Medical Mineralogy and Geochemistry: An Interfacial Science

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Medical mineralogy and geochemistry is a highly interdisciplinary area of research where the complexity of minerals and mineral surface reactivity in the human body is emphasized. Research in this field will lead to an understanding of the biogeochemical processes responsible for medical conditions, both normal and pathological, that involve the interaction of dissolved inorganic species and bioorganic molecules with minerals. In this article, I highlight some fundamental concepts and challenges in this endeavor, and the subsequent articles provide overviews of specific topics.

**Keywords:** reaction mechanisms, mineral–water interface, biomolecules, biominerals, bioceramics, speciation

**WHAT IS MEDICAL MINERALOGY AND GEOCHEMISTRY?**

The connection between human health and the environment we live in has been appreciated by all cultures throughout human history. The physical manifestation of this connection has been dramatically demonstrated by the toll on human life caused by volcanic eruptions, earthquakes, hurricanes, landslides, tsunamis, and other natural disasters, and these effects may be considered under the term “geology and human health.” Among the best-known examples are the Vesuvian eruptions of 79 AD that buried Pompeii and Herculaneum in Italy and the tsunamis represented in the beautiful nineteenth century Japanese woodblock prints by Katsushika Hokusai.

Chemical links between the environment and human health, however, tend to be more difficult to identify and understand in terms of the biogeochemical mechanisms by which they affect human health. Lead (plumbum in Latin) in drinking-water pipes (hence “plumbing”) and in pewter wine goblets has been identified only in recent times as the source of widespread poisoning in ancient Rome. The importance of such links is captured in classic textbooks on bioinorganic chemistry (Fraústo da Silva and Williams 1991; Williams and Fraústo da Silva 1996). The field of medical mineralogy and geochemistry (MMG) focuses on understanding the equilibria and reaction pathways involving normal and pathological interactions of inorganic and organic chemical species in gas or aqueous phases with naturally occurring, inorganic solid phases within the human body.

Medical mineralogy and geochemistry as broadly described here overlaps considerably with other areas of research, such as bioinorganic chemistry, biochemistry, epidemiology, etiology (cause of disease), biomineralization, and biomaterials (Fig. 1). The field also has connections to the huge biological research areas of genetics, molecular biology, and cell biology. The overlap is intentional and necessary, but many of these other research areas focus on the organic and biological aspects of human health, with minimal appreciation for the richness and complexity of the contributions of inorganic solid phases in these processes. Seemingly trivial examples are prosthodontics and calcification of bones and arteries, which are widely used in the medical literature but do not specify the mineral actually involved. These processes might more appropriately be called quartzosis and phosphatization (Glimcher 2006). Thus, I distinguish MMG from the related research fields by the former’s emphasis on the critical role played in the human body by naturally occurring inorganic solid phases, that is, by minerals, amorphous solids, nanocrystals, and nanoclusters. For brevity, and with apologies to mineralogists, in the subsequent discussion the term “mineral” will include true minerals and biominerals (which are composite materials), as well as inorganic amorphous solids, nanoparticles, and nanoclusters.

The range of issues includes the medical condition involving the specific mineral, the affected tissue or organ, the etiology of the condition, exposure pathways, geospatial relationships, pathogenesis, the controlling equilibria and reaction mechanisms, and the cure. In order to solve the pathological case, it is often necessary to understand the normal process. For instance, understanding osteoporosis and normal bone mineralization go hand in hand. MMG, in other words, deals not only with medical problems but also with normal physiological processes involving minerals and inorganic or organic species in the fluid phase.

A partial list of MMG research topics is provided by the recent volume 64 of the Reviews in Mineralogy & Geochemistry series (Sahai and Schoonen 2006) and by the articles in this issue of *Elements*. For example, the toxic and carcinogenic potential of mineral dusts inhaled into the lungs is related, in part, to biochemical reaction mechanisms involving iron and reactive oxygen species that occur at the mineral surface (Fubini et al. 1987; Castranova et al. 1997; Huang et al. 2006; Schoonen et al. 2006; Fubini and Fensoliglio 2007 this issue). Neurodegenerative disorders such as Guam amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS/PDC) and Alzheimer’s disease (AD) may involve misfolding of specific proteins and, in some cases, are specific to certain geographical locations such as Guam, West New Guinea, and the Kii Peninsula of Japan (Gadjusek 1963; Garruto and Yase 1986; Perl and Moalem 2006). An MMG approach combined with geochemistry could also help address the etiology, pathogenesis, geospatial focus, and potential genetic-environmental interactions involved.

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Prions are a type of misfolded protein that are the agents of transmissible spongiform encephalopathies (TSE) such as Creutzfeldt-Jakob disease and kuru in humans, mad cow disease or bovine spongiform encephalopathy, chronic wasting disease in elk, deer, and moose, and scrapie in sheep (Prusiner 1982). The fate of prions, viruses, and other proteins in the geological environment provides a fascinating and growing area of research (Bales et al. 1991, 1993; Schramm et al. 2006; Quiquampoix and Burns 2007 this issue; Charlet et al. 2008).

The formation of bones, teeth, otoconia (calcite crystals in the inner ear for sensing gravity and acceleration), kidney stones, gout and gall stones, as well as the calcification of vasculature present cases of normal and pathological biomineralization (Gilmcher 2006; Boskey 2007 this issue; Wesson and Ward 2007 this issue). A combined approach involving modern genetic, biochemical, spectroscopic, and microscopic methods of analysis, along with molecular modeling of proteins, peptides, and phospholipids, would yield insight into the controlling mechanisms. The challenge in modeling reactions involving large mineral surfaces with biomolecules and water is the development of methods that are computationally affordable yet accurate, especially for interfacial reactions (Harding and Duffy 2006).

Related to bone and teeth mineralization is the area of biomaterials synthesis for orthopaedic and dental implants. The reactivity of oxide and silicate ceramic and composite biomaterials depends, in part, on the composition and structure of the ceramic, the rate at which it dissolves when implanted in the body, and the cellular response elicited by the ions leached from the bioceramic surface (Cerrutti and Sahai 2006; Jones et al. 2007 this issue). The reactions involved in the initial dissolution of the bioceramic when implanted in vivo are very similar to silicate weathering in the geochemical environment!

Supported lipid bilayers (SLB), as suggested by their name, are synthetic phospholipid bilayers deposited on oxide surfaces and used as model cell-membranes (Cremer and Boxer 1999). Proteins may be embedded in the SLB that can bind to other proteins and molecules present in solution. Thus, SLBs have potential applications as biosensors and in making biomaterials more biocompatible. The role of the oxide substrate in the stability and functioning of SLBs is only now beginning to be studied. With their extensive knowledge of oxide surface chemistry, geochemists could potentially contribute significantly to this field.

As a final example, drugs and viable cells encapsulated within oxide nanoparticles have been proposed for drug delivery and cancer therapy (Livage and Coradin 2006). Understanding the synthesis, reactivity, and cytotoxicity and carcinogenic potential of nanoparticles are all within the scope of MMG (Livage and Coradin 2006).

**SOLUTION CHEMISTRY: SPECIATION AND BIOORGANIC MOLECULES**

An accurate consideration of equilibria and reaction pathways between minerals and dissolved species—as well as meaningful definitions of the terms bioavailability, bioaccessibility, biosolubility, and biopersistence for risk assessment of toxic and carcinogenic compounds—requires an accurate knowledge of aqueous speciation in the particular fluid. Excellent examples are provided in reviews of biological Al speciation (Martin 1991; Harris 1996; Stone 1997). Solutions in different physiological environments vary in terms of pH, ionic strength, and dissolved inorganic ion concentrations, and the pH of some fluids even changes with conditions. Thus, gastric fluid varies between pH ~1.5 and 6.5 in the absence and presence of food; sweat pH ranges from ~4 to 6.5; salivary pH changes from ~6.5 to 8 as flow conditions change from low to high; interstitial (between cells) blood plasma and extracellular lung fluid have pH ~7.5, but extracellular lung fluid is slightly more acidic at pH ~7; and macrophage lysosome has a low pH (~4.5) (Plumlee et al. 2006). To cite other examples, Na⁺, K⁺, and Cl⁻ concentrations maintain osmotic balance across the cell membrane; in some cells, Ca⁴⁺ ions control the opening of cell-membrane channels, thus regulating traffic across the membrane; and trace elements such as Cu, Zn, and Mn are usually involved in specific protein functions. Redox conditions also vary in different physiological environments, from an oxygen partial pressure (pO₂) of 0.132 atm in arterial blood to 0.02–0.05 atm in venous blood (Plumlee et al. 2006). Extremely toxic, reactive oxygen species (ROS) are generated inside immune system cells called leukocytes in order to destroy pathogens such as bacteria, viruses, and inhaled dust particles. The concentration of ROS also depends on solution pO₂, pH, etc.

While the inorganic speciation is relatively well known in many cases, it is difficult to obtain information on the myriad types of biological organic molecules and their concentrations, which may also vary with time and conditions (e.g. the rate of physical exertion, time since eating, health status, and age of the individual). These bioorganic molecules can form complexes with ions, function in redox reactions, and adsorb at mineral surfaces, thus affecting solution speciation as well as mineral surface reactivity. One of the challenges in studying biomedical processes from an inorganic physical chemistry perspective is the existence of such gaps in our knowledge.

**SIZE, HIERARCHICAL ARRANGEMENT, AND TEMPORAL VARIATIONS**

In addition to variations with time and conditions, bioorganic molecules vary in size from several angstroms to tens of nanometers. Further, bioorganic molecules are arranged at varying levels of organization, from dissolved enzymes, vitamins, co-factors and other proteins to colloid-sized polysaccharides, phospholipids, antigens, glycoproteins, etc., associated with the surfaces of micron-sized cells. For example, a single molecule of aspartic acid is ~5 Å long; dipalmitoylphosphocholine, a typical cell membrane-forming phospholipid, is ~3 nm in length; the infectious portion of PrPsc(92-138) on montmorillonite surface (Chaperon, Charlet and Sahai, unpublished results); right, supported lipid bilayer at bioceramic implant surface (modified from Kasemo 2002).
a prion protein is estimated at ~10–30 nm; the core of apo-
ferritin protein, within which ferrihydrite is located, has a
diameter of ~6 nm, and the apoferritin cage itself is ~12 nm
across. Accordingly, the principles of solution chemistry, col-
loid and surface chemistry, and bulk materials chemistry
will need to be applied.

The mineral phases associated with biomedical processes
also range in size and in hierarchical arrangement. For
instance, the calcium phosphate phase associated with mature
bone is a non-stoichiometric, Ca-deficient, carbonate-

enriched hydroxyapatite and occurs as plate-shaped nano-
sized crystals 30–45 nm long and wide and ~2–3 nm thick.
The crystals are arranged with their c-axes parallel to the
long axes of collagen fibrils, and the fibrils themselves have
a very particular three-dimensional arrangement. This spe-
cific, hierarchical arrangement of the organic collagen matrix
and the inorganic calcium phosphate crystals gives bone its
fabric and mechanical properties, while the small surface
area of the crystals imparts to them a high surface reactivity,
which is required for a mineral that acts as a reservoir of cal-
cium (Glimcher 2006). Moreover, unlike many other bio-
minerals, bone is resorbed and continually “turned over.”
Osteoporosis occurs when the rate of resorption is greater
than the rate of bone formation. Thus, the composition, size
and, possibly, even the precursor calcium phosphate phase
associated with bone vary with the age of the bone and
the age of the individual. In other words, changes occur over
space and time, so it is critical to understand that variations
in the volume of tissue analyzed relative to the spatial reso-
lution of the spectroscopic or microscopic analytical method
could yield very different results (Glimcher 2006).

In teeth, nanocrystals of apatite associated with collagen are
found in the dentin, but enamel contains much larger
(micron-sized) and better-organized apatite crystals (fewer
substitutions, vacancies, and other defects), which are asso-
ciated with the protein amelogenin. Moreover, teeth are
not normally resorbed (excluding pathological formation of
caries or tooth decay), suggesting different mechanisms of
growth compared to bone. It would, therefore, be simplistic
to state that our bones and teeth are composed of hydroxy-
apatite. It is crucial to recognize this complexity of bionin-
erals when trying to understand the reaction equilibria and
mechanisms involved in controlling their formation (and
destruction, in the case of bone).

REACTION KINETICS

The interactions of minerals with dissolved inorganic and
organic species occur dynamically, so it is important to con-
sider reaction rates and pathways. For instance, silicate bio-
ceramics of specific chemical compositions dissolve when
implanted in bone in the body, with leaching of Ca$^{2+}$ and
silicic acid from the implant and subsequent deposition of
a new layer of hydroxyapatite at the implant surface. This
apatite layer provides a stronger bone–implant bond and
faster postsurgery recovery times. In this scenario, the rate
at which blood plasma flows past a silicate bioceramic
orthopaedic implant may control the silicate dissolution
rate and the deposition rate of the hydroxyapatite layer,
thus affecting the quality of the bone–implant bond, the
post-surgical recovery time, and the lifetime of the implant
in the patient. Poiseuille studied blood flow in capillaries
and veins as early as 1815, so one might imagine that the
rate of blood flow should be well known by now. It may,
therefore, be surprising to learn that this parameter is actu-
ally very poorly known. Blood flow rates vary from one
organ or tissue to another, with different types and levels of
activity, and with the age and health of the individual, and
the practical difficulties in measuring in vivo flow rates are
obvious. In such situations, fluid mechanics models, including
models for flow through porous media, may shed some
much-needed light (Kufahl and Saha 1990; Dillaman et al.

Surface-controlled reaction mechanisms are also critical in
some processes, as exemplified by the ROS and other gen-
erated on freshly fractured minerals in mining, blasting and
construction activities or radicals created in the mineral
due to the presence of ferrous iron or other impurities, as in
the case of anthracritic coal (Schoonen et al. 2006; Huang et al.
2006; Fubini and Fenoglio 2007). The interaction of soluble,
adherent proteins with dissolved ions and mineral surfaces in
the nucleation and growth of biominerals such as apatite in
bone and teeth, calcite otoconia in the inner ear, and the
pathological mineralization of calcium oxalate as kidney
stones and of uric acid crystals in the joints in gout provide
additional examples of heterogeneous reaction mechanisms
in MMG.

ESTIMATION OF SURFACE AREA

Although the importance of reactive surface area of minerals
is appreciated, the specific surface is operationally determined
by a N$_2$ or Ar gas adsorption isotherm such as the Brunauer-
Emmett-Teller (BET) isotherm. Even this value, however,
may not accurately represent the actual surface area involved
in the reaction. For instance, the size of inhaled particles is
an important factor in controlling whether they are cleared
from the respiratory tract or whether they accumulate in the
lungs, where they may cause respiratory disorders and
cancer over long periods of exposure. The aggregation of
smaller particles into larger ones may reduce the effective
surface area accessible to larger biomolecules, while smaller
inorganic ions such as H$^+$ or metal ions may access the entire
surface area represented by the BET value. The amount of
adsorbed biomolecule per unit surface area will then appear
to be anomalously low. Similar considerations apply to
nanoparticles encapsulating drugs, genes, or viable cells for
use as targeted delivery agents in the treatment of cancer
and other diseases.

THE TOOL KIT

From the preceding discussion, it is apparent that the med-
cinal mineralogist and geochemist must use an impressive
array of tools in order to analyze, characterize, and study
inorganic species, bioorganic molecules, and minerals in
aqueous solutions across a variety of spatial and temporal
scales in controlled laboratory experiments. It is even more
challenging to make measurements in vivo. Geochemists
and mineralogists are already skilled in dealing with similar
complexities in the geological environment and in the use of
advanced spectroscopic, microscopic, and solution analysis
methods, as well as quantum and classical approaches to
modeling reactions at the molecular scale. Collaboration with
researchers in the chemical, biological, and biomedical fields
is also inevitable in order to carry out the complementary
and necessary genetic, cellular, and biomolecular studies.

THE MENTAL CHALLENGE

There are many intellectual challenges in the MMG field,
and I have attempted to address some of them above. I dis-
guish these from “mental challenges,” by which I mean
the effort required to establish such interdisciplinary col-
laborations, find the appropriate research funding, and deal
with journal editors and reviewers who resist publishing the
results of such work. In short, educational outreach must be
targeted not only at the general public but also at our own
community of geoscientists and at the larger community of
chemists, biologists, and biomedical researchers. The task is
difficult but not impossible, as evidenced by the existing
collaborations among biomedical researchers, clinical med-
cal practitioners, and certain geochemistry and mineralogy
groups in the United States and internationally; by forward-looking organizations such as the Mineralogical Society of America (MSA) and its journals/journal editors at American Mineralogist who are now beginning to accept manuscripts in MMG. Equally important are the logistical and financial support provided by the MSA, the Geochemical Society, and by specific programs within NSF, DOE, and the USGS towards a Medical Mineralogy and Geochemistry short course in December 2006, and the growing number of books and conference symposia in this subject area in the past five years.

**CONCLUSION**

MMG is an interfacing science in at least two senses. First, the reactions of interest involve biomolecule or cell surface interactions with mineral surfaces in aqueous solutions. Moreover, MMG requires conceptual development and the application of tools across the interface of different scientific disciplines. The continued growth of medical mineralogy and geochemistry lies in characterizing mineral–solution interactions at the nanoscale and in complex systems. The interplay between experimental and modeling work is vital for developing an improved understanding of the reaction mechanisms that control normal and pathological responses to minerals in the human body. Advances can only be made by creating a dialogue among biochemists, molecular biologists, biomedical engineers, epidemiologists, biogeochemists, and mineralogists, so that we may better understand each other’s scientific dialects and share the insights gained. The following articles are a step in that direction, and I thank the invited authors for their contributions.

**REFERENCES**


Cremer PS, Boxer SG (1999) Formation and mineral-induced formation of reactive oxygen species. In: Sahai N, Schoonen MAA (eds) Medical Mineralogy and Geochemistry, Reviews in Mineralogy & Geochemistry 64, pp 115-134

Dillaman RM, Roer RD, Gay DM (1991) Geochemistry 64, pp 135-152


Glimer MH (2006) Bone: Nature of the calcium phosphate crystals and structural, and physical chemical mechanisms of their formation. In: Sahai N, Schoonen MAA (eds) Medical Mineralogy and Geochemistry, Reviews in Mineralogy & Geochemistry 64, pp 223-282


Livage J, Coradin T (2006) Living cells in oxide glasses. In: Sahai N, Schoonen MAA (eds) Medical Mineralogy and Geochemistry, Reviews in Mineralogy & Geochemistry 64, pp 315-332


Plumlee GS, Morman SA, Zieger TL (2006) The toxicological geochemistry of Earth materials: an overview of processes and the interdisciplinary methods used to understand them. In Sahai N, Schoonen MAA (eds) Medical Mineralogy and Geochemistry, Reviews in Mineralogy & Geochemistry 64, pp 5-57


Sahai N, Schoonen MAA (eds) (2006) Medical Mineralogy and Geochemistry, Reviews in Mineralogy & Geochemistry 64, 332 pp


Schramm PT, Johnson CJ, Mathews NE, McKenzie D, Aiken JM, Pedersen JA (2006) Potential role of soil in the transmission of prion disease. In: Sahai N, Schoonen MAA (eds) Medical Mineralogy and Geochemistry, Reviews in Mineralogy & Geochemistry 64, pp 135-152

