

CHAPTER FOUR

# Macronutrients and Minerals

## MACRONUTRIENTS

### Fats

FAT IS A PART OF A FAMILY OF NUTRIENTS known as the lipid family, one of the most misunderstood areas of human nutrition. This list of some members of the lipid family is only a partial representation, but it helps us to appreciate the intriguing complexity of these nutrients, and it highlights the fascinating array of functions of fat in our bodies:

- hydrocarbons (saturated, unsaturated, cyclic, aromatic)
- specialised hydrocarbons (alcohols, aldehydes, fatty acids, amines)
- waxes
- fats and most oils (fatty acids attached to a sugar-derived molecule)
- glycerophospholipids
- sphingolipids (e.g. ceramide, sphingomyelin, gangliosides)
- steroids (sterols such as cholesterol, bile acids, cardiac glycosides, sex and adrenal hormones)
- other lipids (Vitamins A, D, E, K; eicosanoids, acyl CoA, acylcarnitine, lipopolysaccharides, ubiquinone).<sup>1</sup>

A no-fat diet would sooner or later prove fatal. It also can create health problems whose early symptoms may be subtle. When we talk about dietary fats, the three most important groups under discussion are fatty acids, fats and oils, and cholesterol. We will look at the first two here; cholesterol is discussed in Chapters 3 and 8.

## Fatty acids

Fatty acids are one of the main building blocks of most dietary fats. They consist of hydrocarbon chains, at the end of which is a molecule known as a carboxyl group. This latter has an affinity for water, and is therefore termed 'hydrophilic'. This is an important feature of a fatty acid.

Fatty acids come in three kinds: monounsaturated, polyunsaturated and saturated. The terms refer to the availability of carbons in the chain for binding to something else. This occurs wherever there is a double bond between carbons (Chapter 3). One of these bonds can be broken open, and the molecule can form different structures. Monounsaturates have one such double bond, polys have more than one, and saturated fats have none.

Monounsaturates are found in oils such as olive oil, and are believed to have considerable health benefits. Polyunsaturates provide us with the molecules known as the essential fatty acids. While not all polyunsaturates are 'essential', all essential fatty acids are polyunsaturated. These important molecules are discussed in more detail in Chapter 5. Saturated fats are those commonly found in animal fats.

## Fats and oils

Most of the fats in our diet come as fats or oils, complex molecules made up of various components. If we want to measure them in a blood test, we ask for a triglyceride level. A triglyceride consists of a glycerol molecule (derived from sugar), with three fatty acids attached to it. It is also known as a *triacylglycerol*. When we eat oil, cream, fatty meats or foods fried in fat, the fats that we are consuming are largely triglycerides. Numerous combinations of fatty acids, mono-, poly- and saturated, go to make up the end molecule, resulting in hundreds of different complex triglycerides.

If we consume an excess of protein or carbohydrate, the body will readily convert it to fat. Most carbohydrates, along with ingested fat, are stored in this form.<sup>2</sup> Indeed, in contrast to the popular notion that this is a pathological process, it is the normal mechanism by which the body handles its energy supply.

Immediately after a meal we derive much of our energy from the carbohydrates we have just consumed. But the actions of insulin, growth hormone and related factors ensure that within an hour or two of eating, food recently ingested is stored for later use. The liver and fat tissues are two of the main storage sites. Skeletal

muscle also plays a significant role in this storage process by removing glucose from the bloodstream and storing it as glycogen.

Glucose, and the other forms of sugar and carbohydrate, are readily converted to fat. Fat is the most efficient mechanism for storing energy, but liver and muscle glycogen are more readily available for use than fat.

So most intermediate and long-term energy is stored as fat. It is tempting, especially in view of the current obsession with body image and obesity, to regard fatty tissue as undesirable. We think of it as providing insulation at best, as inert and sluggish at worst. In fact, it is one of the most metabolically active organs in the body, with a constant turnover of its component parts. In diabetes, it is the inability to store glucose as fat, and convert fat back into energy, which is the key metabolic disturbance. Diabetes is a disorder of fat metabolism as much as a disorder of sugar metabolism.

## Proteins

As we saw in Chapter 3, the building block of a protein is an amino acid. This structure resembles the organic acids found in nature, but which are not derived from living matter. (A widely held theory is that, in a primeval soup of these carbon-based acids, some found each other and reacted in such a way that life on earth began.) When two amino acids combine, the result is called a peptide. Neurotransmitters such as dopamine and serotonin are peptides. When several peptides combine, the result is a polypeptide, and these link together to make proteins.

The desired end-product of amino acid is usually, although not always, the production of a protein. Proteins are usually large molecules. The proteins making up intestinal cells, muscle cells, ligaments or blood vessels are examples. The specialised form of protein known as an enzyme was discussed in Chapter 3. Hormones, immune globulins and red and white blood cells are also proteins.

Just to get some sense of proportion here, a 'small' protein contains about 50–100 amino acids. The upper limit of a protein size is of the order of 5000 amino acids. The protein discussed in Chapter 8: Cardiovascular Disease, apo-lipoprotein B, is about this size.

Of the hundreds of peptide/protein compounds found in nature, all are made up of the same basic 20 or so amino acids. One implication of this is that living things can feed on each other. The proteins in plants can be broken down to their

component amino acids by the animal which eats them. Those animals can then rearrange the amino acids into the molecules from which they make their own proteins. Likewise, carnivorous species can use the amino acids of other animals, to turn them into their own proteins. The inevitable similarity in proteins between species results in some curious and important medical conditions. These include food allergies and autoimmune disease.

The rearrangement of dietary amino acids to form new proteins is done under the guidance of genes. Indeed, directing this assembly line in protein manufacture is the main purpose of the gene.

## **Carbohydrates**

If proteins provide the components of the living organism, carbohydrates are the primary source of fuel that keeps it running. The glucose molecule is the principal material (substrate) used in the combustion process. Between consumption and combustion, carbohydrates may undergo several transformations, as described in Chapter 8: Obesity. The key point here is that the main purpose of carbohydrate is energy.

Much of that energy is produced through an enzyme-driven cycle known as the citric acid cycle or Krebs Cycle, which takes place in the mitochondria of cells. These are the little energy-producing units found in the cytoplasm of the cell (Chart 3.2). There is a production line known as the electron transport chain, which produces energy in a series of redox reactions. This production line depends on the energy provided by free radicals. Without the free radicals, life would cease. Free radicals demonstrate that 'good' and 'bad' are relative terms in biological systems.

Food produces energy by several other pathways, including the pentose phosphate pathway, which we need not go into. Not all carbohydrate is 'burnt'. Some of it used structurally in making compounds with such impressive sounding names as N-acetyl neuraminic acid, glycolipid, sphingoglycolipid and globoside. These substances can be found in tissues from brain to cartilage. The one most familiar to the public in recent years is glucosamine, an ingredient in cartilage.

## **Nucleic acids**

A protein sub-unit combined with a sugar molecule gives us a nucleic acid. So we could say that there are only three classes of biological compound, because a nucleic

acid is merely a combination of protein and carbohydrate.

It is because of the unique role that nucleic acids play in biological systems (they form the genetic material), that they are afforded a classification of their own. Nucleic acids were discussed in Chapter 3: Genetics.

## MINERALS

Minerals are essential to our health, indeed to our very existence. Calcium and magnesium were introduced in Chapter 1 because it would have been impossible to discuss agriculture without them. Imbalance between the two has important biochemical implications. Sodium and potassium also need to be in balance. But questions of balance are not the main reason that these minerals are well known. Like iron, they are well known because medical science has long been aware of their importance, and this has translated into dietary wisdom. This chapter gives a brief overview of minerals that are less well-known.

Trace and 'ultra-trace' minerals are present in tiny amounts. Although they were previously thought to serve no purpose in humans, they may play significant roles in health. This has become particularly relevant now that our food is grown with superphosphate, NPK and other such fertilisers. If the role of minerals such as germanium, vanadium, boron or molybdenum is unknown, then it is hard to assess the damage that may result from their absence.

Molybdenum is one such trace mineral. We have seen in Chapter 3: Genetics that it may be important in detoxifying certain chemicals. Most of what we know is found in textbooks of veterinary medicine and agricultural science. Germanium is another trace mineral. Most of the clinical studies on germanium have been done in rats, where organic compounds containing germanium have reportedly demonstrated anti-tumour activity. Could a lack of germanium in synthetic fertilisers contribute to the rising incidence of various cancers around the world? We simply don't know. An ingredient which might be vital goes unresearched because it cannot be patented.

About 90 elements naturally occur in the environment; most of them can be described as 'minerals', and 20 or so are known to be essential to human life. Some, such as lead and mercury, are regarded as toxic in any amount. Widespread

planetary pollution has led to the insidious concept of 'acceptable levels' of these substances (Chapter 6).

Most of the essential elements—sodium, iron, calcium and zinc—are toxic in overdose, but at normal exposure they rarely pose a risk. The body has mechanisms to combat excess, such as vomiting to counter sodium (salt) overload, or purging to counter magnesium overload.

Some elements are widely distributed in the body fluids in what is known as the *ionised state*. This means that they have parted company with one or more of the electrons in their outer shell, or have gained some extras (Chapter 3). They are then usually referred to as *electrolytes*. The principal electrolytes are sodium ( $\text{Na}^+$ ), chloride ( $\text{Cl}^-$ ) and potassium ( $\text{K}^+$ ): the pluses and minuses indicate their ionisation. They are found in the blood, the lymph, the cerebrospinal fluid, and the extra and intracellular fluid of every cell in the body.

Elements such as magnesium, zinc and fluoride are often ionised in bodily fluids and can therefore be rightly regarded as electrolytes. Not all of them are serving a specific electrolytic function; some are simply in transit to somewhere else. Some, such as calcium and magnesium, are an important part of the electrolyte balance and serve multiple functions elsewhere.

Minerals and trace minerals play various roles in the body:

- Minerals form the structural part of solid components like bone.
- Minerals can be found floating in fluid, where they maintain osmotic balance and electrical gradients. (In this context the word 'osmotic' simply refers to the density of electrolytes in the solution.)
- Minerals form the structural part of organic compounds. For instance iodine is part of tri-iodothyronine (thyroid hormone), and iron forms the heme part of the haemoglobin molecule.
- Some minerals act as messengers in one of the body's fluid systems. This is often referred to as 'signalling' or as a 'second messenger system'. The role of calcium and magnesium in this regard will be discussed shortly.
- Minerals can form part of an enzyme or other highly complex protein. They play various roles which can be classified as structural, catalytic or regulatory. The most important elements in this regard are the transition elements (Chapter 3).

The importance of some minerals is well known. Calcium is the most abundant element in the body; we can read about it on the labels of everything from baby food to breakfast cereal, milk to mineral water. Iron, by contrast is present in relatively small quantities. However, because it is so easily measured in the blood, it is also well known. Some soils and some food processing methods are associated with markedly low levels of iodine, and the resulting deficiency can cause spectacular goitres or the congenital condition of cretinism. So iodine, too, has achieved deserved attention.

Doctors learned about these nutrients in medical school. But what of the rest? The assumption is that a normal diet will provide the basic requirements. The measurement of minerals has not been given a high priority in human medicine.

Hospital and standard laboratories can determine the level of various minerals in the blood—whether in whole blood or in serum, plasma or red cells. This is a reasonable approach for, say, iron, because blood is one of the main repositories of iron. But to assess magnesium status, a more representative measure would come from a biopsy of muscle or bone. For obvious reasons, this test is rarely performed.

What makes blood values even more unrepresentative is this: blood is an important buffer solution. Because it is critical to maintain a finely tuned electrolyte balance in the blood, the body will do everything it can to maintain the homeostasis (the medical term for status quo) of the blood. It will leach every last bit of calcium and magnesium out of the bones to maintain serum levels if it has to.

Nowhere is this better illustrated than in the condition of hyperparathyroidism, when an excess of parathormone results in bones demineralising. Severe osteoporosis develops as precious calcium and magnesium are lost in the urine. Meanwhile blood levels remain normal, or even high. Sometimes it takes a pathological fracture or a kidney stone to alert the physician to the fact that this patient's bones are literally melting away.

Zinc is another mineral whose status cannot readily be assessed from blood levels. Asked how best to assess zinc status, a pathologist replied that the only truly accurate method was to weigh the patient, incinerate them, and then sift through the ashes to extract the zinc and weigh it. He added that he had never had a volunteer for this test. The next most accurate method was a biopsy of the retina or gonads (testicles or ovaries), but volunteers were in short supply there as well. The next preference was for a well-done mineral analysis of hair or toenail

clippings. Least reliable were blood and serum levels, which were useful only for the extremes of toxicity and deficiency.

Ease of measurement should not determine the emphasis we place on a mineral. Cynics have observed that certain brands of dog food list up to 40 different vitamins and minerals on their labels, but that baby food has less than a dozen.

## Zinc

As my interest in nutritional medicine began with zinc, I will start this part of the mineral story with an account of that experience.

After 10 years of hospital and family practice in Australia, I found myself working as a GP in a busy London clinic under the National Health Service in the mid-1980s. It was Thatcher's England, and it seemed that what had been the best health service in the world had disintegrated through lack of funding. Patients who, in Australia, I would have admitted to hospital, had to be managed in their homes for lack of hospital beds.

Particularly worrying were depressed patients. In the underprivileged area where I worked, services for these people were strained to breaking point. In those days the only medications available were the tricyclic anti-depressants, or MAO inhibitors. Both of these are dangerous in overdose, and the risk of patients using them to suicide is high. In an area of mostly single-parent families and widespread unemployment, the addition of depression made for a lethal mix.

The patient who started me on the nutrition odyssey was a young mother with a new baby. She had a past history of post-natal depression and was showing all the signs of a severe recurrence. I had been reading a book on zinc deficiency by Prof. Derek Bryce-Smith,<sup>3</sup> and decided to give some zinc to this patient. It was a normal commercial product which also contained a bit of magnesium and some Vitamin B6. Within a week the patient was transformed. She greeted me with a smile at the door, cradling the baby in obvious affection. By contrast to her earlier complaint that the baby never stopped crying, both were sleeping well and breastfeeding had become established.

Being cynical about miracle cures, I began to doubt the original diagnosis, but the other doctor and the social worker involved in her care confirmed it and noted the remarkable change. I had to accept that it might have been the supplement which had made the difference.

The book by Bryce-Smith is now almost 20 years old, and unfortunately out of print. The ideas it contains are only now starting to creep into mainstream medicine. The author's background was in chemistry, not in medicine. In discussing veterinary practice in Chapter 1, I compared the entries for zinc deficiency in a textbook of medicine and textbook of veterinary medicine, noting that *Harrison's Principles of Internal Medicine* listed only four zinc-deficiency disorders.

By contrast, Bryce-Smith made a cogent case that zinc deficiency is widespread and common, with multiple possible manifestations including depression. He argued that agricultural change, the use of chemical fertilisers such as NPK, and the modern refining of grains and cereals were at the heart of the problem. If the food is depleted, does this explain serious medical conditions? What evidence do we have? Although one patient of mine appeared to have a good response to zinc, we cannot generalise from that.

Unfortunately, proof in this situation is harder to provide than when testing a drug. We know that laboratory rats fed on refined flours do not survive; they must be given whole grains and soy beans if they are to remain healthy. What are the missing ingredients? Vitamins? Minerals? Essential fatty acids? Zinc?

It is probably all of these, and to isolate the contribution of zinc, while not impossible, can be difficult. Level 1 evidence (Chapter 2) is hard to produce. Instead of applying the RCT model to the investigation, we might take the approach of looking at the known roles of zinc, asking how a deficiency might manifest itself, and whether we can test this clinically. But research into the role of minerals is much less popular than research into drugs. The difficulties, and successes, in answering these questions may be seen in the following account.

In his book, Bryce-Smith made the biochemical case for the role of zinc deficiency in conditions as wide-ranging as depression, anorexia nervosa, acne and benign prostatic hypertrophy. Traditional treatments of those conditions, then as now, were either invasive or ineffective. I felt I had little to lose by offering zinc to my patients as an alternative or an adjunct. One patient, a postman with a large prostate, had found urinary frequency to be such a problem that he'd befriended several elderly people on his route who were always at home and happy for him to use their toilet. After a few weeks on zinc he found he had no further need for this service, only to be met by a dear old soul waiting for him. 'I thought you must have died or something,' she said, distressed that he no longer made his daily visit.

Inspired by this and other happy stories, and with good feedback from some of the specialists who shared the care of these patients, I sought a grant in 1989 from the Royal College of General Practitioners to research the role of zinc in several conditions, citing Bryce-Smith's work on anorexia. Its response was dismissive:

an eminent psychiatrist [unnamed] ... knows of no significant current research work on the role of zinc in [anorexia] ... There does not appear to be good scientific evidence for this role for zinc in this disease and most psychiatrists at present reject this theory. Illnesses such as post-partem depression, anorexia nervosa and bulimia are uncommon in general practice.

I sent the college some well-referenced studies of both humans and animals, supplied by Bryce-Smith, showing an association between zinc deficiency and mood, but there was no further correspondence.

Musing on what might be the medical term for 'closed-mind syndrome', Bryce-Smith also pointed out that, at the time of writing, the *British National Formulary*—then, as now, the college's gold standard of prescription—contained an entry that refuted one of the college's objections: it described a taste test as the most reliable test of zinc deficiency. The zinc taste test consists of giving someone a very weak solution of zinc salts to drink. The expectation is that, if the person has adequate body levels of zinc, the drink will have an unpleasant metallic taste to it. If they are depleted, the drink has no flavour and will be consumed as if it were a glass of water. This can be seen as an 'unscientific' test, and yet it is the principle used by farmers for salt licks. It is probably also the basis of animals' self-medication, discussed in Chapters 1 and 10.

This episode shows that failure to research an idea does not necessarily imply that it lacks merit. For a drug company, research needs to make money; for an academic institution, limited funds need to be well spent. Thus it is hard to get funding for research in an area which is not already being researched. The premise is that 'if this idea were any good, everyone would be researching it'.

## The chemistry

Zinc is an important part of various metallo-enzymes (Chapter 3). There are more than 200 zinc-containing metallo-enzymes throughout the animal world, and many of them operate in humans.

Zinc enzymes are involved in virtually all the major metabolic pathways. This includes the replication, repair, transcription and translation of genes, and also the metabolism of proteins, lipids, carbohydrates and certain neurotransmitters. Zinc enzymes are the rate-limiting factor in protein biosynthesis (the manufacture of proteins, guided by genes, from their component amino acids), and have a role in the production of certain hormones such as insulin and testosterone.

To get some idea of the importance of zinc, let us look at protein metabolism. The zinc enzymes involved have names such as collagenase, alkaline phosphatase and gelatinase, and they take part in such vital processes as ovulation, blastocyst implantation, embryogenesis, mammary development, bone remodelling, angiogenesis and macrophage function. In simple terms this means fertility, wound healing, bone and joint health and immunity. Other protein-related zinc enzymes include aminopeptidase, carboxypeptidase A and B, and neutral protease. These are involved in the digestion of protein, and in all cases, the role of zinc is to catalyse, or speed up the reaction.

The *pathological* processes in which these zinc-containing enzymes exert a regulatory role include cancer invasion and spread, liver cirrhosis, gastric ulcer, cardiomyopathy, atherosclerosis and lung fibrosis.

Zinc is also important for the structural integrity of the DNA molecule. Researchers commented that by this means, zinc deficiency could contribute to problems as serious as cancer.<sup>4</sup>

Zinc has a role in redox enzymes called the superoxide dismutases, which are among the most important antioxidant systems in the body. They are an essential part of the mechanism by which we fight cancer, cardiovascular disease, arthritis, and all the diseases of ageing. Zinc's essential role in the enzyme alcohol dehydrogenase was discussed in Chapter 3: Genetics. Without this enzyme even a glass of wine would be toxic to us.<sup>5</sup> Zinc enzymes are also involved in the metabolism of Vitamin A, and its release from liver stores, the metabolism of essential fatty acids and the control of the storage and release of the stress hormones.

It would be wrong to imply that *only* zinc deficiency will account for the aberrations which can occur in any of these processes, but even a minor deficiency has the potential to disrupt their function, and so compromise the health of the individual.

As well as forming a part of vital enzymes, zinc has been demonstrated to

combat viruses. Zinc ions disrupt the process by which viral invaders usually reproduce. For a long time it had been suspected that zinc inhibited the replication of rhinoviruses, the causative agents in the common cold. Since then it has been demonstrated that zinc ions behave in a similar manner, known as protease inhibition, against the viruses responsible for polio, foot-and-mouth disease, encephalomyocarditis, herpes simplex and herpes zoster, and human Coxsackie disease.<sup>6</sup> Of course, it would be inappropriate to use zinc as the only therapeutic agent against these viruses. But in Western medicine it is not used at all for treatment, and only rarely for prevention.

Zinc is somehow involved in taste sensitivity and appetite regulation. Rats in an experimental situation fed a diet devoid of zinc kept eating until they became morbidly obese. It was as if their brains knew there was an essential element missing and told them to keep eating until they got it. Farm animals which are known to lack zinc become listless and depressed and *lose* their appetite. In contrast, malnourished Aboriginal children regained their appetite when given zinc supplements (Chapter 8).<sup>7</sup> With the current epidemics of eating disorders and morbid obesity, research into the lack of zinc in the modern diet would seem promising.

Oysters and shellfish, red and organ meats, nuts, whole grains and legumes are good sources of zinc, especially when produced from zinc-replete environments. The reference daily intake (RDI) of zinc in the United States is about 15 mg a day.

## Calcium and phosphorus

I will not devote much space to these minerals because there is little need to stress their importance. For both of them the key roles include the function of cell membranes, the maintenance of electrolyte balance within the cell, the structural integrity of bone, and the modifying effects on hormone balance, often referred to as the 'second messenger system'. The importance of calcium for teeth needs no emphasis.

One of the defining characteristics of calcium is the readiness with which it gives up two electrons from its outer shell. This enables it to bind easily to phosphate to form hydroxyapatite—the scaffolding on which bone is built. It binds equally well to lipids and proteins within membranes, and thus has a deciding

role in the passage of other ions through the membrane. Permeability to these ions gives rise to the concept of 'ion channels' within the membrane. Ions affected include sodium, potassium, magnesium and calcium itself.

Detailed discussion of ion channels is beyond the scope of this book, but they have health implications as wide-ranging as hormonal dysfunction, hypertension, renal failure, leaky gut, and many other metabolic disorders. Some readers will be familiar with ion channels through the prescription of 'calcium channel blockers' in the treatment of hypertension, angina, and certain cardiac arrhythmias.

The biochemistry of 'second messenger systems' is complex, but it comes down to this. Many hormones and neurotransmitters use an enzyme system to interface between the messenger molecule (the hormone etc.) and its receptor site. Calcium and magnesium often act as the go-between, 'deciding' which messages will be allowed to activate these enzymes—hence 'second messenger'.

Phosphorus in biological systems is present in the form of phosphate and is involved in a variety of biochemical reactions. Magnesium and calcium in particular have a special relationship with phosphate. As part of ATP (adenosine triphosphate) it plays a major role in energy production. The function of many enzymes depends on the presence of phosphate, including, of course, the family of enzymes known as the 'phosphatases'. It has structural roles in tissues ranging from bone through to DNA and RNA molecules.

Control of calcium and phosphate levels is vital. It is effected through various means including the kidneys, the action of the hormones calcitonin and parathyroid hormone (PTH), and Vitamin D.

Food sources of calcium include milk, tofu, sardines, nuts and green vegetables. Phosphorus can be obtained from meat, milk, eggs and cereals.

## **Magnesium**

In clinical practice, magnesium is one of the most useful of all the prescribed mineral supplements. Magnesium is the second-most common mineral in the animal body (calcium being the commonest). It is the fifth-most important element for green plants, and one of the most abundant elements in the earth's crust. It is not surprising that animal systems have developed with a need for it. Evolution would not have got very far if biological systems required things that were in short supply.

Indeed, it is probably the abundance of magnesium which has resulted in its clinical neglect. Most people know that they need calcium for their bones, but few are aware of a similar need for magnesium. About 70 per cent of all our magnesium is in our bones. Although the actual mass of calcium in bone is much greater both in relative and absolute terms (99 per cent of our calcium is in bone), it is function rather than absolute amount which matters. Even doctors don't understand it, as we can see from the number of patients treated for osteoporosis with calcium alone. This practice is not only ineffective: it is actually counter-productive.

### The relationship of calcium to magnesium

It is difficult to discuss magnesium without discussing calcium, because their atomic structures are very similar. In the body they often have similar functions and are handled similarly. Both are transported from the gut into the bloodstream, and from the extra-cellular fluid into the cell, by similar mechanisms. They have a highly interactive relationship.

The clinical importance of this is that the body works constantly to maintain a balance between these two minerals. Anything which disturbs that balance will affect our health. In the plant as well as the animal world the balance is generally maintained. In a broad-based omnivorous diet, the human organism can expect to get both an adequate amount *and* an appropriate balance of these minerals. Problems arise when either or both minerals are deficient, or when there is an imbalance.

In the developed world, calcium deficiency is less common than magnesium deficiency. One of the main reasons for this is that superphosphate, a key fertiliser, is made up largely of calcium phosphate. Right there at the beginning of the food chain, while the need for calcium is addressed, magnesium deficiency is not.

There is another problem: acid soils can reduce magnesium uptake by plants. So magnesium deficiency can result from eating good food grown in acid soils and in soils fertilised by superphosphate. It can also be caused by a high-calcium diet with lots of dairy foods, or by unbalanced supplementation. If the calcium intake far exceeds magnesium, the calcium can 'swamp' the magnesium. (For more on the contribution of dairy to the disruption of calcium and magnesium ratio, see Chapter 10: Funny Diets.)

## The chemistry

There are an estimated 300 roles for magnesium. Unlike zinc, it is not part of a metallo-enzyme. Its actions are far more diverse.

The biochemical functions of magnesium include:

- regulating cellular energy metabolism with particular importance in cardiac and skeletal muscle
- optimising the actions of the enzyme systems responsible for the transcription, translation and replication of nucleic acids (RNA, DNA), and the synthesis of protein
- participating in the second messenger system, the means by which various hormones and neurotransmitters 'talk' to their target organ
- controlling various ion channels, including that of potassium and calcium.

Clinically, its most important functions are:

- lowering blood pressure and maintaining normal cardiac rhythm (via its action on ion channels)
- forming an integral part of bone
- relaxing smooth and skeletal muscle
- forming part of the energy system in skeletal and cardiac muscles
- continuously repairing all body proteins.

As with zinc, assessment of body status is not easy. More than 99 per cent of all body magnesium is either in the skeleton or is held inside cells.

Gross magnesium deficiency is not difficult to identify. The level in both serum and the red cell levels will be abnormal, and the patient will be in a state of agitation and tetany, have muscle tremors and cramps, and may well be having fits. If they are really unlucky, they may have a cardiac arrhythmia and even a cardiac arrest. These patients will not be sitting in my waiting room — they will be in an ambulance or dead on the floor at home. But it is the much more subtle states which are the concern of this book. How might we identify them? Is it you or me?

## Some effects of lack of magnesium

Some of the most common medical problems involve the malfunction of smooth muscle: asthma and migraine, painful periods (dysmenorrhoea), irritable bowel

syndrome and high blood pressure. Of course, all these conditions involve other factors as well, but magnesium deficiency is easy to fix.

The muscles in the gut are smooth muscles. The uterus is a smooth muscle. And the tiny muscles circling the arteries and airways, controlling their diameter, are also smooth muscles. If these muscles for any reason have difficulty in relaxing, they may go into spasm.

A muscle essentially has two states: one is resting or relaxed, and the other is contracted. Prolonged contraction amounts to spasm. When the muscles in the uterus spasm, the patient will experience cramps or, if she is giving birth, a prolonged and difficult labour. If the circular muscles of the gut are constantly in spasm, the patient will experience cramps and constipation, and will pass hard, segmented stools. If spasm of the longitudinal muscles of the gut predominates, the patient is more likely to experience intestinal hurry and diarrhoea. Patients with irritable bowel syndrome often experience both constipation and diarrhoea, and both are helped by magnesium.

Asthma involves an inflammatory response which includes spasm of the bronchioles. The ability of the bronchioles to relax is determined by several factors (Chapter 7), one of which is magnesium status. If you are low in magnesium and have asthma genes, inhalation of an irritant may precipitate an asthma attack. When I inhale a lungful of dust or pollen, my airways contract. Thus they can limit the amount of irritant entering my lungs, and at the same time, build up pressure so that I can cough and expel the foreign matter. When those airways cannot relax, coughing and wheezing become pathological and an asthma attack ensues.

A 1994 study which looked at a random sample of 2633 adults successfully tested the hypothesis that high dietary magnesium intake is associated with better lung function and reduced airway hyper-reactivity.<sup>8</sup> The results were highly significant. At doses above 400 mg the benefit on lung function levelled out, but hyper-reactivity continued to improve as the dose went up. They also showed that consuming just one standard deviation (about 68 per cent) below the mean of dietary magnesium was the equivalent—in terms of lung expiratory volume, risk of wheezing and lung hyper-reactivity—to 12 pack years of smoking. (A pack year is one packet of cigarettes a day for 12 years, or two packets a day for six years and so on.) Yet despite the rising epidemic of asthma, we do not find magnesium in the prescriptions for asthmatics.

Similar principles operate in regard to the smooth muscles which surround the arteries and control their diameter. A deficiency of magnesium, either in absolute terms or relative to the calcium load, favours the development of hypertension. Of course, other factors operate, but magnesium status is at least as significant as any of those. Various studies support the role of magnesium supplementation in helping to lower blood pressure.

In 1996 a well-conducted double-blind study showed that chronic migraineurs supplemented with 400 mg daily of elemental magnesium showed a decrease of about 50 per cent in both the frequency and severity of their headaches (Chapter 9).<sup>9</sup> At the beginning of a migraine the scalp arteries contract, causing the sense of tightness across the head so often reported by patients. This vasoconstriction often takes place elsewhere as well—in the brain where it causes visual disturbance and even stroke, and in the gut where it causes cramps. Although such vasoconstriction is triggered by a series of biochemical events, it is easy to understand how low levels of magnesium may prolong the headache or increase its severity.

So far we have been considering the role of magnesium and its effects on smooth muscle, but it should be reiterated that with skeletal muscle, leg cramps and generalised muscle pains can be a sign of magnesium deficiency. Cardiac problems, such as cardiac arrhythmia, will be discussed in Chapter 8.

I have mentioned magnesium's role as a 'second messenger'—a mediator—in various hormonal and neurotransmitter systems. This may be one of the ways in which muscle relaxation, just discussed, is effected. We know that there are receptors throughout the body, including the gut and blood vessels, for hormones and neurotransmitters like serotonin and oestrogen. The levels of, and balance between, calcium and magnesium can determine which messages get through. No matter how much oestrogen, serotonin or dopamine we produce, if those chemical messengers can't activate an oestrogen-receptor site or the appropriate nerve cell, they might just as well not be produced at all. The ramifications of this are significant. Magnesium is vital to both the production and the mediation of such chemical transmitters.

Magnesium has a modifying role on serotonin and nitric oxide levels, and in the production of dopamine. These various chemical messengers are involved both in the spasm of smooth muscle which causes the pain of migraine and period pains, and in the cerebral appreciation of that pain. A deficiency of magnesium therefore, can exaggerate not only the factors producing pain, but also the awareness of it.

Stress hormones are neurochemicals which include catecholamines, such as adrenalin, and corticosteroids. The evolutionary purpose of these hormones is to raise blood pressure, release glucose and fatty acids into the bloodstream, and prepare us for flight or fight. This is still sometimes a necessary response in today's world, as when a car runs the red light just when we step off the kerb, but it is often evoked by mental stressors not requiring a physical response. And that, of course, contributes to the whole spectrum of ills known to be stress-related.

The high blood pressure, the coronary and cerebrovascular constriction, and the increased heart rate are fine as a transitory phenomenon; but when they become sustained or are invoked inappropriately, they become a health risk. A low ratio of magnesium to calcium favours the release of catecholamines, as well as the release and formation of factors that lead to further vasoconstriction and platelet aggregation. A low ratio of magnesium to calcium also favours blood coagulation—a lethal addition.

### The patient: Mary

We met Mary in my waiting room in Chapter 1. If we were for the moment to forget that such terms as asthma, dysmenorrhoea and depression had ever been coined, and if human medicine as a discipline had evolved with some of the biochemical understanding now available to us, how might I see a patient like Mary? Just as we might list the problems that go with a diagnosis of scurvy, could she be a 'classic case' of magnesium deficiency? After all, magnesium has roles in asthma, migraine, menstrual cramping, irritable bowel, energy metabolism, mood disorders.

Is it simplistic to say that all of Mary's problems could be solved by the addition of magnesium? Perhaps. But look at some of the other factors.

A US survey found that dietary *intake* of magnesium had fallen below the recommended dietary allowance (RDA) or reference daily intake (RDI) in up to 75 per cent of people (see Appendix 1). Mary is on an average diet; what are her chances of being in that 75 per cent? And independently of her intake, what about her *absorption*? She drinks milk, eats cheese and likes yoghurt. Is this calcium load subtracting from her magnesium status?

Alcohol, the oral contraceptive pill, and some other prescription medications all cause the body to lose magnesium. Mary is on the pill. She drinks alcohol, although not in excess. As for her prescription medications, in some cases the

effects on magnesium status of these have not even been quantified.

If Mary wants to correct a magnesium problem with diet alone, she will need to eat such foods as unpolished grains, nuts, legumes, sea vegetables, citrus fruits, green leafy vegetables and the brassicas (cabbage family). But if these foods are not grown in organic or biodynamic soils, they may not contain adequate levels of magnesium. And although Mary likes all of these foods, do they form a significant part of her average diet?

High levels of magnesium dissolve in hot water and can be absorbed gently through the skin. In a bygone era, Mary would have been told to have a sitz bath or go to a hot spring. It would have worked. Grandma fixed a lot of problems with a judicious dose of Epsom salts. Epsom salts are magnesium sulphate; they were named for the town of Epsom in England, where a natural hot spring was noted for its curative benefits. But for oral administration commercial preparations of magnesium are best: Epsom salts can overdo it, causing an osmotic diarrhoea.

As I look around at the other patients, I see Louise who gets migraine; Sonya who would like a good delivery and wants to avoid post-natal depression; and Mrs Green who wants a smooth transit through menopause. Their stories will be introduced elsewhere in this book, but I am confident that each of them should be taking supplementary magnesium.

The RDA of magnesium is about 400 mg for males and 300 mg for females. As a supplement, it is best absorbed as an amino acid chelate such as magnesium aspartate or orotate. The cheaper preparations containing magnesium oxide and magnesium sulphate are much less suitable.

## Selenium

In December 1996 the results of a clinical trial on the effects of selenium should have made headline news around the world, but it barely rated a mention.<sup>10</sup> The trial was unusual in several ways. First, it was being carried out on a natural element rather than a drug. Second, its results were so significant that it gained publication, even though the effect it sought to demonstrate was not present. Third, the results of the treatment were so beneficial that, by internationally agreed ethical standards, the trial had to be stopped prematurely so that the treatment could be offered to the control group. Fourth, medical indifference to a non-drug treatment of one of the most feared diseases of the modern day reached, I suspect, an unprecedented level.

Some outcomes of this trial are discussed in Chapter 7: Cancer, but the main points are these. A group of 1312 individuals with a history of non-melanoma skin cancer were randomised to receive either a placebo or 200 mcg daily of selenium. The aim was to see whether selenium reduced the incidence of non-melanoma skin cancer. It did not. But those receiving selenium experienced 63 per cent fewer cancers of the prostate, 58 per cent fewer cancers of the colon, and 46 per cent fewer cancers of the lung. Of those who were diagnosed with cancer while taking part in the trial, those taking selenium were 50 per cent less likely to die of their cancer than the control group. *There is no known drug treatment with statistics as good as this.* By almost all measures selenium is the ideal anti-cancer drug.

There were too few women in the trial for any statistically significant data on breast cancer incidence to emerge. Another trial is exploring that question. The same researchers are also investigating the effects of selenium in the deadly problem of ovarian cancer, and have shown beneficial results in women who combine selenium with their standard treatment.

The original trial had been designed to run for ten years, but it was stopped after five. Cancer is generally agreed to have a long incubation period. As such, it has always been assumed that preventative measures could not show benefit in such a short period.

Soon after the selenium trial had been reported, Margaret Rayman, a research fellow in the Department of Chemistry at the University of Surrey in England, pointed out that soil selenium levels were falling dramatically, and there was a parallel drop in both dietary intake and blood levels.<sup>11</sup> She quoted a 1994 report by the British Ministry of Agriculture and Fisheries which showed a drop in average daily intake to 34 mcg from an average of 60 mcg a day in the mid-1970s.

Once again, it is instructive to look at the medical bible. In 1991, the 12th edition of *Harrison's Principles of Internal Medicine* listed five entries on selenium but no clinical conditions as such associated with selenium depletion.<sup>12</sup> By the time the 15th edition was published in 2001, selenium entries had leapt to 11.

### The story unfolds

Selenium was first discovered in 1817 by a Swedish chemist, Berzelius, who gave it the Greek name for the moon. In 1943 it was noted in *mass* doses to cause neoplasia (growth, usually malignant) in the liver of rats, thus identifying it as a potential

carcinogen. In the mid-1950s it was identified as an essential trace element in rats, and by the 1970s evidence was beginning to emerge that it had anti-cancer properties in mammalian systems. Twenty years after it had been shown to be essential for rats and chickens, the first clear evidence was found that it was also essential in humans.

Then in 1979, a New Zealand patient was undergoing total parenteral nutrition — where no food is taken by mouth and life is maintained by what can be fed through a vein. During the course of this treatment he developed cardiomyopathy, a condition in which the heart muscles become weak and flabby. The patient had come from an area in New Zealand which, like many parts of Australia, had some of the world's lowest levels of soil selenium. His doctors thought that they had little to lose by treating their patient as if he had a selenium-deficient cardiomyopathy. His rapid recovery was taken as confirmation of their suspicions.<sup>13</sup>

At about the same time, conclusions were being drawn about an epidemic of childhood cardiomyopathy observed over the previous decade in one part of China. The area was Keshan, which gave its name to the disease. (It, too, was an area known to have low soil levels of selenium.) The condition, it was noted, had similarities to the cardiomyopathy seen in selenium-deficient pigs and mice. A study involving just over 46,000 children was begun. The trial had to be abandoned two years prematurely, because the death rate in the control group was 5.6 children per thousand, compared with 0.08 in the selenium-supplemented group.

Although most patients recovered from Keshan disease on selenium supplements, a few did not. A simple deficiency state should have given close to 100 per cent recovery rate. It was suspected that a virus might also be involved, and what was finally uncovered demonstrates both the complexity and awesome simplicity possible when medical management is based on cause and effect.

By the mid-1990s some researchers from the University of North Carolina were studying the Cocksackie family of viruses, now known to be the mystery virus in Keshan disease. They found that a benign form of the virus could mutate into a virulent form in the heart tissue of mice whose diets lacked selenium. Mice that were given selenium did not become sick, because the selenium not only boosted their immune systems but also prevented the development of a resistant strain in the virus.<sup>14</sup>

This was a new way of looking at host resistance to disease. Traditionally the thinking had been that a virus, bacterium or parasite of fixed virulence invades the host and, depending on the host's ability to mount an appropriate response, it kills or is killed. (Or at least the virus is suppressed, as with chickenpox virus, which re-emerges as shingles only when the host's resistance is seriously compromised.) It was novel to think that the invader might take advantage of a run-down host which can ward off only the weaker germs. The implications embrace not only chronic viral illness such as HIV and herpes, but the actual development of epidemics.

Most of the virulent new strains of influenza sweeping the world seem to originate in China. Could endemic selenium depletion be part of the reason for this? One report of this research certainly raised the possibility. HIV is thought to have originated in northern Zaire, where many people have low blood levels of selenium: could HIV have begun in a similar manner?<sup>15</sup>

## The chemistry

The clinical manifestations of selenium deficiency are protean, and its metabolism in the body is still incompletely understood. Is absorbed highly efficiently from the gut, and a constant level is maintained largely through urinary loss. Most selenium in the body appears as seleno-cysteine in protein complexes known as seleno-proteins. These seleno-proteins are widely distributed; and most, if not all, are enzymes.

The most common way for us to ingest selenium is when it is bound to an amino acid called methionine. Its origin lies in plant foods, or in animals which have eaten those plants. By a series of biochemical reactions seleno-methionine is converted to seleno-cysteine. This selenium-containing amino acid is present in both prokaryotes and eukaryotes (primitive cell lines or micro-organisms). This indicates the ancient origin of the amino acid,<sup>16</sup> and perhaps hints at its importance. Certainly the synthesis of the seleno-proteins is as complex as any in biology, requiring, among other things, a unique RNA gene product.

In all, eleven mammalian seleno-proteins have been identified. They include:

- *The glutathione peroxidases*: These vital enzymes protect cells and tissues — that is, they quench free radicals. They occur in the plasma and

every cell of all animals. Stipanuk suggests that one of these enzymes may have evolved specifically to maintain milk selenium levels rather than, as has previously been assumed, to prevent the peroxidation of milk.<sup>17</sup> (Lipid peroxidation is a serious consequence of uncontrolled free radical attack on unsaturated fats. When it occurs in cell membranes, a chain reaction can lead to mass destruction of cells. The best defence against it is Vitamin E.)

- *The deiodinases*: For 20-odd years we have known that these enzymes convert inactive forms of thyroid hormone into the active forms. It is possible that the reverse may also be true, and that selenium deficiency can cause thyroid deficiency and may also contribute to thyrotoxicosis (thyroid excess).
- *The muscle and plasma seleno-proteins*: These are not yet fully understood, although depletion of the former is associated with white muscle disease in sheep. It is possible that cramps which do not respond to normal treatment, and the muscle weakness and excess tiredness seen in chronic fatigue syndrome, could be related to selenium depletion.

It is estimated that up to 50 more seleno-proteins await delineation in higher animals. In selenium deficiency the body gives priority to glutathione peroxidase and the seleno-enzymes in the brain, the endocrine glands and the reproductive organs.

### The recommended daily allowance

Calculations of the RDI are based on the amount of selenium it takes for all glutathione peroxidase in the plasma to be replete. This is referred to as 'saturation'. The amount of selenium required to saturate glutathione activity, while satisfying the enzymatic or anti-oxidant role of selenium, appears to be *below* the levels needed to optimise the immune response and reduce cancer risk.<sup>18</sup> The implication is that RDIs may be set too low. Similarly, the amount of Vitamin C required to prevent scurvy is almost certainly not the same as the amount required to *optimise* health.

There is as yet no internationally agreed RDI for selenium (see Appendix 1). The current British value is 75 mcg for men and 60 mcg for women; the American level is 55 mcg. If saturation of glutathione activity in platelets rather than plasma

