Chapter 5

Delivery of Trace Elements to Humans

Normally, the human body receives the trace elements it needs through the diet. However, whenever, either through famine, food preferences, ageing, or disease, the quality and/or quantity of the food intake decreases to such a point that the diet can no longer meet the body's requirements, we need to consider ways of making good the trace element deficiencies. The increasing longevity of the populations in many countries, which is one of the achievements of modern chemistry and medicine, frequently leads to overt or sub-clinical deficiencies of one or more trace elements, which need to be addressed if the afflicted person is to enjoy the best possible standard of health.

The present day predilection for 'convenience' foods is making trace element deficiency a problem in industrialized societies, especially in the elderly. For example in Japan the recommended daily intake of calcium is 600 mg but surveys show that the average daily intake is only 540 mg. Most Japanese also hover on the edge of anaemia, suggesting that the daily intake of iron may also be inadequate. In addition, natural physiological events such as pregnancy pose an increased requirement for minerals that may not always be fully met from even the most sensible, normal diet; therefore, supplementation with iron and calcium may be necessary or at least desirable. The importance of a good, sensible diet which offers an adequate, but not excessive, intake of all necessary nutrients, including minerals, cannot be stressed too strongly. However, individual tastes, and financial and social pressures, often may make this ideal difficult to achieve; thus the question of the best ways in which to provide mineral supplements for the body becomes very important.

MEANS OF MINERAL SUPPLEMENTATION

There are two main ways by which substances may be administered to humans: the *enteral* and the *parenteral* routes. For enteral administration the substance is placed directly into the gastrointestinal tract by permitting a tablet to dissolve when it is placed under the tongue (sub-lingual administration), or by swallowing a tablet, capsule or a solution (oral) or by rectal administration as a suppository. In parenteral administration the substance in solution may be injected subcutaneously, intramuscularly or intravascularly, inhaled as an aerosol, applied topically to the skin as a cream or ointment, or, rarely, in the form of a pessary.

In mineral supplementation in humans the oral route is the most commonly used, the supplement being given as a tablet, capsule, solution or as a 'fortified' food. Injections are usually reserved for those cases where the patient is unable to eat due to damage to the gastrointestinal tract or other reason, *e.g.* in patients on total parenteral nutrition it may be difficult to maintain adequate levels of iron, and supplementation by intramuscular injections of iron, for example, as a sorbitol complex will often be required. In view of the importance of the oral route it is helpful to consider the more salient general aspects of gastrointestinal absorption.

ABSORPTION OF LIGANDS FROM THE GASTROINTESTINAL TRACT

In general enteral absorption may occur throughout the whole length of the gastrointestinal tract but three areas are of special importance, depending on the formation constants of the particular metal–ligand complexes. These are the mouth (pH ~ 7.4), the stomach (pH ~ 1.6) and the small intestine (pH ~ 6–6.5 in the duodenum and ~ 6.5–7 in the jejunum).

Specific carrier systems exist for the transport of some species across the intestinal wall (mucosa), *e.g.* glucose or amino acids. However, for other species the important properties for good absorption are the presence of a high proportion of a non-ionized form with a high lipid-water partition coefficient and a small atomic or molecular radius. It is generally assumed that ionized species cannot cross the mucosa whereas non-ionized forms equilibrate fairly freely, providing that they have molecular radii of less than about 3 nm, which corresponds to a molecular mass of ~ 6000 Da. For metals the most important region for absorption is the small intestine, where the pH lies between about 6 and 7.4.

Supplementing the intake of minerals into the body sounds like a deceptively simple task, but, as we shall see, it is far more complicated than it might appear at first sight. The minerals we take in from our diet are generally absorbed from the upper small intestine where the pH lies in the region of 6–7.4; therefore they must reach the site of absorption in a soluble and absorbable form. However, at this pH in the aqueous environment of the small intestine most multivalent metal ions react almost quantitatively with water to form hydrolysed insoluble, and thus non-absorbable, hydroxides and oxides. Other reactions occur with the numerous complexing ligands present in the intestinal contents to form metal complexes, the major fraction of which may be electrically charged and also be non-absorbable; the fraction of electrically net-neutral and thus absorbable species may well represent only a tiny fraction of the total metal which enters the gastrointestinal tract.

High concentrations of minerals in the diet may give foods an unpleasantly astringent taste. Thus the formulation of mineral supplements that combine good bio-availability with little, or no, undesirable side effects or spoiling of the taste of food is no easy task and calls for considerable skill and ingenuity. One possible advance may be seen in recent work from Japan that suggests that poly-γ-glutamic acid, an amino acid produced by *Bacillus natta* bacteria, appears to almost double the solubility of minerals in the small intestine and at the same time confers a 'mellow' flavour that masks the usual astringent taste of minerals.

In formulating metal supplements a suitable complexing ligand may be added with a view to enhancing the proportion of neutral metal complexes which are formed near the absorptive surfaces in the intestine. However, because such complex formation is usually very pH dependent the choice of ligand is not always easy. Figure 5.1 illustrates the variations in the total percentage of neutral complexes formed when ferrous iron reacts with ascorbic acid or with galacturonic acid in the pH range of 5–7.5, and indicates that ascorbic acid appears to be the better ligand for facilitating iron absorption. Figure 5.2 shows the proportions of neutral Fe(II) species formed at pH 6.5 when the metal reacts with five ligands sometimes used in iron supplements.

IRON, ZINC, AND COPPER SUPPLEMENTATION

These metals are the most prevalent metals *in vivo* and supplementation treatments can be traced back thousands of year; for example, in pre-Christian times, solutions of rust in acid wine were used for anaemia and zinc oxide unguents for wounds or skin conditions.

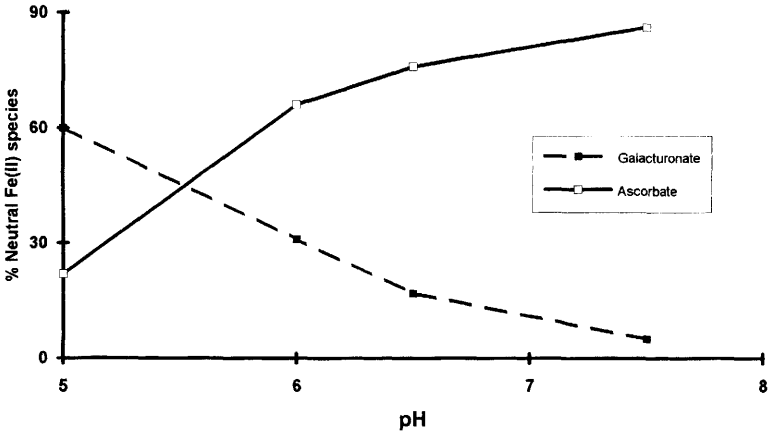

Figure 5.1 *The percentages of electrically net-neutral species formed when Fe*(II) *interacts with galacturonic acid or ascorbic acid in the pH range 5.0–7.5*

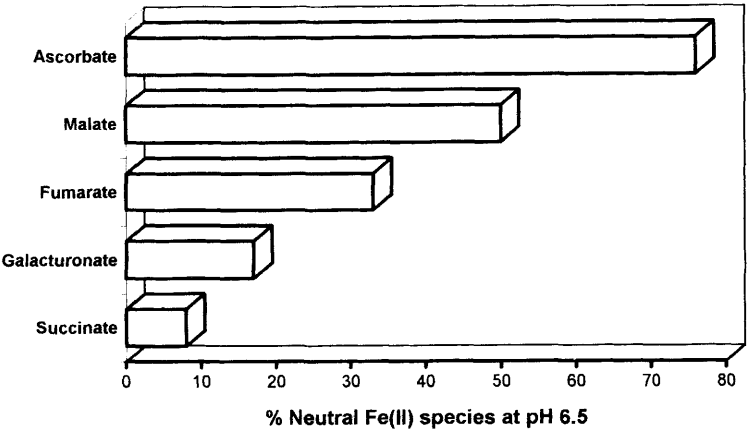

Figure 5.2 *The percentages of electrically net-neutral Fe*(II) *species formed at pH 6.5 with five physiologically important hydroxycarboxylic acids*

Modern oral supplementation therapy is a combination of scientific and commercial approaches which:

1. Aim to increase the flow of metal complexes from intestine to blood by increasing the concentration of lipid-soluble, low molecular mass complexes present in the intestinal fluids;

Table 5.1 *The types and composition of some metal supplement preparations*

Type of preparation	*Principal ingredient(s)*
Oral iron preparations	
Ferrous sulfate (tablets)	Iron(II) sulfate (40–105 mg Fe*)
Ferrous fumarate (tablets)	Iron(II) fumarate (65–10 mg Fe*)
Ferrous gluconate (tablets)	Iron(II) gluconate (35 mg Fe)
Ferrous glycine sulfate (tablets or solution)	Iron(II) glycine sulfate (25–100 mg Fe*)
Ferrous succinate (solution)	Iron(II) succinate (37 mg Fe)
Sodium ironedetate (solution)	Iron(II) chelate of ethylenediaminetetraacetic acid (EDTA) (27.5 mg Fe)
Compound oral iron preparations	
Iron and folic acid (capsules, tablets or solution): numerous proprietary preparations designed to prevent iron and folic acid deficiency during pregnancy	Iron(II) as sulfate or fumarate or glycine sulfate or iron(III)ammonium sulfate (47–110 mg Fe*) + folic acid (350–500 μg)
Injectable iron preparations	
Iron sorbitol injection	5% iron sorbitol (50 mg Fe ml^{-1})
Oral zinc preparations	
Zinc sulfate (tablets or capsules)	Zinc(II) sulfate (22.5–50 mg Zn)

*Range of iron contents found in unit doses of various preparations.

2. Aim to keep such metals in solution at intestinal pH by complexing the metal ions. For example, iron preparations may contain Fe(II) in association with complexing ligands such as ascorbate, malate, fumarate, gluconate or amino acids that promote the formation of neutral complexes at pH ~ 6–7. Gluconate may be used for the same purpose for metals such as Cu, Zn, or Co;
3. Tend to favour iron(II) rather than iron(III) compounds, since the former can be up to ~ 17 orders of magnitude more soluble (K_{sp}* $Fe(OH)_2 = 10^{-15.1}$, $Fe(OH)_3 = 10^{-38.7}$);
4. Cause least irritation to the gastrointestinal tract. For this reason ferrous sulfate is not an agent of choice;
5. Appear to avoid approaches advocated by hundreds of years of folklore medicine, so as not to undeservedly undermine confidence in either the product or its prescriber;
6. Use metal complexes that are capable of being patented.

* The solubility product K_{sp} is defined as the product of the concentrations of the ions present in a saturated solution of a substance. The units are in moles dm^{-3}.

The 'Martindale's Extra Pharmacopoeia' lists more than 40 preparations for iron, but only three for zinc; some of the most frequently used iron and zinc supplements are illustrated in Table 5.1. Irritation of the gastrointestinal tract tends to follow the Irving–Williams series of complex stability, *i.e.*

$$Mn < Fe < Co < Ni < Cu > Zn$$

for divalent ions. Thus oral supplementation with copper is exceedingly difficult and recourse is made to absorption via the skin from copper-impregnated gels used as a dressing being a modern equivalent of the copper bracelet from which the metal can be solubilized by the amino acids in sweat that form neutral lipophilic complexes that can penetrate the epidermis.

In all supplementation therapy it is prudent to assess the trace element status of the patient, by monitoring the blood plasma. For example, for iron the haematinic index can yield useful information that can be used to monitor the success of the treatment. However, simple measurement of the concentrations of the relevant metals in blood plasma is not necessarily the most useful indicator of the effectiveness of supplementation therapy, since the total concentration of metal in the plasma may not reflect the concentration of the particular metal species that is required to counteract the deficiency state.

BIOCHEMISTRY OF TRACE ELEMENT DELIVERY

There are instances in which, despite an apparently adequate intake of trace elements, either in the diet alone or from the combination of diet plus supplementation, the clinical symptoms persist. This may be due to a flaw or deficiency in the underlying, highly complicated biochemistry of trace element absorption and assimilation; such a deficiency may be because there is an inadequate presence of some essential co-factors.

Volumes have been published about the biochemistry and pharmacology of elements such as iron, cobalt, zinc, *etc.* (see, for example, the articles by P.M. May and D.R. Williams in 'Iron Metabolism' edited by A. Jacobs and M. Worwood, Academic Press, London, 1982). Indeed, life science laboratory walls often display large posters concerning the detailed biochemistry of the metal reactions occurring in a range of cells and at a variety of sites in the body.

For various reasons, for example, the hydrolytic reactions discussed above, it is sometimes necessary to 'target' the metal complex to specific organs or sites by such relatively simple arrangements as the enteric

coating of tablet so that they persist unreacted until they reach the small intestine. The fact that humans can live for almost a century on exceedingly small amounts of trace elements (see Table 2.1) underlines the highly complex biochemistry which controls, buffers and, eventually, excretes such trace element species from the different cell types in the body.

However, the weakest biochemical links in the chain may often be the non-metallic, usually, organic, molecules required as reactants. This explains why iron supplementation sometimes needs to be reinforced by concomitant administration of folic acid (see Table 5.1, Compound oral iron preparations), whereby the folate plays a vital role as a co-factor in the biosynthesis of the haem ligand to which the iron becomes attached to form haemoglobin. Similarly, cobalt is required in the form of vitamin B_{12}, cobalamin, which consists of a corrin ring surrounding a central cobalt atom. Cobalamin is unique in biochemistry since it cannot be synthesized by plants or animals, but only by micro-organisms. Thus cobalamin must be supplied by the diet, but in order to be absorbed into the circulation it must first form a complex with a glycoprotein called intrinsic factor present in the intestinal lumen. This intrinsic factor–cobalamin complex then binds to a specific receptor in the lining of the ileum from which the cobalamin is transported into the blood. Thus a deficiency of cobalamin cannot be made good by simple administration of a cobalt salt. In other situations trace element deficiency may result not so much from a shortage of the metal itself, but more from derangement of the mechanisms by which it is absorbed or transported to its sites of action.

FURTHER READING

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