evidence that diuretic-induced magnesium loss resulted in increased ventricular ectopic activity after 2 months of diuretic treatment and therefore concluded that routine supplementation or use of potassium/magnesium conserving agents is unnecessary. These investigators recognised that a small proportion of patients are at risk with diuretic treatment but also pointed out the very large

clinical study which would be needed to accurately quantify the risk.

The debate continues...

PART 4

CHAPTERS 11 - 12

ASSESSMENT OF THE CLINICAL IMPORTANCE OF HYPOMAGNESAEMIA IN THE ELDERLY

CHAPTER 11

THE CLINICAL SIGNIFICANCE OF HYPOMAGNESAEMIA

11.1 Introduction

Hypomagnesaemia is not an uncommon finding in ill patients at the time of hospital admission. It is often associated with other biochemical abnormalities such as hypocalcaemia, hypokalaemia, and hypophosphataemia, which may persist until the altered magnesium status is corrected [86,87,108,212]. In many clinical situations the true relevance of hypomagnesaemia can be difficult to evaluate and this is particularly so in the frail elderly who are more likely to present with complex multiple pathology.

11.2. Clinical outcome in hypomagnesaemic elderly patients admitted to hospital

This study was performed to measure the prevalence of hypomagnesaemia and associated biochemical disturbance in elderly patients at the time of hospital admission and to compare clinical outcome in hypomagnesaemic patients with outcome in patients with normal serum magnesium levels. The prevalence of hypermagnesaemia and clinical outcome in such patients was also recorded.

a) Subjects and methods of determining clinical outcome

Serum magnesium estimations were performed on 1576 consecutive patients admitted to Lightburn hospital over a

two year period beginning January, 1987. Some patients had more than one sample taken so that approximately 2600 samples were taken in total for magnesium estimation during the study period. The first sample from each patient, usually taken within 24 hours of hospital admission, was termed the index sample and used as the baseline for classification and outcome measurements. Clinical outcome in patients with an initial serum magnesium in the lowest 5 per cent of the observed range was compared with outcome in a representative cohort of patients with normal index serum magnesium levels. Outcome was measured in terms of duration of hospital stay and survival to six months from the time of the index sample. Those patients who were discharged from hospital were reviewed on an out-patient basis. In a small number of cases when direct patient contact could not be re-established following hospital discharge, information on survival was obtained from relatives and family doctors.

b) Measurement of associated biochemical disturbance

Blood sampling and magnesium analysis were performed in the fashion already described (see Chapter 4). As part of a standard biochemistry admission profile, samples were also analysed for levels of calcium, phosphorus, and albumin. Serum measurements of sodium, potassium, and creatinine, performed at the same time as magnesium analysis, were included in analysis for the second year of the study.

c) Statistical methods

The Chi-square test, the independent t test and the Mann-Whitney U test were used where appropriate. All mean values are quoted with one standard deviation for Gaussian distributions. Median values and range are quoted for skewed distributions.

d) Results

(i) Population characteristics and serum magnesium levels

The mean age of the study population of 1576 patients was 81.5 years (sd 7.2). During the study period 169 patients (10.7 per cent) had an initial serum magnesium level less than 0.7 mmol/l, the lower limit of the laboratory reference range, and of these 70 were below 0.65 mmol/l (4.4 per cent of the total study population). Thirty-one patients (2 per cent) had a serum magnesium level greater than 1.0 mmol/l. The median serum magnesium for the population was 0.81 mmol/l with the distribution being slightly skewed towards the lower end. Ninety per cent of values were within the range 0.66 - 0.95 mmol/l and there was no sex difference for median serum magnesium, or for the frequency of either hypermagnesaemia or hypomagnesaemia. In practice all patients with an initial serum magnesium below 0.65 mmol/l were classified as hypomagnesaemic and their outcome was compared with 100 consecutive patients with an index serum magnesium in the range 0.80-0.82 mmol/l.

(ii) Outcomes

Table 20 compares the outcome for both hypomagnesaemic and normomagnesaemic groups and shows that there was no significant difference between the two groups for any of the outcome measurements. The 14 hypomagnesaemic patients who died had an initial mean serum magnesium level of 0.57 mmol/l (sd 0.05) compared with a mean level of 0.59 mmol/l (sd 0.04) in the 56 survivors (not significant).

(iii) Factors associated with hypomagnesaemia

Tables 21 and 22 illustrate the spectrum of illness and medications, respectively, at the time of hospital admission in both the hypomagnesaemic patients and in the cohort with normal serum magnesium levels. Diuretic therapy was the factor most commonly associated with hypomagnesaemia. Eight hypomagnesaemic patients were taking more than one type of diuretic. The breakdown of diuretic therapy in both groups of patients is shown in Table 23.

A serum albumin below 33 g/l was considered to be abnormal [98]. Hypoalbuminaemia was noted in 24 (34 per cent) of hypomagnesaemic patients and in 14 per cent of the normomagnesaemic cohort. The mean serum albumin for each group was 34.3 g/l (sd 6.7) and 38.3 g/l (sd 5.0) respectively, significantly lower in the hypomagnesaemic patients ($t = 4.13$, $P < 0.001$). However, apart from those subjects with a very low serum albumin, no correlation was evident between albumin and magnesium for the population

TABLE 20 - Elderly patients admitted to hospital

Patient characteristics and clinical outcome at 6 months

	Hypomagnesaemic Subjects (<0.65 mmol/l)			Normomagnesaemic Subjects (0.80 - 0.82 mmol/l)		
	Male	Female	Combined	Male	Female	Combined
Number	17	53	70	37	63	100
Age: Mean (sd)	78 (6.5)	83 (6.7)	81.7 (6.6)	78.5 (6.5)	80 (6.6)	79.6 (6.3)
Total Deaths Within 6 Months	3	11	14 (20%)	10	10	20%
Deaths in Hospital	2	7	9 (13%)	6	9	15%
Discharged From Hospital	13	41	54 (77%)	27	43	70%
Duration of Hospital Stay (Days)* Median (Range)	27 (2-60)	27 (3-150)	27 (2-150)	34 (5-152)	21 (2-83)	25 (2-152)
Patients Remaining In Hospital At 6 Months	2	5	7 (10%)	4	11	15%

* Excluding patients who died in hospital or who were still in hospital at 6 months.

TABLE 21

Elderly patients admitted to hospital: most common diagnoses

Hypomagnesaemic patients (serum mg < 0.65 mmol/l) n = 70		Normal serum magnesium (serum mg 0.80-0.82 mmol/l) n = 100	
Diagnosis	Number of patients (%)	Diagnosis	Number of patients (%)
Ischaemic heart disease	28 (37)	Cerebrovascular disease	27
Heart failure	19 (27)	Ischaemic heart disease	22
Cerebrovascular disease	12 (17)	Arthritis	20
Arthritis	12 (17)	Heart failure	19
Infections (all types)	11 (15)	Infections (all types)	12
Diabetes mellitus	11 (15)	Chronic airways disease	11
Neoplastic disease	9 (13)	Diabetes mellitus	10
Chronic airways disease	8 (11)	Anaemia	9
Peptic ulceration	6 (9)	Hypertension	8
Anaemia	6 (9)	Hypothyroidism	8
Average of 2.4 diagnoses per patient (range 1 - 6)		Average of 2.1 diagnoses per patient (range 1 - 5)	

TABLE 22

Elderly patients admitted to hospital: most common medications

Hypomagnesaemic patients (serum mg < 0.65 mmol/l) n = 70		Normal serum magnesium (serum mg 0.80-0.82 mmol/l) n = 100	
Medication	Number	Medication	Number
Diuretics	55	Diuretics	38
Simple analgesics	17	Simple analgesics	33
Digitalis	17	Laxatives	19
Bronchodilators	16	NSAIDS*	9
Iron supplements	7	Bronchodilators	8
Oral hypoglycaemics	7	Oral hypoglycaemics	8
Antibiotics	7	Thyroxine	7
NSAIDS*	7	Digitalis	7
H2 receptor antagonists	6	Iron supplements	7
Total medications	**219**	**Total medications**	**226**
3 patients on no medication		11 patients on no medication	

* Non steroidal anti-inflammatory drugs

TABLE 23

Use of diuretic therapy in relation to serum magnesium status in elderly patients on admission to hospital

	Hypomagnesaemia (serum mg < 0.65 mmol/l) n = 70	Normal serum mg. (0.80-0.82 mmol/l) n = 100
Patients taking diuretics	47 (67%)	34
Number of diuretics	55	38
Thiazides	23	9
Loop diuretics	21	19
Potassium sparing agents	11	10

as a whole. A low serum albumin was associated with increased mortality in both hypomagnesaemic patients and patients with normal serum magnesium : eight of 24 (33 per cent) hypomagnesaemic patients ($X^2 = 4.04$; $P < 0.05$), and six of 14 (43 per cent) normomagnesaemic patients ($X^2 = 5.31$; $P < 0.02$) died within six months. Of patients with a serum albumin above 33 g/l, six of 48 (13 per cent) died in the hypomagnesaemic group compared with 14 of 86 (17 per cent) in the normomagnesaemic group. Assuming 30 per cent binding of magnesium to albumin, no case of hypomagnesaemia was considered to be due solely to a low serum albumin.

(iv) Associated electolyte depletion

The frequency of depletion of other electrolytes in the 70 hypomagnesaemic patients is shown in Table 24, and can be compared with the population frequency of depletion of these same electrolytes and coincident hypomagnesaemia shown in Table 25. Thus 13% of hypomagnesaemic patients had a serum potassium below 3.0 mmol/l, whereas 56% of hypokalaemic patients were also hypomagnesaemic. The occurence of hypocalcaemia was considerably reduced when corrected for albumin binding (normal range for corrected serum calcium = 2.22 - 2.60 mmol/l).

Six month mortality rates for the nine hypokalaemic subjects and 16 hyponatraemic subjects, identified during the second year of the study, were 0 and 8 (50%) respectively.

TABLE 24

Coincident electrolyte depletion in 70 hypomagnesaemic elderly patients on admission to hospital

		Number of Patients (%)
Hypokalaemia	(< 3.5 mmol/l)	15 (21)
	(< 3.0 mmol/l)	9 (13)
Hypocalcaemia	(< 2.0 mmol/l)	9 (13)
	(< 2.2 mmol/l)*	2 (3)
Hypophosphataemia	(< 0.7 mmol/l)	2 (3)
Hyponatraemia	(< 130 mmol/l)	1 (1)

* Corrected calcium = measured calcium + 0.02 x (47 - albumin g/l)

TABLE 25

Frequency of electroyte depletion in 1576 elderly patients on admission to hospital

			Coexistent Hypomagnesaemia (< 0.65mmol/l)	
	Number	%	No.	%
Hypomagnesaemia (< 0.65 mmol/l)	70	4		
Hypocalcaemia* (< 2.0 mmol/l)	37	2	9	24
Hypophosphataemia (< 0.7 mmol/l)	16	1	2	13
Hypokalaemia** (< 3.0 mmol/l)	9	1	5	56
Hyponatraemia** (< 130 mmol/l)	16	2	1	6

* Not corrected for protein binding

** Study population 902

(v) Hypermagnesaemia

The diagnoses of the 31 patients with elevated serum magnesium (greater than 1.0 mmol/l) are listed in Table 26. Some patients had multiple problems. Within the six month period, fifteen (48%) of these 31 hypermagnesaemic patients died ($X^2 = 7.4$: $P < 0.01$). All 15 patients had biochemical evidence of chronic renal impairment (serum creatinine persistently above 150 umol/l), and their mean presenting serum magnesium was 1.11 mmol/l (sd 0.11), compared with a mean of 1.06 mmol/l (sd 0.06) for the 16 hypermagnesaemic survivors (difference not significant). The serum level of the hypermagnesaemic survivors generally returned to within the normal range, reaching a mean of 0.92 mmol/l (sd 0.09) at six months. In contrast the serum levels of those who died tended to remain high until death.

e) Discussion

The prevalence of hypomagnesaemia encountered in this study is similar to that found in other populations of elderly in-patients (see Chapter 4), and once again diuretic therapy, particularly with thiazides, seems to confer an increased risk of hypomagnesaemia (see Chapter 10). The rates of associated electrolyte disturbance are close to those previously reported with the interdependence of magnesium and potassium again being apparent. The association of hypermagnesaemia with renal impairment has been recognised [84], and as the latter condition is not

TABLE 26

Diagnoses in 31 elderly hypermagnesaemic patients on admission to hospital. (Serum magnesium > 1.0 mmol/l)

Diagnosis	No. of patients
Chronic Renal Failure	17
Heart disease	8
Pulmonary disease	7
Respiratory infection	5
Dehydration	4
Parkinson's disease	4
Carcinomatosis	3
Other conditions	10
Contributing causes	
K+ conserving diuretics	10
Magnesium supplementation	1

uncommon in seriously ill elderly patients, the high mortality in patients with hypermagnesaemia and chronic renal failure is perhaps not surprising.

In view of the severe morbidity and risks which have been attributed to magnesium depletion, it is perhaps rather surprising that this study failed to reveal any difference in outcome between patients admitted with hypomagnesaemia and those admitted with normal serum magnesium levels. Furthermore, mortality in hypomagnesaemic patients was much lower than that in hyponatraemic and hypoalbuminaemic patients from the same population.

The fact that outcome for patients hypomagnesaemic on hospital admission was virtually the same as outcome for patients with normal serum magnesium levels could be due to several factors.

Many of the patients who presented with hypomagnesaemia in this study subsequently received treatment which directly or indirectly could have improved magnesium status; e.g. oral magnesium supplements (a few cases), cessation of diuretic therapy, improvement of diet, and control of diabetes mellitus. Furthermore, serum can be a misleading guide to true body status and, as there is evidence that normal serum levels can occur despite tissue depletion (see Chapter 4), some of the normomagnesaemic cohort may have been tissue depleted.

A study of patients admitted to surgical intensive care, many of whom were hypomagnesaemic, failed to reveal any

correlation between serum magnesium and severity of illness or clinical outcome [89]. Evidence now indicates that the stress of acute illness can result in temporary hypomagnesaemia caused by a shift of magnesium from serum into cells. This magnesium shift is mediated by catecholamine release and occurs especially if pain is present [103,104]. In such circumstances the serum level generally returns to normal after a few days. However, in this study of elderly patients, almost half of the hypomagnesaemic survivors were still hypomagnesaemic on re-testing at six months, suggesting genuine depletion of magnesium, yet they did not seem to be particularly disadvantaged by this.

11.3. Clinical outcome in severe hypomagnesaemia

Since completion of the above study **(11.2)** it has been possible to review the clinical outcome in all cases of severe hypomagnesaemia encountered in elderly patients admitted to hospital during a six year period.

a) Methods

Patients with a serum magnesium less than 0.50mmol/l whilst in the Geriatric Assessment Unit at Lightburn Hospital during the period 1987-1992 were identified by means of a Department of Clinical Chemistry computer archives search. Data on clinical diagnoses, approximate duration of illness and outcome at six months were then obtained by review of individual case records. Six months survival data were

checked with family medical practitioner records in 5 cases with incomplete hospital records.

b) Results

Serum magnesium was measured in 4,088 individual in-patients during the six year period and 22 patients (0.5%) had one or more samples less than 0.50 mmol/l. Most of these severely hypomagnesaemic patients were very ill; 4 patients died within two weeks of the lowest recorded serum magnesium level and a total of 8 (36%) died within six months. Hypomagnesaemia was associated with hyponatraemia (serum sodium < 130 mmol/l) in 7 patients of whom 3 died, and 6 patients were hypokalaemic (serum potassium < 3.0 mmol/l) of whom 1 died. Low serum magnesium levels often recurred or persisted for several weeks despite efforts to correct magnesium status in such patients using oral and/or parenteral supplements. Three patients were again severely hypomagnesaemic during a second hospital admission within six months, two of these being related to excessive alcohol intake, and all 3 survived for at least a further six months. Further patient details are given in Appendix 3.

Despite evidence of severe illness in most of these 22 severely hypomagnesaemic patients, mortality rate at six months was not significantly greater than in the cohort of 100 normomagnesaemic patients referred to previously in section 11.2. ($X^2 = 2.72$).

11.4 Conclusions

The common association of hypomagnesaemia with hypokalaemia is confirmed and more profound hypomagnesaemia in severe illness is also often associated with hyponatraemia. However the relative importance of hypomagnesaemia in ill elderly subjects, many of whom present with multiple pathology, remains uncertain. An abnormally high serum magnesium in the presence of renal impairment appears to be a poor prognostic indicator in ill elderly patients.

CHAPTER 12

EFFECTS OF MAGNESIUM SUPPLEMENTATION: A STUDY OF ELDERLY HYPOMAGNESAEMIC SUBJECTS GIVEN ORAL MAGNESIUM SUPPLEMENTS

EFFECTS OF MAGNESIUM SUPPLEMENTATION: A STUDY OF ELDERLY HYPOMAGNESAEMIC SUBJECTS GIVEN ORAL MAGNESIUM SUPPLEMENTS

12.1. Introduction

Routine serum magnesium estimation is advised whenever knowledge of electrolyte levels is required and prophylactic low dose oral therapy is recommended in patients at risk of magnesium depletion [4,213]. However the effects of such therapy have recieved little detailed study and thus the evidence of benefit is sparse. Older subjects are already prescribed a disproportionately high number of medications and as many as three quarters have problems with compliance [214]. I was unable to find convincing evidence that hypomagnesaemia worsenes clinical outcome in in-patients (see Chapter 11), and this study was performed to assess whether routine treatment of the condition in the elderly can be justified on the basis that such treatment produces beneficial effects.

Constrained by the limited resources available in routine clinical practice, an explanatory type study [215] was devised based on a relatively homogeneous group of patients considered likely to respond to treatment. Hospital ethical committee permission was obtained to study the effects of oral magnesium therapy in elderly hypomagnesaemic out-patients.

12.2. Patients and methods

Elderly subjects attending the out-patient department or

day hospital and found to be hypomagnesaemic (serum magnesium < 0.70 mmol/l) were considered for inclusion in the study. Informed consent was sought from subjects with stable clinical conditions who were considered unlikely to require alterations to their existing medication regimens during the study period. Subjects with renal impairment, defined as serum urea above 10 mmol/l and/or serum creatinine above 130 umol/l were excluded from study.

12.3. Study design

Magnesium deficiency is associated with various biochemical, electrocardiographic, neuromuscular and psychiatric abnormalities (see Chapter 2). With the potential for many beneficial effects resulting from correction of magnesium deficit, it was necessary to focus on a few parameters whilst also monitoring the effects of treatment as widely as was feasible in the circumstances of the study. The effects of magnesium supplements on serum potassium were considered of primary interest (see Chapters 9, 10 and 11).

Though desirable, it was not feasible in the circumstances of the study to compare the effects of magnesium supplementation with placebo by means of a completely double blind crossover design, and so the following compromise was used. The study was supervised by myself in a single blind fashion, but all clinical mesasurements were performed in a double blind fashion by selected members of clinic staff. Identical capsules containing either 300mg

magnesium oxide (7.5 mmol magnesium) or placebo were supplied by the hospital pharmacy. Capsules were prescibed twice daily, each treatment phase lasted 8 weeks, and measurements were made at 4 points as follows:

1 (week 0)	2 (week 8)	3 (week 16)	4 (week 24)
Start	End of placebo	End of magnesium	Follow up

This daily dose of 15 mmol magnesium is considered adequate for treatment of mild magnesium deficiency although considerably larger doses can be administered with safety. As repletion continues progressively less of the oral dose is absorbed from the gastrointestinal tract [216,217,218].

12.4. Biochemical measurements

Venous blood samples were taken without undue stasis between 0900 and 1000h following an overnight fast. Three mls of each sample were immediately centrifuged to separate serum which was then frozen at minus 50 degees centigrade until analysed in batches for concentration of parathyroid hormone (1-84) (PTH) by two-site immunoradiometric assay [219]. Remaining blood was sent for standard hospital laboratory analysis of magnesium in serum and erythrocytes (atomic absorption spectrophotometry), other routine serum electrolytes (SMAC II autoanalyser), glucose (hexokinase method, Hitachi 747), glycosylated haemoglobin A1 (Corning electrophoresis), concentrations of triglyceride and total cholesterol (Hitachi 704 enzymatic process, Boheringer Mannheim) and HDL (manganese precipitation method).
In addition 24 hour urine magnesium excretion was measured

before and after magnesium supplementation in 9 subjects recruited to the study.

12.5. Other measurements

The following measurements were made late morning, 11 am - noon, with the subjects relaxed following a light snack.

1) Supine and erect blood pressure were measured by a trained nurse (the same individual for most of the study), using a standard mercury sphygmomanometer.

2) Hand grip strength was measured by the same trained nurse using an adjustable hand dynamometer (Jamar model 1A, Asimow Engineering Company), recording the highest of 3 measurements for each hand.

3) A standard electrocardiogram was recorded at 50 mm/second for measurement of heart rate and rhythm, PR and QT intervals. ECG recordings were performed by the clinic technician, coded and randomised, and analysed all together at the end of the study by an independent analyst. QT intervals were corrected for rate using Bazett's formula viz;

$$QTc = \frac{\text{measured QT interval (seconds)}}{\sqrt{\text{preceding RR interval}}}$$

4) Morale and psychological wellbeing were assessed using 3 quick and simple self-rating scales.

a) A scaled down (12 item) version of the General Health Questionaire (GHQ) [220] (Appendix 4) was used to assess symptoms of depression and anxiety. A bimodal response scale was used to interpret the GHQ score with "less" or "no more" than usual, scoring zero and "rather" or "much

more" scoring one. This method gets around the problem of "end-users" or "middle users", that is those subjects who always respond at the extremes of scales or always use the middle options. A similar method was used to record responses to the "faces" scale (see below).

b) The Wakefield Self Assessment Depression Inventory [221] (Appendix 5), also a 12 item questionaire, was used as a further measure of depressive symptoms.

These two self assessment questionaires were both designed for non medically sick individuals and have been widely used. They have been validated and are considered reliable [222,223,224].

c) The "faces" scale (Appendix 6) has been developed by the Department of Behavioural Sciences, University of Glasgow, to assess morale in elderly patients in various clinical settings. Experience at Lightburn Day Hospital has indicated that it is liked and easily understood by elderly subjects who have problems reading or understanding more commonly used visual analogue scales and quality of life questionaires. A bimodal response scale was again used with faces A and B scoring -1, C scoring 0, and D and E scoring +1.

All 3 questionaires were administered by the trained nurse who provided guidance or assistance when required.

12.6. Statistical analysis

For each variable, results at all 4 measurement points were compared using one way analysis of variance for normally

distributed data and Friedman's test for non-parametric data. Significant differences were further examined by applying the paired t test and the Wilcoxon test respectively to compare data between two measurement points. Because they were of primary interest changes in serum potassium were taken at face value but, to compensate for the effect of multiple comparisons, changes in other parameters were adjusted by means of the Bonferroni correction [215].

12.7. Results

Twenty-five subjects entered the study and twenty-two subjects, nineteen female, mean age 81 years (sd 6.6), commenced the magnesium supplementation phase. Capsule counts indicated fairly good medication compliance among participants but two misunderstood instructions and took only one capsule daily and a third stopped treatment after 4 weeks, having misplaced the remainder of her supply. Data from these three subjects have been included in results analysis. Follow up at 8 weeks after cessation of oral magnesium was achieved in nineteen subjects. There were no complaints of excessive bowel frequency or any other significant symptoms in association with magnesium supplementation. Appendix 7 contains details of the participants, medical conditions and treatment regimens at entry.

a) Biochemical measurements

The results of biochemical measurements are summarised in Table 27. Serum magnesium rose significantly as a consequence of oral supplementation and the level at 8 weeks follow up was still significantly higher than the baseline level at entry. One subject showed no change in serum magnesium following administration of oral supplements, the level being static at 0.66 mmol/l. Twenty-four hour urine magnesium excretion for this subject pre supplementation was 3.5 mmol rising to 5.2 mmol at the end of supplementation; this suggests a degree of renal magnesium wasting rather than poor compliance with supplements or poor gastrointestinal absorption.

Urine magnesium excretion rose in association with oral supplements in 8 subjects and was unchanged in one subject. Mean value for all 9 subjects rose from 1.37 (sd 1.05) to 2.82 (sd 1.64) mmol/day ($P < 0.01$).

There was a significant rise in serum potassium following magnesium treatment, compared with placebo. Other biochemical comparisons of secondary interest did not reach statistical significance at the 5% level following Bonferroni correction. However, the five subjects with NIDDM or glucose intolerance appeared to have a larger average reduction in fasting glucose level than other subjects in association with magnesium treatment, changes being 0.76 mmol/l and 0.26 mmol/l respectively. Unfortunately much of the PTH data were rendered invalid by accidental premature thawing of samples.

TABLE 27 Effects of oral magnesium treatment on biochemical indices in elderly subjects with persistent mild hypomagnesaemia

Measurement (lab. ref. range)	1 Start	2 Post placebo	3 Post magnesium	4 Follow up
Serum Mg (0.7-1.0 mmol/l)	0.64 (0.05)	0.65 (0.05)	0.80 (0.08) P < 0.001	0.71 (0.06) P < 0.001
Erythrocyte magnesium (1.75-3.25 mmol/l)	2.17 (0.21)	2.19 (0.23)	2.36 (0.38)	2.23 (0.41)
Serum K (3.5-5.0 mmol/l)	4.1 (0.45)	4.2 (0.36)	4.5 (0.47) P = 0.02	4.3 (0.37)
Serum Ca (corrected) (2.2-2.6 mmol/l)	2.46 (0.11)	2.41 (0.13)	2.46 (0.09)	2.50 (0.01)
P. glucose* (4.0-5.5 mmol/l)	5.9 (2.09)	6.4 (2.99)	5.5 (1.84)	5.7 (2.18)
% glycated haemoglobin* (5.5-8.4)	7.4 (1.61)	7.6 (1.77)	7.1 (1.39)	6.9 (0.90)
Total cholesterol* (< 6.5 mmol/l)	4.95 (1.34)	5.14 (1.00)	5.09 (1.28)	5.21 (1.59)
HDL cholesterol* (>1.0 mmol/l)	1.17 (0.47)	1.18 (0.37)	1.52 (0.48)	1.43 (0.51)
Triglcerides (< 2.3 mmol/l)*	1.33 (0.60)	1.54 (0.52)	1.35 (0.74)	1.29 (0.68)
Parathyroid hormone* (1.0-5.0 pmol/l)	5.4 (3.63)	**	3.6 (2.17)	**

All values are quoted as mean (sd).
* = data incomplete (paired data in 19 subjects for glucose and lipids, in 18 subjects for glycated haemoglobin and in 15 subjects for parathyroid hormone).
** = less than 8 samples available for comparison

b) Other measurements

Blood pressure recordings were quite variable. There were slight reductions in blood pressure following placebo and again following magnesium but changes were not significant (Table 28). Furthermore there was no detectable difference in magnesium effects on blood pressure in comparing hypertensive subjects (supine BP >160/90 mmHg) and normotensive subjects.

Hand grip strength was unchanged before and after magnesium supplementation with mean values of 17 (sd 5.9) and 17 (sd 6.2) kg force respectively. These are normal values for such an elderly population sample (manufacturer's data).

There were 7 subjects in atrial fibrillation before and after magnesium treatment in whom PR and QTc intervals could not be measured and, despite using ECG recording speeds of 50mm/second, accurate measurement of PR and QTc intervals in the remaining subjects was difficult. Both intervals were quite variable and there was no significant change in either as a result of magnesium treatment. Mean baseline measurements for PR and QTc respectively of 0.13 (sd 0.04) and 0.43 (sd 0.028) seconds changed to 0.14 (sd 0.05) and 0.42 (sd 0.037) seconds following magnesium treatment.

Scores from the 3 self rating tests measuring wellbeing and morale did not change significantly as a result of magnesium treatment.

TABLE 28

Effects of oral magnesium treatment on blood pressure in elderly subjects with persistent mild hypomagnesaemia

Blood pressure mmHg	Before magnesium mean (sd)		After magnesium mean (sd)
	Start	Post placebo	
Supine systolic	158 (27.9)	154 (28.7)	151 (25.7)
Supine diastolic	81 (16.5)	79 (18.0)	78 (12.0)
Erect systolic	151 (24.5)	148 (26.4)	145 (27.4)
Erect diastolic	81 (14.0)	80 (12,6)	77 (12.0)

12.8. Discussion

a) Biochemical measurements

Magnesium deficiency in illness has been associated with abnormalities of other electrolytes including hyponatraemia, hypokalaemia, hypocalcaemia and hypophosphataemia [86]. In the circumstances described it is unlikely that all of these abnormalities were due to magnesium deficit but, more likely, most shared a common aetiology with magnesium depletion. However, clinical problems due to hypokalaemia and hypocalcaemia can arise as a result of secondary disturbances in homeostatic mechanisms caused by primary magnesium deficit [22], and this close relationship of magnesium metabolism with that of other electrolytes often makes it difficult to ascribe signs and symptoms solely to magnesium deficiency [225].

(1) Magnesium and potassium

Magnesium modulates many of the major potassium transport systems and refractory potassium depletion associated with magnesium deficiency is a recognised phenomenon. Potassium loss in magnesium deficiency seems to be multifactorial and various mechanisms have been postulated including reduced Na-K-ATPase density and activity in cell membranes [183,204,226].

It is interesting, therefore, that there was a rise in serum potassium in association with magnesium supplementation in this study even though the mean pre-treatment serum potassium level was within the normal

range and no subject was hypokalaemic at the start. In a previous study of oral magnesium treatment versus placebo in hypomagnesaemic elderly subjects (70-year-old in-patients given 12.5 mmol magnesium chloride daily for 3 weeks), there was a similar significant rise in serum potassium within the normal laboratory range. However in that study the rise in potassium occured within 8 days of starting oral magnesium and was no longer significant after 3 weeks of treatment [94].

(2) Other biochemical measurements

Through correction for multiple comparisons there was inevitable loss of sensitivity in other biochemical measurements. Some of the potential benefits of magnesium treatment on these measurements merit discussion.

Magnesium, calcium and PTH

Hypocalcaemia can be a prominent manifestation of magnesium deficiency and with magnesium replacement both serum calcium and serum magnesium return to normal [22]. However, as with serum potassium in this study, mean values for serum calcium were normal prior to magnesium treatment, leaving little scope for significant change.
Although neuromuscular symptoms of magnesium deficiency rarely occur in the absence of hypocalcaemia it is unlikely that magnesium defiency leads to net calcium loss. Rather it appears that there is impairment of the regulatory mechanisms which maintain serum calcium in the normal

range [32]. Two mechanisms have been suggested for magnesium dependent hypocalcaemia and both involve parathyroid hormone (PTH). There is evidence of end-organ resistance to the action of PTH at kidney tubules and bone as well as reduced synthesis and secretion of the hormone in magnesium deficiency [227,228,229]. Furthermore, PTH enhances magnesium resorption from the kidney and secretion of the hormone is stimulated by moderately low serum magnesium levels [230,231]. It is not surprising therefore that PTH levels can be high, normal or low in hypomagnesaemic states depending on the degree and duration of magnesium deficiency [232].

The biochemical actions of magnesium, calcium and PTH are therefore interdependent. Calcium appears to be more potent than magnesium in altering the rate of PTH secretion, although serum levels of the hormone change rapidly in response to changes in serum magnesium. In magnesium deficiency there is a rapid rise in PTH following magnesium administration, whereas in magnesium excess the reverse occurs [228,233,234].

There is a circadian rhythm of PTH secretion with a broad peak between 0200 and 0600 hours and a steep but variable decline thereafter. Ideally, PTH samples should be taken between 1100 and 1400 hours for reproducible results [235]. PTH levels in this study were slightly elevated prior to magnesium treatment but fell to within the normal range with supplementation. Sampling later in the day between 1100 and 1400 would probably have given lower values all

round. The fall in serum PTH following magnesium repletion for 8 weeks is not surprising, although it is likely that PTH rose to a variable degree in at least some subjects at the start of magnesium treatment, especially in more severely magnesium deficient subjects. However the detection of such changes would have required multiple blood sampling techniques which were outwith the scope of this study.

Magnesium and glucose metabolism

The frequent co-existence of hypomagnesaemia and diabetes mellitus was clearly demonstrated by Jackson and Meir in 1968 [84], and several studies have since shown evidence of a relationship between hypomagnesaemia and poor diabetic control [125,236,237]. The role of magnesium in diabetes has recently been reviewed [238]. Studies suggest that insulin secretion and sensitivity in elderly subjects with non-insulin dependent diabetes mellitus can be improved by chronic magnesium supplementation [113,239]. However the doses of magnesium given in these studies (120mmol per day for 3 weeks) were greatly in excess of the recommended dietary requirement and, furthermore, the subjects had serum magnesium levels within the normal range prior to magnesium administration. It is possible therefore, that the beneficial effects observed were due at least in part to a pharmacological rather than a physiological effect of magnesium.

However, results from this study tend to support the view that magnesium treatment, if taken for long enough at

normal dietary levels, could improve glycaemic status in magnesium deficient subjects with glucose intolerance. Although the improvements in blood glucose and glycated haemoglobin did not reach statistical significance within the limits of the study, favourable changes were more apparent in subjects with glucose intolerance. Since glycated haemoglobin changes more gradually, it would be interesting to study the effect of low dose oral magnesium treatment in such subjects over a longer period.

Magnesium and blood lipids

Both magnesium deficiency and supplementation have been shown to produce changes in blood lipid profile. Magnesium may induce a decrease in lipolysis and/or an increase in lipoprotein lipase activity leading to an increase in high density lipoprotein (HDL) cholesterol and a reduction in low density lipoprotein (LDL) cholesterol and triglyceride. In contrast, magnesium deficiency enhances catecholamine secretion, which results in an increase in lipolysis, leading in turn to an increase in very low density lipoprotein (VLDL) cholesterol and triglyceride [240,241,242,243].

However the evidence of the effects of magnesium therapy on lipid profile is conflicting. One supplementation study which showed a beneficial effect was not placebo controlled [240], whilst in another dietary change probably influenced the outcome (the intervention diet, as well as having more magnesium, had higher fibre and lower cholesterol content than the control diet) [244].

Two studies which failed to show an effect were performed on middle-aged individuals who had normal serum magnesium levels and thus had had reduced scope for beneficial change [245,246]. A recent double-blind placebo controlled study in older subjects, mean age 60 years, with ischaemic heart disease but normal serum magnesium levels demonstrated a small significant rise in HDL cholesterol and a lowering of VLDL cholesterol and triglyceride with magnesium therapy [247]. Finally a crossover study comparing the effects of magnesium therapy and a bulk laxative on lipids in elderly patients, mean age 81 years, detected a slight increase in HDL cholesterol and slight lowering of triglyceride values, but the magnesium status of the patients was not stated though many had been receiving long-term magnesium treatment prior to the study [248].

The failure to detect a significant change in the lipid profile of elderly hypomagnesaemic subjects in this study may be due to inadequate duration of magnesium treatment.

b) <u>Other measurements</u>

Magnesium and electrocardiographic changes

Magnesium depletion may predispose to cardiac arrhythmias especially in digitalised patients and atrial fibrillation may be refractory to digitalis therapy in hypomagnesaemia [46,189,249]. Magnesium therapy has been used to treat and prevent ventricular arrhythmias [49,250,251] but serum magnesium has often been normal in such reports and the abolition of arrhythmias may have been due to a

non-specific pharmacologic effect rather than due to correction of magnesium depletion [48,252]. Electrocardiographic changes associated with magnesium depletion include prolongation of the PR, QRS and QTc intervals as well as ST segment depression but, in most clinical circumstances, the relative effects of magnesium are difficult to separate from those of calcium and potassium [224,253]. Two controlled studies which have examined the effect of oral magnesium therapy on the length of the QTc interval in digitalised patients produced conflicting results.

Lewis et al [254] documented a rise in serum magnesium and serum potassium and a reduction in ventricular ectopy with magnesium treatment, but there was no significant change in QTc interval. However the patients studied had relatively normal serum magnesium levels prior to supplementation. In contrast, Krasner et al [255] observed a significant shortening of the QTc interval following a few days treatment with oral magnesium, but serum levels of magnesium and potassium were not reported at any stage. Furthermore, neither study reported on serum calcium status although changes in this could have been important.

The lack of ECG changes in association with magnesium supplementation in this study may reflect normal serum levels of potassium and calcium in the subjects studied.

Magnesium and blood pressure

Extensive studies on experimental animals have shown that

magnesium exerts a regulatory role on vascular tone and vascular reactivity and that disturbances of magnesium metabolism may have profound effects on blood pressure [256,257]. A clinical study of 73 randomly selected subjects, not receiving diuretics, showed an inverse correlation between serum magnesium and blood pressure [93]. The evidence for magnesium having a blood pressure lowering effect in hypertension in clinical practice is mixed. Two open studies of oral magnesium supplementation in subjects receiving long term diuretic treatment for hypertension showed a significant reduction in blood pressure following magnesium. One study gave magneium aspartate HCL, 15 mmol daily, for 6 months [258] while the other gave magnesium oxide, 15 mmol daily, for only 4 weeks [155].

However two double blind placebo controlled studies have failed to show a significant blood pressure lowering effect with magnesium supplementation. One study gave magnesium aspartate HCL, 15 mmol daily, for 4 weeks to untreated hypertensive subjects [154] and the other gave magnesium oxide, 12 mmol daily, for 6 months to hypertensive subjects receiving long term diuretics [259].

Subjects who received oral magnesium in the above 4 studies had normal serum magnesium levels prior to supplementation and in one study the pre-treatment level was rather high at 0.86mmol/l [154]. It could be argued that there was little scope for benefit from low dose oral magnesium therapy in such subjects. In this current study subjects were clearly

hypomagnesaemic before receiving magnesium and yet there was no significant fall in blood pressure even though mean serum magnesium level rose to near normal with treatment. However there was a wide range of blood pressure within the study group, many subjects being normotensive, and magnesium repletion was probably incomplete in most at the end of the treatment phase.

It seems likely that magnesium treatment can have a marginal blood pressure lowering effect in hypertension, the degree depending on a variety of factors including magnesium status, the form and duration of magnesium treatment, other electrolytes and therapy, and the degree as well as the underlying cause of hypertension. The pharmacological and physiological effects of magnesium in hypertension need to be more clearly distinguished. A study of higher dose magnesium treatment in hypertensive subjects would be interesting if a preparation suitable for oral administration could be found.

Magnesium in neuromuscular and psychiatric disturbance

Experimental studies in animals and in human volunteers have shown that magnesium depletion causes a variety of neuromuscular abnormalities which include tremor, irritability, muscle weakness and tetany, all of which resolve following repletion of magnesium [22,32]. However in the various clinical cases which have been reported magnesium deficiency has been severe, and symptoms have almost always been associated with coexistent abnormalities of other electrolytes [224,260,261,262,263].

The effect of mild isolated hypomagnesaemia on muscle strength has not previously been evaluated in clinical practice. Hand grip strength has been used to study the relationship between potassium and muscle strength in elderly subjects. An initial study found a positive correlation between dietary potassium intake and grip strength [264], but subsequent studies did not find any relationship between serum or erythrocyte potassium and grip strength and potassium supplementation made no difference [265,266]. The lack of effect of magnesium supplementation on hand grip strength in this study is in keeping with the findings for potassium and would support the view that clinically significant muscle weaknes only occurs when magnesium depletion is severe and associated with abnormal serum calcium [225].

Mood disturbance with symptoms of apathy and depression has been reported in association with hypomagnesaemia [1,267,268]. In one study depression improved with magnesium treatment [189], but affected individuals were also suffering from physical illnesses such as heart failure and digitalis toxicity and improved mood coincided with physical recovery. Furthermore the method of mood assessment was not described. A more recent report provides good documentation of a case of depression associated with severe magnesium depletion. The patient responded to correction of magnesium status but serum potassium was also low and, once again, mood improvement coincided with physical improvement (cessation of severe diarrhoea following introduction of a low fat diet) [269].

In this present study treatment of mild isolated hypomagnesaemia did not have any apparent effect on mood although none of the subjects were clinically depressed. It would therefore seem that mild isolated hypomagnesaemia is unlikely to cause significant mood disturbance, and even in severe magnesium depletion it may be inappropriate to attribute depressive symptoms solely to the magnesium deficit.

c) Degree of depletion and adequacy of treatment

In the present study, as well as reduced sensitivity through correction for multiple comparisons, inadequate correction of magnesium deficit could explain the relative lack of change in most measurements in response to oral magnesium. The mean 24 hour urine magnesium excretion rose following supplementation but the level of excretion was still lower than would be expected in younger subjects in normal magnesium balance (3.5 - 6.0 mmol/day) [154,155,156]. Even allowing for the effects of ageing on renal magnesium handling, the relatively low urine magnesium excretion at the end of the supplementation phase suggests incomplete repletion in some subjects.

On the other hand whilst values of magnesium in serum and urine support a degree of magnesium depletion prior to supplementation, most of the other biochemical indices which might theoretically have been affected by magnesium depletion were normal or near normal. This would suggest that overall cellular magnesium deficiency,if present, was mild, an argument supported by the normal erythrocyte

magnesium level before supplementation. In this context the lack of change in most of the other biochemical indices is perhaps not surprising. However it is also possible that some other significant biochemical changes did occur and would have been detected by more frequent sampling, especially early in the treatment schedule [94].

At the time of commencing the study there were no absorption studies comparing the various magnesium salts (oxide, hydroxide, carbonate, chloride, acetate, citrate and sulphate), and none had proved to be superior to others in treatment of magnesium deficiency by oral repletion [216,217,218]. There is now some evidence that magnesium citrate is better absorbed in normal healthy individuals [270], although the evidence is conflicting [156]. However in non-gastrointestinal causes of magnesium deficiency absorption of all magnesium salts is likely to be improved sufficient for replacement [215,271]. Acidic conditions improve solubility of magnesium salts and they should therefore be administered with meals [272].

12.9. Summary and conclusion

Apart from a favourable influence on serum potassium, administration of oral magnesium treatment to these relatively well elderly subjects with mild hypomagnesaemia appeared to be of little short term benefit. It is possible that cellular magnesium depletion, where it existed, was mild and/or magnesium repletion was incomplete. Further studies should focus on assessing the effects of

correcting magnesium deficit in certain single disease pathologies such as diabetes mellitus.

PART 5

CHAPTER 13

REVIEW OF STUDIES AND COMMENTS ON RECENT DEVELOPMENTS

13.1. Introduction

Twelve years have elapsed since I first developed a particular interest in the contribution of magnesium deficiency to illness in elderly patients and, during the intervening period as I have carried out my own investigations, I have become deeply impressed by the sustained efforts and dedication of other more eminent researchers in this field. The questions arising from clinical practice which I have sought to answer with regard to elderly patients have also been addressed in varying detail by numerous other investigators who have usually been concerned with problems affecting younger patients. As well as clinical studies during this time there has been extensive laboratory research which, with the aid of new technologies, has resulted in a much greater understanding of the actions of magnesium at molecular and cellular level. One consequence has been the developing interest in possible therapeutic uses for magnesium, most notably in cardoivascular disease. Yet, despite this growth in knowledge, much remains uncertain about the role of magnesium in disease and especially in illnesses affecting older people.

13.2. Progress on answers to my original questions

Some of my original questions can be answered. Despite dietary magnesium intake in the elderly tending to be lower

than recommended (see Chapter 3), there is generally a slight rise in serum magnesium with age probably reflecting the decline in renal function with ageing (see Chapter 4). Nevertheless, the average serum level in old age is usually very close to that in younger adults. Mean values in illness usually coincide with those of the healthy population whereas ranges tend to be wider. The mean serum magnesium level in the Glasgow population is 0.79 mmol/l and approximately 5% of ill elderly patients admitted to hospital have a level less than 0.66 mmol/l (see Chapter 11). A serum level below 0.50 mmol/l is found in 0.05% of elderly hospital patients and is usually associated with severe illness. Diuretic drugs, diabetes mellitus and excessive alcohol intake are factors which commonly feature in milder cases of hypomagnesaemia (see Chapters 10 and 11).

However the there is still great uncertainty as to the significance of hypomagnesaemia in illness. In my experience it has been difficult to find clear evidence of extra morbidity in elderly patients with hypomagnesaemia when compared with those with normal serum magnesium levels (see Chapter 11). Mild chronic hypomagnesaemia seems to be well tolerated in many elderly subjects and restoration of the serum level to normal does not appear to confer any great clinical benefit in the short term (see Chapter 12).

Although serum magnesium is the most easily obtained and commonly used measure of magnesium status in clinical practice, it represents less than 1% of the body content and its lack of reliability as a guide to magnesium status

in illness has been recognised for a long time. Much investigative effort has therefore focused on developing other more reliable and clinically applicable methods for estimation of body magnesium content in order that the relative contribution of magnesium deficiency to the pathogenesis of various diseases can be more easily quantified. Measurement of magnesium in blood cells and urine and development of protocols for parenteral magnesium load/retention studies have all received much attention in recent years. Each technique in turn tends to have been heralded as the answer to assessment of magnesium status but, with the passage of time, the limitations of each have become apparent. Like serum measurements, cellular magnesium measurements can act as a guide to the magnesium status of a healthy population but biological variability and analytical imprecision greatly limit their use in a single individual. Furthermore, it is often uncertain to what extent changes in cell magnesium during illness reflect altered body magnesium content as oppose to mere alterations in the characteristics of the cells themselves (see Chapters 5 and 6). The decline in renal function with age and the difficulty with accurate urine collection pose problems in the execution and interpretation of both standard urine measurements and parenteral magnesium load studies in ill elderly patients (see Chapters 7 and 8).

Autopsy evidence points to a reduction in muscle magnesium stores with age (see Chapter 9). Muscle and bone biopsies have been used in some clinical studies but these procedures are neither acceptable nor practical for routine

use in ill elderly patients. Furthermore, the significance of low muscle values in relation to the readily exchangeable magnesium pool during illness is unclear. At present, therefore, there is no single laboratory test in routine clinical use which unequivocally reveals magnesium deficiency.

13.3. Advanced techniques for future use

Most studies to date including my own have measured total magnesium in serum, urine, cells and tissues but it is now generally accepted that free ionised magnesium (Mg^{2+}) is the important component in magnesium-dependent biological processes. Free Mg^{2+} normally comprises 60% of serum magnesium and 10 - 20% of cellular magnesium [74,274,275]. The equilibrium between free Mg^{2+} and total magnesium varies especially during illness, thus rendering measurements of the latter in various body compartments less valuable than previously appreciated.

The ability to measure free Mg^{2+} easily would be a major step forward. Technology that would permit the rapid accurate determination of Mg^{2+} flux into and out of cells would contribute immensely to our understanding of the contribution of magnesium to various clinical deficiency syndromes and illness. However accurate measurement of free Mg^{2+} in serum alone requires rigorous analytic techniques which are currently beyond the resources of most clinicians. Protein-magnesium bonds are extremely labile and serum samples must therefore be collected in strictly

anaerobic conditions to prevent any loss of carbon dioxide which would change the pH and the protein-bound fraction. Strict temperature control is necessary for the same reason [276,277,278]

Measurement of intracellular free Mg^{2+} is even more difficult but various advanced laboratory techniques have been developed and evaluated in vitro. These include use of nuclear magnetic resonance spectroscopy (NMR) [275,279,280,281], Mg^{2+} selective microelectrodes [282], zero point titration techniques (ZPT) [281,283,284] and fluorescent dyes [285,286,287].

Each of these methods has limitations but thus far ZPT and NMR have shown promise for future clinical use [281]. One NMR study has revealed a relationship between low intracellular Mg^{2+}, raised Ca^{2+} and the degree of blood pressure elevation in hypertensive subjects [288]. More recently, again from NMR studies, there is evidence of reduced intracellular Mg^{2+} in non-insulin dependent diabetes mellitus with the possibility that magnesium deficiency may be a key factor leading to enhanced platelet reactivity in affected subjects [289,290].

Such information supports existing evidence linking magnesium deficiency to cardiovascular disease and diabetes mellitus and has led to the hypothesis that both diseases have a common ionic basis in intracellular magnesium deficiency [291].

However, at present the cell separation technology

available to most clinicians for measurement of total magnesium in cells is unreliable. Therefore, for the forseeable future, it is difficult to envisage measurement of intracellular free Mg^{2+} in routine clinical practice, since the problems of cell separation would have to be overcome without disturbing the ionic equilibrium within the cell.

13.4. Concluding remarks

Like many more eminent researchers I have found that the search for answers to apparently simple questions about magnesium in clinical practice has produced few satisfactory solutions, but rather has resulted in a series of more complicated enquiries. This enigmatic element still holds many secrets and for the time being clinicians like myself must continue rely on clinical experience and simple laboratory measurements to judge the contribution of magnesium deficiency to illness in the individual patient.

REFERENCES

1. Wacker WEC, Parisi AF. Magnesium metabolism. N Engl J Med 1968; **278**: 658-61.

2. Seelig MS. Magnesium and trace substance deficiencies in the pathogenesis of cancer. Biol Trace Elem Res 1979; **1**: 273-79.

3. Durlach J. The properties of magnesium. In: Durlach J ed. Magnesium in clinical practice. London: John Libbey, 1988; 7-15.

4. Ryan MF. The role of magnesium in clinical biochemistry: an overview. Ann Clin Biochem 1991; **28**: 19-26.

5. Alfrey AC, Miller NL. Bone magnesium pools in uraemia. J Clin Invest 1973; **52**: 3019-27.

6. Alfrey AC, Miller NL, Butkus D. Evaluation of body magnesium stores. J Lab Clin Med 1974; **84**: 153-62.

7. Rude RK, Singer FR. Magnesium deficiency and excess. Annu Rev Med 1984; **32**: 245-49.

8. Brannan PG, Vergne-Marini P, Pak CYC, Hull AR, Fordtran JS. Magnesium absorption in the human small intestine: results in normal subjects, patients with chronic renal disease and patients with absorptive hypercalciuria. J Clin Invest 1976; **57**: 1412-18.

9. Graham LA, Caesar JJ, Burgen ASV. Gastrointestinal absorption and excretion of Mg^{28} in man. Metabolism 1960; **9**: 646-59.

10. Schwartz R, Spencer H, Welsh JI. Magnesium absorption in human subjects from leafy vegetables intrinsically labelled with stable Mg^{26}. Am J Clin Nutr 1984; **39**: 571-76.

11. Wilkinson R. In: Nordin BEC ed. Calcium, Phosphate and Magnesium Metabolism. London: Churchill Livingstone, 1976; 96.

12. Friedman M, Hatcher G, Watson L. Primary hypomagnesaemia with secondary hypocalcaemia in an infant. Lancet 1967; **1**: 703-5.

13. Milla PJ, Aggett PJ, Wolff OH, Harries JT. Studies in primary hypomagnesaemia: evidence for defective carrier mediated small intestinal transport of magnesium. Gut 1979; **20**: 1028-33.

14. Levine BS, Walling MW, Coburn JW. Effect of vitamin D sterols and dietary magnesium on calcium and phosphate homeostasis. Am J Physiol 1981; **241**: 35-41.

15. Slavin JS, Marlett MS, Marlett JA. Influence of refined cellulose on human bowel function and calcium and magnesium. Am J Clin Nutr 1980; **33**: 1932-39.

16. Hodkinson A, Marshall DH, Nordin BE. Vitamin D and magnesium absorption in man. Clin Sci 1979; 57: 121-3.

17. Krejs GJ, Nicar MJ, Zerwekh JE, Norman DA, Kane MG, Pak CYC. Effect of 1,25-dihydroxyvitamin D3 on calcium and magnesium absorption in the healthy human jejunum and ileum. Am J Med 1983; 75: 973-6.

18. Seelig MS. The requirement of magnesium by the normal adult. Summary and analysis of published data. Am J Clin Nutr 1964; 14: 342-90.

19. Leary WP, Reyes AJ. Diuretic-induced magnesium losses. Drugs 1984; 28 (suppl 1): 182-187.

20. Beyenbach KW. Unresolved questions of renal magnesium homeostasis. Magnesium 1986; 5: 234-247.

21. Nordin BEC. ed. Calcium, Phosphate and Magnesium Metabolism. London: Churchill Livingston 1976; 26-29.

22. Shils ME. Experimental human magnesium depletion. Medicine 1969; 48: 61-82.

23. Dirks JH. The kidney and magnesiuim metabolism. Kidney Int 1983; 23: 771-7.

24. Quamme GA, Dirks JH. Renal magnesium transport. Rev Physiol Biochem Pharmacol 1983; 97: 69-110.

25. Horton R, Biglieri EG. Effect of aldosterone on the metabolism of magnesium. J Clin Endocrinol Metab 1962; **22**: 1187-92.

26. Beller GA, Maher JT, Hartley LH, Bass DE, Wacker WEC. Changes in serum and sweat magnesium levels during work in the heat. Aviat Space Environ Med 1975; **46**: 709-12.

27. Horn DB, Latner WL. Estimation of magnesium by atomic absorption spectrophotometry. Clin Chim Acta 1963; **8**: 974-76.

28. Stewart WK, Hutchinson F, Fleming LW. Estimation of magnesium in serum and urine by atomic absorption. J Lab Clin Med 1963; **61**: 858-72.

29. Flink EB. Magnesium deficiency. Etiology and clinical spectrum. Acta Med Scand 1981; **647** (suppl 1): 125-37.

30. Juan D. The clinical importance of hypomagnesaemia. Surgery. 1982; **91**: 510-517.

31. Chernow B, Smith J, Rainey TG, Finton C. Hypomagnesaemia: implications for the critical care specialist. Crit Care Med 1982; **10**: 193-96.

32. Cronin RE, Knochel JP. Magnesium deficiency. Adv Int Med 1983; **28**: 509-33.

33. Drenick EJ, Hunt IF, Swendsied ME. Magnesium depletion during prolonged fasting of obese males. J Clin Endocrinol Metab 1969; **29**: 1341-48.

34. Hersch T, Siddiqui DA. Magnesium and the pancreas. Am J Clin Nutr 1973; **23**: 362-79.

35. Evans RA, Carter JN, George CRP, et al. The congenital "magnesium losing kidney". Q J Med 1981; **197**: 39-52.

36. Massry SB. Pharmacology of magnesium. Annu Rev Pharmacol Toxicol 1977; **17**: 67-82.

37. Mendelson JH, Ogata M, Mello NK. Effects of alcohol ingestion and withdrawal on magnesium status of alcoholics. Ann N Y Acad Sci 1969; **22**: 918-33.

38. Lim P, Jacob E. Magnesium status of alcoholic patients. Metabolism 1972; **21**: 1045-51.

39. McMullen JK. Asystole and hypomagnesaemia during recovery from diabetic ketoacidosis. Br Med J 1977; **1**: 690.

40. Iseri LT. Magnesium and cardiac arrhythmias. Magnesium 1986; **5**: 111-26.

41. Altura BM. Ischaemic heart disease and magnesium. Magnesium. 1988; **7**: 57-67.

42. Sjogren A, Edvinsson L, Fallgren B. Magnesium deficiency in coronary artery disease and cardiac arrhythmias. J Intern Med 1989; **226**: 213-22.

43. Luoma H, Aromaa A, Helminen, et al. Risk of myocardial infarction in Finnish men in relation to fluoride, magnesium and calcium concentration in drinking water. Acta Med Scand 1983; **213**: 171-6.

44. Elwood PC, Sweetnam PM, Beasley WH, Jones D, France R. Magnesium and calcium in the myocardium: cause of death and area difference. Lancet 1980; **11**: 720-2.

45. Rasmussen HS, Aurup P, Hojberg S, Jensen EK, McNair P Magnesium and acute myocardial infarction: transient hypomagnesaemia not induced by renal magnesium loss in patients with acute myocardial infarction. Arch Int Med 1986; **146**: 872-4.

46. Dyckner T. Serum magnesium in acute myocardial infarcation. Relation to arrhythmias. Acta Med Scand 1980; **207**: 59-66.

47. Teo KK, Yusef S, Collins R, Held PH, Peto P. Effects of intravenous magnesium in suspected acute myocardial infarctions: overview of randomised trials. Br Med J 1991; **303**: 1499-1503.

48. Laban E, Charbon GA. Magnesium and cardiac arrhythmias: nutrient or drug. J Am Coll Nutr 1986; **5**: 521-32.

49. Iseri LT, Freed J, Bures AR. Magnesium deficiency and cardiac disorders. Am J Med 1975; **58**: 837-46.

50. Varma N. Intravenous magnesium in suspected myocardial infarction. Br Med J 1992; **304**: 447-8.

51. Seelig MS. Possible role of magnesium in disorders of the aged. In: Regelson W, Sinex FM. eds. Intervention in the Aging Process, Part A; Quantification, Epidemiology, and Clinical Research. New York: Alan R. Liss, 1983; 279-305.

52. Paul AA, Southgate DAT, eds. McCance and Widdowson: The composition of foods. 5th ed. London: HMSO, 1991.

53. Seelig MS. Nutritional status and requirements of magnesium. Magnesium Bulletin 1986; **8**: 170-85.

54. Halpern MJ. Magnesium physiopathology. In: Halpern MJ Durlach J eds. Magnesium Deficiency. First Eur Congr Magnesium, Lisbon 1983. Basel: Karger, 1985; 1-8.

55. Jones JE, Manalo R, Flink EB. Magnesium requirements in Adults. Am J Clin Nutr 1967; **20**: 632-5.

56. Seelig MS. Magnesium requirements in human nutrition. Magnesium Bulletin 1981; **3** (suppl a): 26-47.

57. Leszek G, Del Campo O. Role of magnesium in the dietotherapy of degenerative Diseases - Importance of magnesium supplementation of diets of elderly patients. In: Halpern MJ, Durlach J eds. Magnesium Deficiency. First Eur Congr Magnesium, Lisbon 1983. Basel: Karger, 1985; 239-43.

58. Durlach J. Magnesium in Clinical Practice. London: John Libbey, 1988; 75.

59. Food and Nutrition Board. Recommended Dietary Allowances. Washington DC: National Academy of Sciences, 1980.

60. Dietary Reference Values for Food, Energy and Nutrients for the United Kingdom. London: HMSO, 1991.

61. Spring JA, Robertson J, Buss DH, Trace nutrients. Magnesium, copper, zinc, vitamin B6, vitamin B12 and folic acid in the British household food supply. Br J Nutr 1979; **41**: 487-93.

62. The Dietary and Nutritional Survey of British Adults. London: HMSO, 1990.

63. Morgan KJ, Stampley GL, Zabik ME, Fischer DR. Magnesium and calcium dietary intakes of the U.S. population. J Am Coll Nutr 1985; **4**: 195-206.

64. Baghurst KI, Record SJ. The vitamin and mineral intake of a free-living young elderly Australian population in relation to total diet and supplementation practices. Hum Nutr Appl Nutr 1987; **41A**: 327-37.

65. MacLeod CC, Judge TG, Caird FI. Nutrition of the elderly at home. III Intakes of minerals. Age Ageing 1975; **4**: 49-57.

66. Vir SC, Love AHG. Nutritional status of institutionalised and non-institutionalised aged in Belfast, Northern Ireland. Am J Clin Nutr 1979; **32**: 1934-47.

67. Bunker VW, Lawson MS, Stansfield MF, Clayton BE. The intake and excretion of calcium, magnesium and phosphorus in apparently healthy elderly people and those who are housebound. J Clin Exp Gerontol 1989; **11**: 71-86.

68. Martin BJ, Milligan K. Diuretic associated hypomagnesaemia in the elderly. Arch Intern Med 1987; **147**: 1768-71.

69. Paul AA, Southgate DAT, eds. McCance and Widdowson. The Composition of Foods. 4th ed. London: HMSO, 1978.

70. Household Food Consumption and Expenditure, 1989. London: HMSO 1990.

71. Nutrition and Health in Old Age. London: HMSO, 1979.

72. Regional Laboratory, Strathclyde Region Water Department.

73. Thomas AJ, Bunker VW, Brennan E, Clayton BE. The trace element content of hospital meals and potential low intake by elderly patients. Hum Nutr Appl Nutr 1986; **40**: 440-6.

74. Speich M, Bousquet B, Nicolas G. Reference values for ionized, complexed and protein-bound plasma magnesium in men and women. Clin Chem 1981; **27**: 246-8.

75. Zaloga GP, Wilkens R, Tourville J, Wood D, Klyme DM. A simple method for determining physiologically active calcium and magnesium concentrations in critically ill patients. Crit Care Med 1987; **15**: 813-6.

76. Teears RJ, Barnes BA, Batsakis JG, Bloch DM. Serum Magnesium. A CAP survey. Am J Clin Pathol 1977; **68**: 159-61.

77. Wills MR, Sunderman FW, Savory J. Methods for the estimation of serum magnesium in clinical laboratories. Magnesium 1986; **5**: 317-27.

78. Engel RR, Elin RJ. Hypermagnesaemia from birth asphyxia. J Pediatr 1970; **77**: 631-7.

79. Petersen B, Christiansen C, Transbol I. The influence of fasting and venous stasis on the serum values of calcium, magnesium and protein. Dan Med Bull 1976; **23**: 198-9.

80. Martin BJ, McGregor CW. Measurement of serum magnesium - Effect of delay in separation from erythrocytes. Clin Chem 1986; **32**: 564.

81. Touitou Y, Touitou C, Bogdan A, Beck H, Reinberg A Serum magnesium circadian rhythm in human adults with respect to age, sex and mental status. Clin Chim Acta 1978; **87**: 35-41.

82. Lowenstein FW, Stanton MF. Serum magnesium levels in the United States, 1971 - 1974. J Am Coll Nutr 1986; **5**: 399-414.

83. Good Hearted Glasgow - The Greater Glasgow Health Board Multiple Risk Factor Intervention Programme for Cardiovascular Disease. Progress report. Greater Glasgow Health Board 1987.

84. Jackson CE, Meier DW. Routine serum magnesium analysis. Correlation with clinical state in 5,100 patients. Ann Int Med 1968; **69**: 743-8.

85. Whang R, Aikawa JK, Oei TO, Hamiter T. Routine serum magnesium determination. An unrecognised need. In: Cantin M, Seelig MS eds. Magnesium in health and disease. New York: S.P. Medical and Scientific books, 1980 1-5.

86. Whang R, Oei TO, Aikawa JK et al. Predictors of clinical hypomagnesaemia. Arch Intern Med 1984; **144**: 1794-6.

87. Wong ET, Rude RK, Singer FR, Shaw ST. A high prevalence of hypomagnesaemia and hypermagnesaemia in hospitalised patients. Am J Clin Pathol. 1983; **79**: 348-52.

88. Ryzen E, Wagers PW, Singer FR, Rude RK. Magnesium deficiency in a medical ICU population. Crit Care Med 1985; **13**: 19-21.

89. Chernow B, Bamberger S, Stoiko M, et al. Hypomagnesaemia in patients in postoperative intensive care. Chest 1989; **95**: 391-7.

90. Abraham AS, Rosenmann D, Meshulam Z, Zion M, Eylath U. Serum, lymphocyte and erythrocyte potassium, magnesium and calcium concentrations and their relation to tachyarrhythmias in patients with acute myocardial infarction. Am J Med 1986; **81**: 983-8.

91. Petersen B, Christiansen C, Transbol I. Blood minerals in cardiac emergencies. Dan Med Bull 1978; **25**: 116-8.

92. Duncanson GO, Worth HGJ. Determination of reference intervals for serum magnesium. Clin Chem 1990; **36**: 756-8.

93. Petersen B, Schroll M, Christiansen C, Transbol I. Serum and erythrocyte magnesium in normal elderly Danish people. Acta Med Scand 1977; **201**: 31-4.

94. Landahl S. Prevalence and treatment of hypomagnesaemia in the elderly. Aktuelle Geront 1980; **10**: 397-402.

95. Hayes JP, Ryan MF, Brazil N, Riordan TO, Walsh JB, Coakley D. Serum hypomagnesaemia in an elderly Day Hospital population. Ir Med J. 1989; **82**: 117-9.

96. Sherwood RA, Aryanayagam P, Ricks BF, Mankikar GD. Hypomagnesium in the elderly. Gerontology 1986; **32**: 105-9.

97. Touitou Y, Godard J, Ferment O, et al. Prevalence of magnesium and potassium deficiencies in the elderly. Clin Chem 1987; **3**: 518-23.

98. Leask RGS, Andrews GR, Caird FI. Normal values for sixteen blood constituents in the elderly. Age and Ageing 1973; **2**: 14-23.

99. Orange M, Rhein HC. Micro-estimation of magnesium in body fluids. J Biol Chem 1951; **189**: 379.

100. McConway MG, Martin BJ, Nugent M, Lennox IM, Glen ACA. Magnesium status in the elderly on hospital admission. J Clin Exp Gerontol 1981; **3**: 367-79.

101. Martin BJ, Black J, McLelland A. Hypomagnesaemia in elderly hospital admissions: A study of clinical significance. Q J Med 1991; **78**: 177-84.

102. Zaloga GP. Interpretation of the serum magnesium level. Chest 1989; **95**: 257-8.

103. Abraham AS, Shaoul R, Shimonovitz S, Eylath U, Weinstein M. Serum magnesium levels in acute medical and surgical conditions. Biochem Med 1980; **24**: 21-6.

104. Whyte KF, Addis GJ, Whitesmith R, Reid JL. Adrenergic control of plasma magnesium in man. Clin Sci 1987; **72**: 135-8.

105. Devane J, Donnelly B, Ryan MP. Postoperative changes in lymphocyte potassium and magnesium. Ir J Med Sci 1980; **49**: 73-6.

106. Elliot DA, Rizack MS. Epinephrine and adrenal corticotrophic hormone stimulated magnesium accumulation in adipocytes and their plasma membranes. J Biol Chem 1970; **249**: 3985-91.

107. Abraham AS, Eylath U, Weinstein M, Czaczkes E. Serum magnesium levels in patients with acute myocardial infarction. N Engl J Med; 1977: **296** 862-4.

108. Whang R, Ryder KW. Frequency of hypomagnesaemia and hypermagnesaemia. JAMA 1990; **263**: 3063-4.

109. Durlach J. Erythrocyte magnesium. In: Magnesium in clinical practice. London: John Libbey & Co, 1988, 48-9.

110. Cox IM, Campbell MJ, Dowson D. Red blood cell magnesium and chronic fatigue syndrome. Lancet 1991; **337**: 757-60.

111. Abraham GE, Lubran MM. Serum and red cell magnesium in patients with pre-menstrual tension. Am J Clin Nutr 1981; **35**: 2364-6.

112. Abraham AA, Meshulam Z, Rosenman D, Eylath U. Influence of chronic diuretic therapy on serum, lymphocyte and erythrocyte potassium, magnesium and calcium concentrations. Cardiology 1988; **75**: 17-23

113. Paolisso G, Sgambato S, Pizza G, Passariello N, Varricchio M, D'Onofrio F. Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. Diabetes Care 1989; **12**: 265-9.

114. Ginsburg S, Smith JG, Ginsburg FM, Reardon JZ, Aikawa JK. Magnesium metabolism in human and rabbit erythrocytes. Blood 1962; **20**: 722-9

115. Watson WS, Lyon TDB, Hilditch TE. Red cell magnesium as a function of cell age. Metabolism 1980; **29**: 397-9.

116. Watson WS, Hilditch TE, Horton PW, Davies DL, Lindsay R. Magnesium metabolism in blood and the whole body in man using ^{28} magnesium. Metabolism 1979: **28**; 90-5.

117. Erlandson ME, Golobow J, Wehman J, Smith CH. Bivalent cations in homozygous thalassaemia. J Paediatr 1965; **66**: 637-48.

118. Seelig MS ed. Magnesium deficiency in the pathogenesis of disease. London: Plenum Medical Book Co., 1980, 361-5.

119. Keitel HG, Berman H, Jones H, MacLachlan E. The chemical composition of normal human red blood cells including variability among centrifuged cells. Blood 1955: **20**; 370-6.

120. Gallacher RE, Browning MCK, Fraser CG, Wilkinson SP, MacLennan WM. A method for simultaneously estimating plasma, erythrocyte and leucocyte sodium, potassium and magnesium. Clin Chem 1987; **33**: 1326-30.

121. Henrotte JG. Genetic regulation of red blood cell magnesium content and major histocompatibility complex. Magnesium 1982; **1**: 69-80.

122. Girardin E, Paunier L. Relationship between magnesium, potassium, and sodium concentrations in lymphocytes and erythrocytes from normal subjects. Magnesium 1985; **4**: 188-92.

123. Olukoga AO, Erasmus RT, Adewoye HO. Erythrocyte and plasma magnesium status in Nigerians with diabetes mellitus. Ann Clin Biochem 1989; **26**: 74-7.

124. Dyckner T, Wester PO. Skeletal muscle magnesium and potassium determinations : correlation with lymphocyte contents of magnesium and potassium. J Am Coll Nutr 1985; **4**: 619-25.

125. Sjogren A, Floren CH, Nilsson A. Magnesium deficiency in IDDM related to level of glycosylated haemoglobin. Diabetes 1986; **35**: 459-63.

126. Reinhart RA, Marx JJ, Hass RG, Desbiens NA. Intracellular magnesium of mononuclear cells from venous blood of clinically healthy subjects. Clin Chim Acta 1987; **167**: 187-95.

127. Elin RJ, Johnson E. A method for the determination of the magnesium content of blood mononuclear cells. Magnesium 1982; **1**: 115-21

128. Ryzen E, Elkayam U, Rude RK. Low blood mononuclear cell magnesium in intensive care unit patients. Am Heart J 1986; **3**: 475-80

129. Abraham AS, Rosenmann D, Zion MM, Eylath U. Lymphocyte potassium and magnesium concentrations as prognostic factors after acute myocardial infarction. Cardiology 1988; **75**: 194-99.

130. Reinhart RA. Magnesium metabolism. A review with special reference to the relationship between intracellular content and serum levels. Arch Intern Med 1988; **148**: 2415-20.

131. Boyum A. A one-stage procedure for the isolation of granulocytes and lymphocytes from human blood. Scand J Clin Lab Invest 1968; **97** suppl 21: 51-76.

132. Boyum A. Isolation of lymphocyes, granulocytes and macrophages. Scand J Immunol 1976; **5** suppl 5: 9-15.

133. Lowry O, Rosebrough N, Farr A, Randall R. Protein measurement with Folin phenol reagent. J Biol Chem 1951; **193**: 265-75.

134. Jenkins LL, Pleban PA. Distribution of copper, magnesium and zinc in plasma and cellular components of blood from Type 1 diabetic children. Clin Chem 1986; **32**: 1089. (abstract)

135. Urdal P, Landmark K. Measurement of magnesium in mononuclear blood cells. Clin Chem 1989; **35**: 1559-60.

136. Geven WB, Vogels-Mentink GM, Willems JL, de Boo T, Lemmens W, Monnens LAH. Reference values for magnesium and potassium in mononuclear cells and erythrocytes of children. Clin Chem 1990; **36**: 1323-7.

137. Schwinger EH, Antoni DH. Magnesium and potassium content in patients with heart failure and in healthy persons. Determination in lymphocytes, erythrocytes and plasma. Z Kardiol 1990; **79**: 735-41.

138. Yang XY, Hosseini JM, Ruddel ME, Elin RJ. Blood magnesium parameters do not differ with age. J Am Coll Nutr 1990; **9**: 308-13.

139. Elin RJ, Hosseini JM. Magnesium content of mononuclear blood cells. Clin Chem 1985; **31**: 377-80.

140. Hosseini JM, Elin RJ. Magnesium variability of lymphocytes from cell culture. J Am Coll Nutr 1985; **4**: 613-7

141. Elin RJ. Status of the mononuclear blood cell magnesium assay. J Am Coll Nutr 1987; **6**: 105-7.

142. Buckton KE, Brown WM, Smith PG. Lymphocyte survival in men treated with X-rays for ankylosing spondylitis Nature 1967; **214**: 470-3.

143. Nowel PC. Unstable chromosome changes in tuberculin-stimulated leucocyte cultures from irradiated patient. Evidence for immunologically committed long-lived lymphocytes in human blood. Blood 1965; **26**: 798-804.

144. Ottensen J. On the age of human white blood cells in peripheral blood. Acta Physiol Scand 1954; **32**: 75-93.

145. Yoffey JM, Courtice FC. Lymphatics, lymph and the lymphomyeloid complex. New York: Academic Press, 1970

146. MacLennan ICM. The lymphocytes: formation and function. In: Hardisty RM, Wetherall DJ, eds. Blood and its Disorders, 2nd ed. London: Blackwell Scientific Publications, 1982, 647-74.

147. Hayhoe FGJ, Quaglino D, eds. Haematological Cytochemistry. New York: Churchill Livingstone, 1980; 22-3.

148. Szafarz BF, Szafarz D. DNA and protein content as cellular biochemical parameters. Anal Biochem 1984; **138**: 255-8.

149. Elin RJ, Hosseini JM, Banks SM, Reinhart RA. Precision of cellular magnesium assays. Clin Chem 1990; **36**: 821-2.

150. Clarke JR, Gangon RF, Gotch FM, et al. The effect of prednisolone on leucocyte function in man: a double blind controlled study. Clin Exp Immunol 1977; **28**: 292.

151. Heaton FW. The kidney and magnesium homeostasis. Ann N Y Acad Sci 1969; **162**: 775-85.

152. Elin RJ. Assessment of magnesium status. Clin Chem 1987; **33**: 1965-70.

153. Durlach J ed. Magnesium in clinical practice. London: John Libby, 1988, 43-5.

154. Cappuchio FP, Markandu ND, Benyon GW, Shore AC, Sampson B, MacGregor GA. Lack of effect of oral magnesium on high blood pressure: a double blind study. Br Med J 1985; **291**: 235-8.

155. Saito K, Hattori K, Omatsu T, Hirouchi H, Sano H, Fukuzaki H. Effects of oral magnesium on blood pressure and red cell sodium transport in patients receiving long-term thiazide diuretics for hypertension. Am J Hypertens 1988; **1**: 71-4.

156. Bohmer T, Roseth L, Holm H, Weberg-Teigen S, Wahl L. Bioavailability of oral magnesium supplementation in female students evaluated from elimination of magnesium in 24 hour urine. Magnes Trace Elem 1990; **9**: 272-8.

157. Cox JR, Shalaby WA. Renal disease. in: Pathy MSJ, ed. Principles and Practice of Geriatric Medicine. New York: John Wiley @ Sons Ltd, 1985, 1121-39.

158. Randall RE. Magnesium metabolism in chronic renal disease. Ann N Y Acad Sci. 1969; **162**: 831-45.

159. Ryzen E, Elbaum N, Singer FR, Rude RK. Parenteral magnesium tolerance testing in the evaluation of magnesium deficiency. Magnesium 1985; **4**: 137-47.

160. Berkelhammer C, Bear RA. A clinical approach to common electrolyte problems. Hypomagnesaemia. Can Med Assoc J 1985; **132**: 360-8.

161. Faulker WR. Magnesium deficiency and excess. Lab Report for Physicians 1988; **10**: 25-8.

162. Reinhart RA. Magnesium metabolism. Wis Med J 1990; **89**: 579-83.

163. Thoren L. Magnesium deficiency in gastrointestinal fluid loss. Acta Chir Scand 1962; Suppl **306**; 5-60.

164. Fourman P, Morgav DB. Chronic magnesium deficiency. Proc Nutr Soc 1962; **21**: 34-41.

165. Barnes BA, Cope O, Gordon EB. Magnesium requirements and deficits: an evaluation in two surgical patients. Ann Surg 1960; **152**; 518-25.

166. Bohmer T, Mathieson B. Magnesium deficiency in chronic alcoholic patients uncovered by an intravenous loading test. Scan J Clin Lab Invest 1982; **42**: 633-6.

167. Cohen L, Kitzes R, Schnaider H. The myth of long term thiazide-induced magnesium deficiency. Magnesium 1985; **4**: 176-81.

168. Jones JE, Shane SR, Jacobs WH, Flink EB. Magnesium balance studies in chronic alcoholism. Ann N Y Acad Sci 1969; **162**: 934-45.

169. Caddell JL, Saier FL, Thomason CA. Parenteral magnesium load tests in postpartum American women. Am J Clin Nutr 1975; **28**: 1099-1104.

170. Goto K, Yasue H, Okumura K, et al. Magnesium deficiency detected by intravenous loading test in variant angina pectoris. Am J Cardiol 1990; **65**: 702-12.

171. Cohen L, Kitzes R. Characterization of the Mg status of elderly people by the Mg tolerance test. Magnesium Bulletin 1992; **14**: 133-4.

172. Kampmann J, Siersbaek-Nielsen K, Kristensen M, Molholm Hansen J. Rapid evaluation of creatinine clearance. Acta Med Scand 1974; **196**: 517-20.

173. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. The effect of age on creatinine clearance in men. A cross sectional and longitudinal study. J Gerontol 1976; **31**: 155-63.

174. Lim P, Jacob E. Tissue magnesium level in chronic diarrhoea. J Lab Clin Med 1972; **80**: 313-21.

175. Lim P, Jacob E. Magnesium deficiency in patients on long term diuretic therapy for heart failure. Br Med J 1972; **3**: 620-2.

176. Wester PO, Dyckner T. Diuretic treatment and magnesium losses. Acta Med Scand 1981; **647**: 145-52.

177. Lyon TDB, Fell GS, Halls D, Clark J, McKenna F. Determination of nine organic elements in human autopsy tissue. J Trace Elem Electrolytes Health Dis 1989; **3**: 109-18.

178. Baskin SI, Uricchio FJ, Kendrick ZV. The effect of age on the regional distribution of four cations in the rat heart. Age 1979; **2**: 64 (abstract)

179. Shah BG, Belonje B. Levels of magnesium, copper, chromium, manganese and cadmium in the livers of Canadians. Trace Elements in Medicine 1990; **7**: 11-18.

180. Anderson TW, Neri LC, Schreiber GB, Talbot FDF, Zdrojewski A. Ischemic heart disease, water hardness and myocardial magnesium. Can Med Assoc J 1975; **113**: 199-203.

181. Dorup I, Skajaa K, Clausen T, Kjendsen K. Reduced concentrations of potassium, magnesium, and sodium-potassium pumps in human skeletal muscle during treatmemt with diuretics. Br Med J 1988; **296**: 455-8.

182. Adam WR, Craik DJ, Kneen M, Wellard RM. Effect of magnesium depletion and potassium depletion and chlorothiazide on intracellular pH in the rat, studied by ^{31}p NMR. Clin Exp Pharmacol Physiol 1989; **16**: 33-40.

183. Dyckner T, Wester PO, Potassium/magnesium depletion in patients with cardiovascular disease. Am J Med 1987; **82**: 11-17.

184. Swales JD. Magnesium deficiency and diuretics. Br Med J 1982; **285**: 1377-8.

185. Ryan MP. Diuretics and potassium/magnesium depletion. Am J Med 1987; **82**: 38-47.

186. Hollifield JW. Magnesium depletion, diuretics, and arrhythmias. Am J Med 1987; **82**: 30-37.

187. Williamson J. Prescribing problems in the elderly. Practitioner 1978; **220**: 749-58.

188. Duarte CG. Effects of ethacrynic acid and frusemide on urinary calcium, phosphate and magnesium. Metabolism 1968; **17**: 867-76

189. Sheehan J, White A. Diuretic-associated hypomagnesaemia. Br Med J 1982; **285**: 1157-59.

190. Ryan MP, Ryan MF, Counihan TB. The effects of diuretics on lymphocyte magnesium and potassium. Acta Med Scand 1981; suppl **647**: 153-61.

191. Ross EJ. Aldosterone and aldosteronism. London: Lloyd-Luke, 1975; 93-113.

192. Reyes AJ, Leary WP. Cardiovascular toxicity of diuretics related to magnesium depletion. Hum Exp Toxicol. 1984; **3**: 351-72.

193. Wacker WEC. The effect of hydrochlorothiazide on magnesium excretion. J Clin Invest 1961; **40**: 1086-87.

194. Quamme GA. Effect of hypercalcaemia on renal tubular handling of calcium and magnesium. Can J Physiol 1982; **60**: 1275-80.

195. Kuller L, Farrier N, Caggiula A, Borhani N, Dunkle S. Relationship of diuretic therapy and serum magnesium levels among participants in the Multiple Risk Factor Intervention Trial. Am J Epidemiol 1985; **122**: 1045-59.

196. Hollifield JW, Stanton PE. Thiazide diuretics, hypokalaemia and cardiac arrythmias. Acta Med Scand 1981; suppl **647**: 67-74

197. Hollifield JW. Thiazide treatment of hypertension: effects of thiazide diuretics on serum potassium, magnesium and ventricular ectopy. Am J Med 1986; **80** suppl 4A: 8-12.

198. Kroenke K, Wood D, Hanley J. The value of serum magnesium determination in hypertensive patients receiving diuretics. Arch Intern Med 1987; **147**: 1553-6.

199. Dyckner T, Wester PO. Intracellular magnesium loss after diuretic administration. Drugs 1984; **28** suppl 1: 161-6.

200. Thomas AJ, Hodkinson HM. Which diuretics cause hypomagnesaemia? J Clin Exp Gerontol 1981: **3**: 269-83.

201. Petri M, Bryant R, Cumber P. Thiazide treatment in elderly patients: the metabolic cost. Br Med J 1985; **291**: 1616.

202. Cocco G, Iselin HU, Strozzi C, Cesana B, Baumeler HR. Magnesium depletion in patients on long-term Chlorthalidone therapy for essential hypertension. Eur J Clin Pharmacol. 1987; **32**: 335-8.

203. Siegal D, Hulley SB, Black DM et al. Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. JAMA 1992; **267**: 1083-9.

204. Whang R, Whang D, Ryan M. Refractory potassium repletion. A consequence of magnesium deficiency. Arch Intern Med 1992; **152**: 40-5.

205. Edmonds CJ, Jasani B. Total body potassium in hypertensive patients during prolonged diuretic therapy. Lancet 1972; **2**: 8-12.

206. Editorial. Who needs potassium ? Br Med J 1977; **2**: 307-8.

207. Morgan DM, Davidson C. Hypokalaemia and diuretics: an analysis of publications. Br Med J 1980; **280**: 905-8.

208. Harrington JT, Isner JM, Kassirer JP. Our national obsession with potassium. Am J Med 1982; **73**: 155-9.

209. Kaplan NM. Our appropriate concern about hypokalaemia. Am J Med 1984; **77**: 1-4.

210. Madias JE, Madias NE, Gavras HP. Nonarrhythmogenicity of diuretic-induced hypokalaemia. Its evidence in patients with uncomplicated hypertension. Arch Int Med 1984; **144**: 2171-6.

211. Attwood JE, Gardin JM. Diuretics, Hypokalaemia, and ventricular ectopy. The controversy continues. Arch Intern Med 1985; **145**: 1185-7.

212. Massry SG, Brautbar N. Interrelationships between phosphate and magnesium matabolism. Adv Exp Med Biol 1980; **128**: 51-66.

213. Whang R. Magnesium deficiency: pathogenesis, prevalence and clinical implications. Am J Med 1987 suppl 3A; **82**: 24-9.

214. Medication for the Elderly. A report of the Royal College of Physicians. J R Coll Physicians Lond 1984; **8**.

215. Murray GD. Statistical aspects of research methodology. Br J Surg 1991; **78**: 777-81.

216. Gums JG. Clinical significance of magnesium. A review. Drug Intell Clin Pharm 1987; **21**: 240-6.

217. Dyckner T, Wester PO. Magnesium deficiency. Guidelines for diagnosis and substitution therapy. Acta Med Scand 1982; Suppl **661**: 37-41.

218. Classen HG, Achilles W, Bachem MG et al. Magnesium: indications concerning diagnosis and treatment in man. Magnesium Bulletin 1986; **8**: 117-21.

219. Logue FC, Perry B, Chapman RS, Milne I, James K, Beastall GH. A two-site immunoradiometric assay for PTH(1-84) using N and C terminal specific monoclonal antibodies. Ann Clin Biochem 1991; **28**: 160-6.

220. Goldberg DP, Hillier VF. A scaled version of the General Health Questionaire. Psychol Med 1979; **9**: 139-45.

221. Snaith RP, Ahmed SN, Mehta S, Hamilton M. Asessment of the severity of primary depressive illness: Wakefield self-assessment depression inventory. Psychol Med 1971; **1**: 143-9.

222. Robinson RG, Price TR. Post-stroke depressive disorders: a follow up study of 103 patients. Stroke 1982; **13**: 635-41.

223. Wade DT, Leigh-Smith J, Hewer RA. Depressed mood after stroke: a community study of its frequency. Br J Psychiatr 1987; **151**: 200-5.

224. Fallowfield L. The Quality of Life. The missing measurement in health care. London: Souvenir Press, 1990.

225. Kingston ME, Badawi Al-Siba'l M, Skooge WC. Clinical manifestations of hypomagnesaemia. Crit Care Med 1986; **14**: 950-4.

226. Whang R, Aikawa JK. Magnesium deficiency and refractoriness to potassium repletion. J Chron Dis 1977; **30**: 65-8.

227. Anast CS, Mohn JM, Kaplan SL, Burns TW. Evidence for parathyroid failure in magnesium deficiency. Science 1972; **177**: 606-8.

228. Rude RK, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone end-organ resistance in human magnesium deficiency. Clin Endocrinol 1976; **5**: 209-24.

229. Rude RK, Oldham SB, Sharp CR, Singer FR. Parathyroid hormone secretion in magnesium deficiency. J Clin Endocrinol Metab 1978; **47**: 800-6.

230. Burnatowska MA, Harris CA, Sutton AH, Dirks JH. Effect of parathyroid hormone and cyclic AMP on renal handling of calcium and magnesium and phosphate in the hamster. Am J Physiol 1977; **233**: 514-8.

231. Allgrove J, Adami S, Fraher L, Reuben A, O'Riordan JLH. Hypomagnesaemia: studies of parathyroid hormone secretion and function. Clin Endocrinol 1984; **21**: 435-49.

232. Shils ME. Magnesium deficiency and parathyroid hormone levels in man. Am J Clin Nutr 1975; **28**: 421.

233. Habener JF, Potts JT. Relative effectiveness of magnesium and calcium on the secretion and biosynthesis of parathyroid hormone in vitro. Endocrinology 1975; **98**: 197-202.

234. Cholst IN, Steinberg SF, Tropper PJ, Fox HE, Segre GV, Bilezikian JP. The influence of hypermagnesaemia on serum calcium and parathyroid hormone levels in human subjects. N Engl J Med 1984; **310**: 1221-5.

235. Logue FC, Beastall GH, Fraser WD, O'Reilly DStJ. Intact parathyroid hormone assays. Br Med J 1990; **300**: 210-1.

236. Mather HM, Nisbet JA, Burton GH et al. Hypomagnesaemia in diabetes. Clin Chim Acta 1979; **95**: 235-42

237. McNair P, Christiansen MS, Christiansen C, Madsbad S, Transbol IB. Renal hypomagnesaemia in human diabetes mellitus: its relation to glucose homeostasis. Eur J Clin Invest 1982; **12**: 81-5.

238. Paolisso G, Scheen A, D'Onofrio F, Lefebvre P. Magnesium and glucose homeostasis. Diabetologia 1990; **33**: 511-4.

239. Paolisso G, Passariello N, Pizza G et al. Dietary magnesium supplements improve B-cell response to glucose and arginine in elderly non-insulin dependent diabetic subjects. Acta Endocrinol 1989; **121**: 16-20

240. Davis WH, Leary WP, Reyes AJ, Olhaberry JV. Monotherapy with magnesium increases abnormally low High Density Lipoprotein Cholesterol: a clinical assay. Curr Ther Res 1984; **36**: 341-6

241. Rayssiguier Y. Magnesium and lipid interrelationships in the pathogenesis of vascular diseases. Magnesium Bull 1981; **3**: 165-77.

242. Steiner AJ. Lipid lowering by magnesium - a trace element. J Appl Nutr 1963; **16**: 125-9.

243. Haywood J, Sylvester R. Effect of oral magnesium and potassium on serum lipids. Clin Med 1962; **10**: 87.

244. Singh RB, Rastogi SS, Sharma VK, Saharia Rb, Kulshretha SK. Can dietary magnesium modulate lipoprotein metabolism? Magnes Trace Elem 1990; **9**: 255-64.

245. Petersen B, Christiansen C, From Hansen P. Treatment of hypercholesterolaemia and hypertriglyceridaemia with magnesium. Acta Med Scand 1976; **200**: 59-61.

246. Marken PA, Weart CW, Carson DS, Gums JG, Lopez-Virella MF. Effects of magnesium oxide on the lipid profile of healthy volunteers. Atherosclerosis 1989; **77**: 37-42.

247. Rasmussen HS, Aurup P, Goldstein K et al. Influence of magnesium substitution therapy on blood lipid composition in patients with ischemic heart disease. Arch Intern Med 1989; **149**: 1050-3.

248. Kinnunin O, Salokannel J. Comparison of the effects of magnesium hydroxide and a bulk laxative on lipids, carbohydrates, and vitamins A and E, and minerals in geriatric hospital patients in the treatment of constipation. J Int Med Res 1989; **17**: 442-54.

249. Seller RH, Cangiano J, Kim KE, Mendelssohn S, Brest AN, Schwartz C. Digitalis toxicity and hypomagnesaemia. Am Heart J 1970; **79**: 57-68.

250. Loeb HS, Pietras RJ, Gunnar RM, Tobin JR. Paroxysmal ventricular fibrillation in two patients with hypomagnesemia. Circulation 1968; **37**: 210-5.

251. Cohen L, Kitzes R. Magnesium sulphate and digitalis-toxic arrhythmias. JAMA 1983; **249**: 2808-10

252. Ghani MF, Rabah M. Effect of magnesium chloride on electrical stability of the heart. Am Heart J 1977; **94**: 600-2

253. Seelig MS. Electrocardiographic patterns of magnesium depletion appearing in alcoholic heart disease. Ann N Y Acad Sci 1969; **162**: 906-17

254. Lewis RV, Tregaskis B, McLay J, Service E, McDevitt DG. Oral magnesium reduces ventricular ectopy in digitalised patients with chronic atrial fibrillation. Eur J Clin Pharmacol 1990; **38**: 107-110.

255. Krasner BS, Girdwood R, Smith H. The effect of slow release oral magnesium chloride on the QTc interval of the electrocardiogram during open heart surgery. Can Anaesth Soc J 1981: **28**: 329-33.

256. Altura BM, Altura BT. New perspectives on the role of magnesium in the pathophysiology of the cardiovascular system. Magnesium 1985; **4**: 245-71.

257. Charbon GA. Cardiac and peripheral vascular actions by Ca++ and Mg++. Am J Nephrol 1986; **6** suppl 1: 134-8.

258. Dyckner T, Wester PO. Effect of magnesium on blood pressure. Br Med J 1983; **286**: 1847-9.

259. Henderson DG, Schierup J, Schodt T. Effect of magnesium supplementation on blood pressure and electrolyte concentrations in hypertensive patients receiving long-term diuretic treatment. Br Med J 1986; **293**: 664-5.

260. Vallee BL, Wacker WEC, Ulmer DD. The magnesium deficiency tetany syndrome in man. N Engl J Med 1960; **262**: 155-61.

261. Hanna S, Harrison M, McIntyre I, Fraser R. Syndrome of magnesium deficiency in man. Lancet 1960; **2**: 172-6.

262. Fishman RA. Neurological aspects of magnesium metabolism. Arch Neurol 1965; **12**: 562-9.

263. Pall HS, Williams AC, Heath DA, Sheppard M, Wilson R. Hypomagnesaemia causing myopathy and hypocalcaemia in an alcoholic. Postgrad Med J 1987; **63**: 665-7.

264. Judge TG, Cowan NR. Dietary potassium intake and grip strength in older people. Geront Clin 1971; **13**: 221-6.

265. Bahemuka M, Hodkinson HM. Red-blood-cell potassium and hand-grip strength in healthy elderly people. Age Ageing 1976; **5**: 116-8.

266. Burr ML, St Leger AS, Westlake CA, Davies HEF. Dietary potassium deficiency in the elderly: a controlled trial. Age Ageing 1975; **4**: 148-51.

267. Wacker WEC, Parisi AF. Magnesium metabolism. N Engl J Med 1968; **278**: 712-76.

268. Hall RCW, Joffe JR. Hypomagnesaemia: physical and psychiatric symptoms. JAMA 1973; **224**: 1749-51.

269. Carney MWP, Sheffield BF, Sebastian J. Serum magnesium, diagnosis, ECT and season. Br J Psychiatry 1973; **122**: 427-9

270. Rasmussen HS, Mortensen PB, Jensen IW. Depression and magnesium deficiency. Int J Psychiatry Med 1989; **19**: 57-63.

271. Lindberg JS, Zobitz MM, Poindexter JR, Pak CY. Magnesium bioavailability from magnesium citrate and magnesium oxide. J Am Coll Nutr 1990; **9**: 48-55.

272. Reynolds JEF (ed). Martindale - The Extra Pharmacopoeia. 28th edition. London: The Pharmaceutical Press, 1990.

273. Lindberg JS, Harvey J, Pak CY. Effect of magnesium citrate and magnesium oxide on the crystallization of calcium salts in urine. J Urol 1990; **143**: 248-51.

274. Grubbs RD, Collins SD, Maguire ME. Differential compartmentation of magnesium and calcium in murine S49 lymphoma cells. J Biol Chem 1984; **259**: 12184-90.

275. Santarromana M, Delepierre M, Feray JC, Franck G, Garay R, Henrotte JG. Correlation between total and free magnesium levels in human red blood cells. Influence of HLA antigens. Magnesium Research 1989; **2**: 281-3.

276. Heaton FW. The determination of ionized magnesium in serum and urine. Clin Chim Acta 1967; **15**: 139-44.

277. Frizel DE, Malleson AG, Marks V. Measurement of plasma ionized calcium and magnesium by ion exchange strip. Clin Chim Acta 1967; **16**: 45-56.

278. Frye RM, Lees H, Rechnitz GA. Magnesium-albumin binding measurements using ion-selective electrodes. Clin Biochem 1974; **7**: 258-70.

279. Gupta RK, Benovic JL, Rose ZB. The determination of the free magnesium level in the human red blood cell by ^{31}P NMR. J Biol Chem 1978; **253**: 6172-6.

280. Ryzen E, Servis KL, DeRusso P, Kershaw A, Stephen T, Rude RK. Determination of intracellular free magnesium by nuclear magnetic resonance in human magnesium deficiency. J Am Coll Nutr 1989; **8**: 580-7.

281. Geven WB, Vogels-Mentink GM, Willems JL, et al. ^{31}P nuclear magnetic resonance and zero-point titration compared for measuring free magnesium concentration in erythrocytes. Clin Chem 1991; **37**: 2076-80.

282. Fry CH, Hall SK, Blatter LA, McGuigan JA. Analysis and presentation of intracellular magnesium measurements obtained with ion-selective microelectrodes. Exp Physiol 1990; **75**: 187-98.

283. Flatman PW. Magnesium and transport in red cells. J Trace Elem Elect Health Dis 1992; **6**: 1-5.

284. Corkey BE, Duszynski J, Rich TE, Matschinsky B, Williamson JR. Regulation of free and bound magnesium in rat hepatocytes and isolated mitochondria. J Biol Chem 1986; **261**: 2567-74.

285. Raju B, Murphy E, Levy LA, Hall RD, London RE. A fluorescent indicator for measuring cytosolic free magnesium. Am J Physiol 1989; **256**: 540-8.

286. Ng LL, Davies JE, Garrido MC. Intracellular free magnesium in human lymphocytes and the response to lectins. Clin Sci 1991; **80**: 539-47.

287. Wohlfart P, Vienhues R, Cook NJ. Spectrophotometric determination of photoreceptor cGMP-gated channel Mg^{2+} fluxes using dichlorophosphonazo III. Biochim Biophys Acta 1990; **1022**: 283-90.

288. Resnick L. Intracellular free magnesium in erythrocytes of essential hypertension: relation to blood pressure and serum divalent cations. Proc Natl Acad Sci USA 1984; **81**: 6511-5.

289. Nadler JL, Malayan S, Luong H, Shaw S, Natarajan RD, Rude RK. Intracellular free magnesium plays a key role in increased platelet reactivity in type II diabetes mellitus. Diabetes Care 1992; 15: 835-141.

290. Resnick L, Gupta R, Gruenspan H, Alderman M, Laragh J Hypertension and peripheral insulin resistance: mediating role of intracellular free magnesium. Am J Hypertens 1990; 3: 373-9.

291. Resnick LM. Cellular calcium and magnesium metabolism in the pathophysiology and treatment of hypertension and related metabolic disorders. Am J Med 1992; 93 (supp 2A): 2-11.

LIST OF APPENDICES

APPENDIX 1

Magnesium content of various foods

Food	Magnesium/Portion weight (mmol/kg)
Porridge (made with water)	7.4
All Bran	86.4
Weetabix (2)	49.4
Wheat Bran	214
Soya Flour	98.8
Wholemeal Bread	31.3
Rye Crispbread	41.2
Oatcakes	41.2
Sardines (excluding oil)	21.4
Prawn, boiled	17.3
Nuts e.g. peanuts	86.4
Apricots (fresh, raw)	18.1
Bananas (without skin)	14
Figs	30.5
Dried fruits e.g. sultanas	12.3
Sweetcorn	9.9
Pulses e.g. tinned peas	8.2
Potatoes, boiled	5.7
Potato crisps (1 small packet)	19.2
Cabbage, boiled	1.6
Carrots, boiled	2.5
Spinach, boiled	14.0
Whole milk	4.5
Instant coffee (powder or granules)	160
Cocoa powder	214
Black Treacle	57.6
Peanut Butter	74.1
Chocolate, plain	41.2

Adapted from McCance and Widdowson: The composition of foods, 5th Ed. London: HMSO 1991 [52].

APPENDIX 2

Characteristics of aged autopsy subjects (Chapter 9)

	Sex	Age	Duration of illness	Diseases contributing to death
1	m	73	chronic	PVD, CVI, pneumonia
2	m	84	chronic	Pneumonia, COAD
3	m	72	chronic	Pneumonia, IHD, cirrhosis
4	m	86	chronic	Pneumonia,IHD, pulmonary fibrosis
5	f	72	chronic	CVD, IHD
6	f	73	chronic	Bladder carcinoma, peritonitis
7	f	85	short	PTE, IHD, CRF
8	f	91	chronic	IHD, pneumonia
9	f	85	chronic	PVD, bacterial meningitis
10	m	73	chronic	Bronchial carcinoma
11	m	82	chronic	IHD, pneumonia, peptic ulceration
12	m	69	sudden	IHD, MI
13	f	82	short	CVI, MI, IHD
14	f	84	chronic	IHD, CCF, chronic pancreatitis
15	f	83	chronic	Bowel infarction, CRF, CVD
16	f	77	chronic	IHD, CCF, pneumonia
17	m	88	chronic	Emphysema, CRF
18	m	80	chronic	IHD,pneumonia,Parkinson's disease
19	f	84	chronic	Bronchial carcinoma
20	m	71	sudden	Peritonitis
21	m	73	chronic	Prostatic carcinoma, CRF
22	f	85	sudden	MI, IHD
23	f	88	chronic	IHD, CCF, ruptured gall bladder
24	m	84	short	Pneumonia
25	m	77	chronic	CVD, carcinoma of caecum
26	f	84	short	CVI, IHD, CRF
27	f	94	sudden	Pneumonia,cholecystitis,diabetes
28	m	85	chronic	IHD, CCF, mitral valve disease
29	f	84	chronic	IHD, PVD, PTE
30	f	83	chronic	Emphysema
31	f	76	sudden	CVI, pneumonia
32	m	72	chronic	Pneumonia, prostatic carcinoma
33	f	76	short	MI, IHD, CCF, diabetes

PVD = peripheral vascular disease
CVD = cerebrovascular disease
CRF = chronic renal failure
PTE = pulmonary thromboembolism
CVI = cerebrovascular incident
IHD = ischaemic heart disease
COAD = chronic obstructive airways disease
MI = myocardial infarction
CCF = congestive cardiac failure

APPENDIX 3

Characteristics and clinical outcome in elderly patients with severe hypomagnesaemia on admission to hospital (serum magnesium < 0.50 mmol/l)

Sex	Age	Serum mg mmol/l (lowest value)	Diagnoses and comment (duration of illness)	Clinical outcome at six months
F	68	0.31	Dysphagia Oesophagitis Diverticulitis Presented with weight loss and diarrhoea. (4 months)	Survived
F	67	0.47*	Multiple fractures (road traffic accident) Epilepsy Hypertension (2 months)	Survived
F	93	0.49*	Metastatic carcinoma of colon (2 weeks)	Died (PM)
F	84	0.44*	Pneumonia NIDDM CCF (12 weeks) Serum magnesium rose to 0.67 mmol/l before death	Died (PM)
F	84	0.48* **	Peripheral vascular disease CCF (one week)	Survived
F	80	0.38*	CCF Alcohol excess Recurrent hypomagnesaemia (2 episodes in 6 months: 2 weeks and 1 week)	Survived
F	80	0.48*	CCF Pneumonia Recurrent hypomagnesaemia (2 episodes in 5 months: 1 week each)	Survived
F	71	0.48	Alcohol excess Recurrent hypomagnesaemia (2 episodes in 5 months: 2 weeks and 1 week)	Survived

APPENDIX 3 continued

Sex	Age	Serum mg mmol/l (lowest value)	Diagnoses and comment (duration of illness)	Clinical outcome at six months
F	70	0.42	Septicaemia (Staph aureus) Profuse diarrhoea (1 week)	Survived
F	76	0.22*	CCF Jaundice Gall stones Henoch-Schonlein purpura (2 months)	Survived
F	96	0.45* **	CCF (one week)	Survived
F	77	0.48	Iatrogenic hypercalcaemia (calcium supplements post thyroidectomy: serum calcium 3.70 mmol/l) (2 weeks)	Survived
M	66	0.45	Metastatic carcinoma of prostate (4 months)	Died
M	70	0.44	Alcohol excess (2 weeks)	Survived
F	71	0.49*	Pneumonia Renal artery stenosis Hypertension (3 days)	Died (PM)
F	80	0.48	Metastatic carcinoma of bronchus Profuse diarrhoea (4 days)	Died (PM)
M	73	0.41	Alcohol excess (1 week)	Survived
F	75	0.42	Rheumatoid arthritis Ulcerative colitis Acute renal failure (3 weeks)	Survived
F	79	0.27*	CCF Pulmonary fibrosis Biliary obstruction (4 days)	Died (PM)

APPENDIX 3 continued

Sex	Age	Serum mg mmol/l (lowest value)	Diagnoses and comment (duration of illness)	Clinical outcome at six months
F	88	0.42*	CCF Chronic renal failure Carcinoma of colon (recurrent hypomagnesaemia until death at 10 months)	Survived
F	88	0.49* **	Pseudomembranous colitis Myocardial infarction (4 weeks)	Died (4 weeks)
F	77	0.45 **	Cerebrovascular disease Pneumonia (5 weeks)	Died (PM) (5 weeks)

* receiving diuretic treatment

** single serum magnesium sample less than 0.50 mmol/l. (All other patients had multiple samples less than 0.50 mmol/l)

Abbreviation key

CCF = congestive cardiac failure
NIDDM = non insulin dependent diabetes mellitus
PM = post-mortem examination performed

APPENDIX 4 (Chapter 12)

GENERAL HEALTH QUESTIONAIRE

Please read each question carefully. Think about your own situation and tick one answer in each case.

HAVE YOU RECENTLY:

1 been able to concentrate on whatever you're doing?	better than usual	same as usual	less than usual	much less than usual
2 lost much sleep over worry?	not at all	no more than usual	rather more than usual	much more than usual
3 felt that you were playing a useful part in things?	more so than usual	same as usual	less useful than usual	much less useful
4 felt capable about making decisions about things?	more so than usual	same as usual	less so than usual	much less than usual
5 felt constantly under strain?	not at all	no more than usual	rather more than usual	much more than usual
6 felt you couldn't overcome difficulties?	not at all	no more than usual	rather more than usual	much more than usual
7 been able to enjoy your normal day to day activities?	more so than usual	same as usual	less so than usual	much less than usual
8 been able to face up to your problems?	more so than usual	same as usual	less so than usual	much less able
9 been feeling unhappy or depressed?	not at all	no more than usual	rather more than usual	much more than usual
10 been losing confidence in yourself?	not at all	no more than usual	rather more than usual	much more than usual
11 been thinking of yourself as a worthless person?	not at all	no more than usual	rather more than usual	much more than usual
12 been feeling quite happy, all things considered?	more so than usual	about the same as usual	less so than usual	much less than usual

APPENDIX 5 (Chapter 12)

WAKEFIELD SELF-ASSESSMENT INVENTORY

Read these statements carefully, one at a time, and underline the response which best indicates how you are. It is important to indicate how you are now, not how you were, or how you would hope to be.

1 I feel miserable and sad
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(d) No, not at all

2 I find it easy to do the things I used to
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(d) No, not at all

3 I get frightened or panic for no reason at all
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(d) No, not at all

4 I have weeping spells, or I feel like it
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(d) No, not at all

5 I still enjoy the things I used to
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(d) No, not at all

6 I am restless and can't keep still
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(d) No, not at all

7 I get off to sleep easily without sleeping tablets
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(c) No, not at all

8 I feel anxious when I go out of the house on my own
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(c) No, not at all

9 I have lost interest in things
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(c) No, not at all

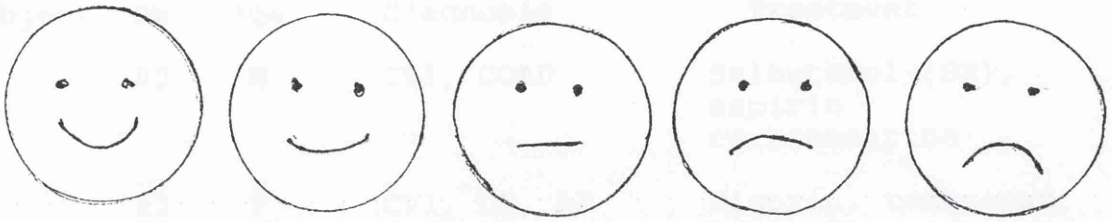
10 I get tired for no reason
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(c) No, not at all

11 I am more irritable than usual
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(c) No, not at all

12 I wake early and sleep badly for the rest of the night
(a) Yes, definitely
(b) Yes, sometimes
(c) No, not much
(c) No, not at all

APPENDIX 6 (Chapter 12)

THE "FACES" SCALE



A B C D E

1 Which of these faces best represents how you feel right now? .....

2 Which of these faces best represents how you feel most of the time? .....

Insert one letter for each answer

APPENDIX 7

Characteristics of elderly subjects with mild persistent hypomagnesaemia who participated in the study of oral magnesium treatment (Chapter 12)

Subject	Sex	Age	Diagnosis	Treatment
1	80	M	CVI, COAD	Salbutamol (SR), aspirin carbamezapine
2	93	F	CVI, CF, AF	Digoxin, temazepam bendrofluazide, lactulose
3	86	F	CF, AF	Digoxin, bendrofluazide
4	82	F	CF, AF	Digoxin, bumetanide
5	81	F	Hypertension	Bendrofluazide
6	73	F	Osteomalacia, malabsorption	1-alpha,OH,vit D ibuprofen
7	72	F	OA, PU	Cimetidine, paracetamol
8	95	F	CF, AF	Digoxin, bendroflazide
9	76	F	Hypertension NIDDM (diet)	Bendrofluazide, nifedipine
10	82	F	CF, CHO intolerance	Frusemide + potassium
11	89	F	CF	Frusemide + amiloride
12	73	F	OA, gastritis	Piroxicam, misoprostol
13	76	F	Hypertension NIDDM (diet)	Bendrofluazide, nifedipine
14	86	F	Hypothyroidism, hypertension	Thyroxine, bendrofluazide

APPENDIX 7 continued

Characteristics of elderly subjects with mild persistent hypomagnesaemia who participated in the study of oral magnesium treatment (Chapter 12)

Subject	Sex	Age	Diagnosis	Treatment
15	75	F	CVI	Aspirin
16	78	F	RA, PU	Ibuprofen, misoprostol
17	80	M	Crohn's disease CF	Frusemide, digoxin, nifedipine, prednisolone
18	86	F	CF	Bumetanide + potassium
19	70	M	CVI	Aspirin
20	78	F	CF, AF	Frusemide, digoxin potassium,
21	81	F	CF, AF CHO intolerance	Hydrochlorothiazide amiloride, digoxin
22	82	F	CF, AF, OA CHO intolerance	Digoxin, ibuprofen bendrofluazide,

Appendix 7 diagnostic key

CF = cardiac failure
CVI = cerebrovascular incident
AF = atrial fibrillation
PU = peptic ulceration
OA = osteoarthritis
RA = rheumatoid arthritis
NIDDM = non-insulin dependent diabetes mellitus
CHO = carbohydrate

PUBLICATIONS

The following is a chronological list of personal publications relating to some of the work described in this thesis

1. McConway MG, Martin BJ, Nugent M, Lennox IM, Glen ACA. Magnesium status in the elderly on hospital admission. J Clin Exp Gerontol 1981; 3: 367-79

2. Martin BJ, McGregor CW. Measurement of serum magnesium; effect of delay in separation from erythrocytes. Clin Chem 1986; 36: 564. (letter).

3. Martin BJ, Lennox IM, Ballantyne D. Electrocardiographic effects of magnesium replacement in the elderly. J Clin Exp Gerontol 1986; 7: 347-58

4. Martin BJ, Milligan K. Diuretic associated hypomagnesaemia in the elderly. Arch Int Med 1987; 147: 1768-71

5. Martin BJ, McAlpine JK, Devine BL. Hypomagnesaemia in elderly digitalised patients. Scot Med J 1988; 33: 273-4

6. Martin BJ. The magnesium load test: experience in elderly subjects. Aging 1990; 2: 291-96

7. Martin BJ, Black J, McLelland AS. Hypomagnesaemia in elderly hospital admissions: a study of clinical significance. Q J Med. 1991; 78: 177-84

8. Martin BJ, Lyon TDB, Fell GS. Comparison of inorganic elements from autopsy tissue of young and elderly subjects. J Trace Elem Electrolytes Health Dis 1991; 5: 203-11

9. Martin BJ, Lyon TDB, Walker W, Fell GS. Mononuclear blood cell magnesium in older subjects: evaluation of its use in clinical practice. Ann Clin Biochem 1993; 30: 23-7