Solubility and Body Fluids

Erich Königsberger and Lan-Chi Königsberger

School of Chemical and Mathematical Sciences, Murdoch University, Murdoch, WA 6150, Australia

1. INTRODUCTION

Solubility phenomena (i.e. dissolution and precipitation reactions) are the physicochemical basis of numerous biological processes. These include, for instance:

- gas solubilities in respiratory and photosynthetic processes; the solubility of volatile anaesthetics;
- the crystallisation, both in biologically controlled and pathological processes, of biogenic minerals in a variety of body fluids; the resorption of mineralised tissue;
- the accumulation, due to their higher solubility, of lipophilic substances, such as pesticides, in liquid fat contained, e.g. in adipose tissue or human milk;
- the incorporation of metal ions such as strontium (including the radioactive ^{90}Sr isotope) in bone, by co-precipitation and solid-solution formation. Since Sr stabilises bone apatite crystals (i.e. decreases solubility), it may retard the resorption of the calcified matrix and thus have therapeutic potential in the prevention and treatment of osteopenic disorders [1]. In dental enamel, a combination of strontium and fluoride was reported to be more effective in stabilising the apatetic structure than each element alone [2]. This results in an improved crystal resistance to degradation by bacterial acids and hence may be useful for the prevention of dental caries [3].

All of these solubility phenomena are governed by the laws of thermodynamics and kinetics. The human body is essentially an isothermal system (a notable exception, related to gout, has been reported in the literature – see

below). Thus, the pertinent in vitro measurements have almost always been performed at 37°C. However, reactions in body fluids are complicated by the presence of organic complexing agents which affect the speciation of metal ions (i.e. their distribution among these complexes). Computer speciation modelling of biofluids, which has a long history [4], has also to be considered in the modelling of solubility equilibria. The presence of organic macromolecules such as proteins provides templates or matrices which control the crystallisation of biogenic minerals and modify their morphologies. The mineral phase in organic/inorganic composites (such as teeth or bone) may form nanosized crystals, which exhibit unusual dissolution and crystallisation behaviour [5]. A new biomineralisation mechanism invoking liquid precursors and their importance for normal and pathological biomineralisation processes has been proposed [6]. These and other aspects of normal and pathological biomineralisation processes have been reviewed recently [7].

2. BODY FLUIDS

The human body contains 60% water, which is an excellent solvent for electrolytes and plasma proteins [8]. Because all cell membranes are freely permeable to water, intra- and extracellular fluids are generally considered to be in osmotic equilibrium. Therefore, the *osmolality* (the total molality of individual ionic and neutral solute species that contribute to the osmotic pressure) of the extracellular fluid is approximately equal to that of the intracellular fluid (ICF) and hence plasma osmolality is a guide to intracellular osmolality. Normal osmolality in plasma is ~0.30 'osmoles' (kg water)$^{-1}$. This is contributed mainly by sodium, chloride, potassium, urea and glucose, and additionally by other ions and substances in the blood. Most of the body fluids are *isotonic* ("of equal osmotic pressure", when only impermeant solutes are taken into account), with the notable exceptions of urine, sweat and saliva [9].

Forty-two litres of solutions involved in the major body fluids of a 70 kg human are distributed as follows [8]:

1. *Intracellular fluid* (ICF, 28 l) is the sum of all the solutions inside the ca. 10^{14} cells of the body. Although each of them contains a separate individual solution and different cell types are chemically different, their internal solutions all share a few common features that distinguish them from extracellular fluids. For instance, intracellular solutions are high in potassium, magnesium and phosphate ions and low in

sodium and chloride, and contain high concentrations of organic acids and proteins. These bind metal ions efficiently so that crystallisation of solids does not normally occur in ICF.

2. *Extracellular fluids* have various functions that are beneficial to the organism [9]. These include heat homeostasis (through blood and sweat), transport functions (energy sources, nutrients, electrolytes, dissolved gases, hormones, excretory products, etc.), wetting (saliva), lubrication (tears, synovial fluid) and neutralisation (saliva, biliary and pancreatic juices), among others [9]. Various extracellular fluids are prone to pathological calcification and stone formation. They are commonly subdivided as follows:
   a. *Interstitial fluid* (ISF, 10.5 l) is the sum of all the thin layers of tissue fluid in the interstices between cells throughout the body and constitutes the internal environment whose stable composition is essential for homeostasis. Its major chemical features are low potassium and magnesium ion concentrations, high sodium, chloride and bicarbonate concentrations, and very low or negligible concentrations of proteins or other organic acids. A special subset of ISF is the lymphatic fluid, or lymph, which plays a part in the transport of tissue fluid until it rejoins the blood. Since tissue fluid passes into the surrounding lymph vessels and lymph can thus be sampled and analysed, measurements of lymph composition are often cited as approximations of the composition of ISF.
   b. *Blood plasma* (3 l) is the ISF of a very special (liquid) tissue, namely whole blood. It circulates rapidly throughout the body and is in effective diffusion equilibrium with the ISF for most solutes except macromolecules. Plasma therefore differs in composition from ISF mainly in its protein content.
   c. *Other fluids* amount to 0.5 l. This category includes a variety of small volumes of special, usually rather small and localised, solutions such as aqueous humour (the clear, watery fluid in the eye that fills the space between the back surface of the cornea and the front surface of the vitreous humour [10]), synovial fluid (in joints), bile, saliva and many others. These are sometimes referred to as ‘transcellular’ fluids. Two of these special fluids have extreme pH values: gastric and pancreatic secretion. Gastric acid can be as concentrated as $0.15\,\mathrm{mol\,kg^{-1}}$ HCl, and the alkaline pancreatic juice contains high concentrations of sodium, calcium and hydrogen carbonate, but almost no chloride.

3. SOLUBILITY PHENOMENA IN BODY FLUIDS

3.1. Gas Solubilities

Except for blood plasma passing the pulmonary capillaries, body fluids are not even in contact with, let alone at equilibrium with, a gas phase. They nonetheless contain dissolved gases, especially CO_2, whose concentration is an important determinant of pH and therefore of acid–base behaviour in all body fluids [11]. Attempts to correlate and predict the solubilities of non-electrolytes, particularly gases and volatile anaesthetics [12], in biological tissues and fluids are more complicated compared to pure solvents, since biological systems are heterogeneous and cases of specific binding of solute molecules are common. In these situations, Henry's law is no longer obeyed. For instance, oxygen solubility in blood plasma is ca. $5\,\mathrm{ml\,l^{-1}}$ at 37°C but considerably higher (ca. $200\,\mathrm{ml\,l^{-1}}$) in whole blood due to the binding of oxygen to haemoglobin, which follows a well-known sigmoid binding curve resulting from the cooperative action of the haemoglobin alpha and beta chains. The effect of haematocrit (the fraction of blood composed of red blood cells) on the solubility of several volatile anaesthetics in blood is much less pronounced but significant (10–20%) [13].

Abraham et al. [14] have reported solubility correlations for a wide variety of systems that follow Henry's law. Gas/liquid partition coefficients for biofluids are modelled by a suitable combination of gas/water and gas/oil partition coefficients, thus allowing for the hydrophobicity of a given biological tissue or fluid. This method is furthermore able to provide a measure for the tissue/blood distribution of non-electrolytes (which may also be estimated using octanol–water partition coefficients [15]).

3.2. Normal Biogenic Mineralisation

Biomineralisation commonly refers to the complex biological process by which living organisms synthesise the inorganic materials of their hard tissues. Normal (as opposed to pathological) biomineralisation is frequently characterised by a high degree of specificity and control, which is exerted during the interaction between the mineral and the organic constituents on different hierarchical levels and directs the nucleation, growth and morphology of 'normal' biomaterials such as bone and teeth. The structure and mechanism of formation of these organic/mineral biocomposites, as well as the amazing diversity and beauty of the very elaborate and complex crystal morphologies produced by various organisms, have been comprehensively described in classical and modern textbooks, e.g. [16–18], and reviews, e.g. [6].

The authors of the latter review present a somewhat different perspective on biomineralisation, with emphasis on the role of amorphous precursor phases, which may be relevant to biologically controlled mineralisation in bones and teeth (and also to pathological mineralisation such as in kidney stones) [6].

The solubilities of the various calcium phosphates found in mineralised tissues at different states of maturation have been systematically reviewed [19]. Besides its skeletal support function, bone also provides an important metabolic function in the regulation of the ionic composition of the body fluids, serving as a reservoir for cationic and anionic species by resorption and deposition of this mineralised tissue [20]. The mineral phase in bones and teeth consists of apatite nanocrystals, which are not only crucial for the superior mechanical properties of these biocomposites, but also exhibit some unusual solubility behaviour. While these nanocrystals are usually considered to be stabilised by their intimate association with the organic matrix and thus become unstable once the collagen is removed (such as by osteoclastic secretion of enzymes enabling the biological resorption of bone) [6], studies of their dissolution kinetics have shown that they can become dynamically stabilised (i.e. they do not dissolve any further) even at considerable undersaturation. These and other aspects of peculiar solubility phenomena concerning nanosized biominerals have been discussed recently [5].

3.3. Pathogenic ‘Calcifications’

Pathological intra- and extracellular calcifications are frequently initiated at the biologic membranes of mitochondria or matrix vesicles, respectively, through the interaction of phosphatase enzymes with calcium-binding phospholipids, both of which are membrane-bound [21]. Sequestration of calcium by mitochondria is a common biochemical mechanism mediating various forms of toxic cell death. Pathological cellular calcification may therefore be characterised by mineral-laden mitochondria, as described for a case of hepatocellular calcification [22]. Cellular microcalcification has also been observed in a diversity of human pathologies, such as vascular dementia, Alzheimer’s disease, Parkinson’s disease, astrogliomas and post-traumatic epilepsy. Rodent models of central nervous system neurodegeneration indicate that this is due to the inability of neurons to regulate intracellular calcium levels properly [23]. Hydroxyapatite crystals are formed first within the protective microenvironment of the membrane-enclosed microspace, aggregate progressively throughout the cell and at exposure to the Ca^{2+}-rich extracellular fluid, for instance, after cell death, they can serve as nuclei or templates supporting progressive, autocatalytic mineral crystal proliferation [21]. The nucleoside

triphosphates have been found to have a significant inhibiting effect on the hydroxyapatite crystal growth process and thus may play a beneficial role in regulating intracellular calcification [24].

In dystrophic calcifications, the mineralisation occurs without a systemic mineral imbalance as a response to previous cell injury on the microscopic level or any soft tissue damage, including that involved in implantation of medical devices or bioprosthetic heart valves [25]. Injury and cell death can cause the release of intracellular phosphate ions and fatty acids into the extracellular environment, where sparingly soluble calcium salts are precipitated in tissues. This type of calcification is particularly common in atherosclerosis and diseases associated with chronic inflammation.

Pathological intracellular calcifications can also occur in conditions associated with hypercalcaemia [26] – excess levels of calcium in the blood, caused, e.g. by hyperparathyroidism (excess secretion of parathyroid hormone by overactive parathyroid glands which normally regulate calcium levels tightly) or malignancy [27]. Intramitochondrial calcifications often precede necrosis, and fusion or rupture of calcified mitochondria results in calcareous masses in the cytoplasm or outside of the cell. Much progress has been made in the ultramicroscopic identification and systematic classification of these calcifications [28].

Since extracellular body fluids exhibit high calcium concentrations, many of them are supersaturated with respect to calcium compounds, even in the healthy organism. Examples of supersaturated body fluids are urine (oxalates, phosphates), blood plasma and saliva (phosphates), pancreatic secretions and bile (carbonates). Body fluids may also become supersaturated with respect to intermediate or final metabolic products, e.g. urine (uric acid, xanthine, cystine), bile and blood plasma (cholesterol), and synovial fluid (sodium hydrogenurate monohydrate). Despite considerable research effort, it is presently not clear why pathological mineralisation does not occur indiscriminately in the supersaturated body fluids occurring in all humans. It seems that (i) the presence of heterogeneous nucleants and (ii) a deficit of crystallisation inhibitors play a crucial role in pathological situations [29]. For instance, magnesium has found to be an important inhibitor of many pathological calcifications [30]. Macromolecules can interact with crystals both as inhibitors and as promoters of crystallisation and the relationship between pathological and benign mineralisation is not fully understood as yet [31]. A paramount example is the multifaceted role of the glycoprotein osteopontin in bone remodelling, urolithiasis, atherosclerosis, inflammatory and immune response, and cancer progression [32]. A somewhat controversial debate

concerns the role of putative *nanobacteria* in various forms of calcification (see the discussion in Ref. 5).

3.3.1. Renal Calculi

Approximately 10% of the human population (with regional differences indicating both genetic and environmental factors [33]) is affected by the formation of stones or calculi in the urinary tract. Urolithiasis is not only a painful condition, but also causes annual costs to the health system in the order of billions of dollars in the USA alone [34, 35]. Based on their composition, structure and location in the urinary tract, renal stones have been classified into 11 groups and their formation mechanisms have been discussed together with alterations in urinary parameters and metabolic risk factors for renal lithiasis [35]. Approximately 70% of these stones contain calcium oxalate monohydrate (COM) and dihydrate as major components, while other calculi are composed of ammonium magnesium phosphate (struvite), calcium phosphates (hydroxyapatite and brushite), uric acid and urates, cystine and xanthine. An accurate knowledge of the solubilities of these substances is necessary to understand the cause of renal or bladder calculi formation and find ways towards its prevention and treatment [36].

Due to its vital functions related to water balance and the excretion of metabolic end products, the composition and pH of urine can vary widely (which is in contrast to the homeostatic internal environment provided by most other body fluids). Although the solubilities of uric acid (the end product of purine metabolism in humans), xanthine (an intermediate product of purine metabolism) and L-cystine (the least soluble amino acid) strongly depend on pH, accurate measurements performed by our group (Fig. 1) have shown that they hardly depend on the nature and concentration of urinary constituents [36–41], including organic urine components such as urea and creatinine [38]. The solubility of cystine in real urine was found to be comparable to that in synthetic solutions [39]. For xanthine [40] and uric acid [42], thermodynamic consistency of solubility and calorimetric data has been demonstrated.

Calcium oxalate and phosphate solubilities, on the other hand, strongly depend on the concentration of ions that form complexes with calcium, phosphate or oxalate, particularly citrate or magnesium ions [43–45]. Due to the protonation of these anions, the concentration of these complexes depends on pH, which contributes to the pH dependence of solubility. Whereas the solubility of calcium oxalate is only slightly pH dependant in the urinary pH range [45], the solubility of phosphates decreases with pH [43, 44]. We have developed a urine model [43–45] based on the JESS Expert Speciation

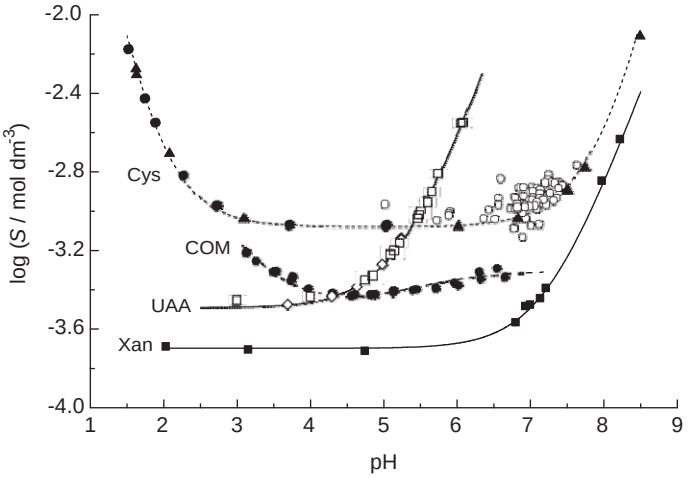

Fig. 1. Solubilities *S* of stone-forming substances in urine-like liquors at 37°C. (Cys) L-Cystine in standard-reference artificial urine (dots), real urine (circles) and 0.30 mol kg^{-1} NaCl (triangles) [39]. (COM) Calcium oxalate monohydrate (as $[Ca^{2+}]_{tot}$) in standard-reference artificial urine (dots) [45]. (UAA) Anhydrous uric acid in standard-reference artificial urine (diamonds) and 0.30 mol kg^{-1} NaCl + 0.30 mol kg^{-1} urea (squares) [37, 38]. (Xan) Xanthine in 0.30 mol kg^{-1} NaCl (squares) [40]. The experimental data are compared to model calculations (lines) described in the respective publications.

System [46–49] that permits reliable solubility calculations by taking all of these complexes into account. This and other urine models and their applications have been reviewed recently [5].

Due to deprotonation reactions occurring at higher pH, the solubilities of uric acid, xanthine and cystine increase with pH. For cystine and particularly for uric acid stones, therapies based on the administration of substances that increase the urinary pH have been successfully applied. However, the solubility increase of xanthine at high pH is of little therapeutical use, as is that of cystine at low pH (caused by the protonation of the amino groups). Both of these pH ranges are outside the normal urinary pH range and attempts to access them by medication may cause the precipitation of uric acid and phosphates at low and high pH, respectively. It should be noted that the solubility of the metastable uric acid dihydrate, which is also found in kidney stones and is regarded as the kinetically favoured precipitation product, is twice as high as that of anhydrous uric acid [37].

The solubility of COM in artificial urine is almost pH independent (at low pH the solubility increases because of the protonation of the oxalate

ion and at high pH it increases slightly because of the deprotonation of citrate which then complexes Ca^{2+}). The solubility of calcium oxalate dihydrate, which is also found in kidney stones and whose precipitation in complex solutions is often kinetically controlled, in artificial urine is three times higher than that of the monohydrate [45].

Renal lithiasis is a multifactorial disease, with numerous factors contributing to the actual stone formation [6, 33, 35]. Although various conditions promote, or fail to inhibit, the crystallisation of stone-forming substances, supersaturation is an indispensable factor. Solubility modelling can therefore give crucial information on the risk of pathological mineralisation in general and renal lithiasis in particular. A variety of computer codes have been applied to assess the effects of diet, fluid intake and medication [5], and an application of a JESS speciation model similar to ours [43–45] has been reported [50].

3.3.2. Atherosclerosis

Cardiovascular disease due to atherosclerosis is the major cause of mortality and morbidity in industrialised countries. Atherosclerosis is characterised by hardening (and loss of elasticity) of medium or large arteries, eventually leading to narrowing of the vessel lumen. Initial steps are an immune reaction to cell damage caused by oxidation of low-density lipoprotein (LDL) in the blood vessel lining (endothelium), which involves redox-active copper and iron ions [51]. The resulting inflammation response leads to deposition of atheromatous plaques in the inner wall of the arteries (intima), followed by intracellular microcalcifications within vascular smooth muscle cells of the muscular layer surrounding the plaques. As cells die, extracellular calcium salt deposits are formed between the muscular wall and the outer portion of the atheromatous plaques [52]. The main components of human atherosclerotic lesions are calcium salts, particularly apatites, and cholesterol crystals [53, 54], which accumulate predominantly within the central core region of the lesions and probably nucleate the deposition of apatite [55].

3.3.3. Crystal Arthritis: Gout and Pseudogout

The very painful inflammations associated with gouty arthritis are induced by the deposition of needle-shaped sodium hydrogenurate monohydrate crystals in synovial fluids around joints [56]. The solubility of sodium hydrogenurate monohydrate is strongly pH dependant and is lowest at physiological pH [37]. It has been observed that only a small percentage of individuals with hyperuricaemic body fluids (which are supersaturated

with respect to sodium hydrogenurate monohydrate) have ever had a gouty attack. Indeed, normal synovial fluids, serum albumin and heparin have been found to inhibit sodium hydrogenurate monohydrate crystallisation, whereas synovial fluids of gouty patients have nucleated this substance [57]. It has also been established in our solubility study [37] that even in 0.15 mol kg^{-1} NaCl at higher pH, saturated uric acid solutions can become highly supersaturated with respect to sodium hydrogenurate monohydrate without any crystallisation occurring. The solubility of sodium hydrogenurate monohydrate is markedly temperature dependant (Fig. 2) [37] and it has been speculated that the preferred occurrence of gouty attacks in the joints of the extremities is due to the lower temperature of these parts of the body [58].

Pseudogout refers to the clinical syndrome associated with the deposition of calcium diphosphate dihydrate crystals in the hyaline articular cartilage or fibrocartilage. The shedding of crystals in the joint space after rupture of a calcium diphosphate dihydrate deposit produces an acute inflammatory synovitis, which resembles a classic gouty attack and is thus often misdiagnosed as gout. Calcium diphosphate dihydrate crystal deposition is often the result of an underlying disease (such as haemochromatosis or hyperparathyroidism) and cannot be reversed. These and other aspects of pseudogout and the solubilities of the substances involved have been reviewed recently [19].

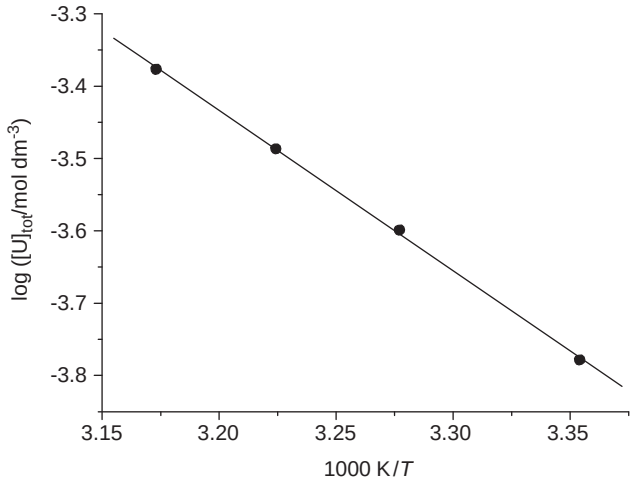

Fig. 2. Solubility of sodium hydrogenurate monohydrate in 0.15 mol kg^{-1} NaCl at physiological pH at 25, 32, 37 and 42°C [37].

3.3.4. Gallstones

More than 80% of gallstones in the Western world are cholesterol gallstones [59]. Other gallstones contain bilirubin as their main constituent, but inorganic or organic calcium salts (carbonate, phosphate, bilirubinate, palmitate) are almost always present [19].

Crystallisation of biliary cholesterol monohydrate is a multiphase process not yet fully understood [60]. Bile is normally supersaturated with respect to cholesterol [61] which is solubilised by bile salts (the soluble end product of cholesterol metabolism, such as sodium glycocholate and sodium taurocholate [9]) within micelles, whose solubilising capacity is considerably increased by the incorporation of phospholipid molecules such as lecithin [62]. Biliary vesicles contain virtually no bile salts but may accumulate cholesterol up to a cholesterol/phospholipid ratio of 2:1 (by phospholipid transfer to micelles) [63]. These thermodynamically unstable (but kinetically stabilised) vesicles then aggregate and nucleate cholesterol crystals [64, 65]. The mechanism of this crucial micelle-to-vesicle transition has been the subject of various physicochemical studies, including, e.g. calorimetric, turbidimetric, dynamic light and neutron scattering methods [66–69].

The solubility of cholesterol has been studied as a function of several physiologically important variables, such as the concentrations of various bile salts and phospholipids, e.g. [70, 71]. Carey [72] has generated extensive cholesterol solubility tables for native bile by identifying two key physicochemical variables, the bile salt-to-lecithin ratio and the total lipid concentration (bile salts + lecithin + cholesterol), that determine the solubility of cholesterol in bile [70]. These tables permit calculation of the lithogenic index or percent cholesterol saturation of native bile.

3.3.5. Pancreatic Stones

Calcium carbonate is a major constituent of pancreatic stones (consisting of ca. 95% calcite) and is found occasionally in salivary stones and many pigment gallstones, since these three gastrointestinal secretions have high pH values and contain high hydrogen carbonate concentrations. The normal function of pancreatic secretion is to contribute to the neutralisation of gastric acid and support digestion by a variety of enzymes. A physicochemical model of calcite solubility in pancreatic juice has been developed that takes the complexation constants of calcium ions with (hydrogen-) carbonate and proteins into account [73]. All of these ligands are important buffers for calcium ions in the juice [73] and various in vitro studies have been performed to investigate the dissolution of stones as well

as the influence of additives on calcium carbonate saturation in pancreatic secretions (see Ref. 5).

3.3.6. Salivary and Dental Calculi

Williams et al. [74] have developed a thermodynamic model of saliva which is able to simulate the distribution and speciation of metal ions in this biological fluid. The model predicts that in the pH range of 5–6, saliva becomes supersaturated with respect to calcium phosphates in the order octacalcium phosphate $<$ hydroxyapatite $<$ fluoroapatite. This indicates that under normal conditions, no demineralisation of teeth should occur. However, dietary acids are detrimental and are thus normally neutralised by increased secretion of saliva.

Therefore, a thermodynamic driving force also exists for the formation of pathological calcifications that obstruct the salivary glands. These salivary calculi or sialoliths usually contain organic matter and various calcium phosphates [19], particularly carbonateapatites and hydroxyapatite. The latter exhibit macro- and microstructures that are practically identical to those found in hydroxyapatite renal calculi [35]. It has also been reported that the saliva of stone formers, when compared to that of healthy subjects, was characterised by a higher calcium phosphate supersaturation and deficit of crystallisation inhibitors (magnesium, phytate). These factors thus favoured crystallisation, particularly when combined with morphoanatomic disorders (stenosis, diverticuli) within the salivary duct [35].

Dental calculi, i.e. calcifications of the dental plaque biofilm, contain various calcium phosphates, since these inorganic ions are provided by saliva or crevicular fluids. Although the pattern of calcification of oral microorganisms, either intra- or extracellularly, is mainly a characteristic of each bacterial species or strain [75], it may be influenced by nutritional factors, such as saliva proteins, as well [76]. The interactions of saliva with dental calculi and its role in preventing dental caries by controlling the enamel de- and remineralisation processes have been reviewed [19].

3.4. Solubility of Other Metal Compounds

The deposition of other sparingly soluble metal compounds is usually associated with disturbances in homeostasis, i.e. the delicate regulation of metal ion concentrations in body fluids, due to various forms of disease. If these disorders result in metal overload of body fluids, solids may deposit in various tissues and damage them. In humans, metal overload diseases concern primarily iron and copper ions, which are moreover intimately

involved in free radical reactions associated with, e.g. atherosclerosis and central nervous system diseases [77]. The toxicity due to oxidative cell damage of iron oxyhydroxide deposits has been related to their solubilities [78].

Iron overload in humans can be non-anaemic (primary haemochromatosis) or anaemic (thalassemia). While non-anaemic iron overload is effectively treated by phlebotomy (bloodletting), a chelating agent is necessary to increase iron excretion in the case of thalassemia [79]. Without treatment, excess iron deposits as haemosiderin, which may contain iron(III) oxyhydroxides that are either amorphous or based on ferrihydrite or goethite structures [78]. Recent progress on the (Mössbauer) spectroscopic characterisation of these deposits and their reactivity with chelating agents has been reviewed [78]. Copper overload in humans is mainly caused by Wilson's disease and has to be treated by life-long chelation therapy, cf. [5].

Other metals, which may precipitate in body fluids or affect the solubilities of other biominerals, are sometimes ingested with food or medications. A prominent example is aluminium, which is contained in food and various antacids in variable amounts. Although acute aluminium intoxications are very rare, subacute and chronic forms of aluminium intoxications due to oral intake have been debated [80]. In particular, a combination of aluminium-containing medications with (complexing) citrate or tartrate solutions (often administered to uraemic patients or contained in soft drinks, respectively) can substantially elevate the absorption of aluminium [81] and has been repeatedly associated with the onset of neurological illness [80]. The evidence implicating aluminium with Alzheimer's disease is controversial [82]. Aluminium hydroxide has a very low solubility at physiological (and intestinal) pH, but the metal rather complexes with phosphate in the intestine, resulting in excess phosphate excretion, inhibition of phosphate adsorption and reduced urinary and serum phosphate levels. This phosphorous depletion syndrome induces adverse effects on calcium metabolism and may cause severe calcium loss which eventually leads to the development of osteoporosis or osteomalacia [83]. Aluminium also forms complexes with intestinal fluoride, an element important for the normal bone structure [83].

4. CONCLUSION

With the exception of urine whose composition can vary over wide ranges, physiological solutions are usually not highly supersaturated with respect to biominerals. A careful control of ion balance, which must be maintained for physiological function, including avoidance of undesirable precipitates, can

then be accomplished by biologically controlled resorption and deposition of mineralised tissue. Homeostatic regulation of ion concentration is true of all biological systems, and most likely lies at the evolutionary foundation of regulating biomineral deposition [6].

Considerable research has been devoted to the study of solubility phenomena in body fluids, particularly in the field of pathological mineralisation, aiming at its prevention and treatment. Although the underlying mechanisms and interactions with low-molecular-weight ligands and biological macromolecules are inherently complex, computerised modelling of solubility equilibria in body fluids has proven a valuable tool for predicting supersaturation and hence the risk of undesirable precipitation.

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