Deflocculation. Soluble silicates suppress the formation of ordered structures within clay slurries, thus increasing the solids which can be incorporated into a clay water system. This interesting surface phenomenon finds practical expression in the manufacture of bricks and cement.

These examples attest to the diversity of values to be extracted from these important industrial materials. This brief review only highlights the applied chemistry in this system. The interested reader is directed to the general references that follow for further insight.

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Silicon–Aluminum Interactions and Biology

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Silicon is listed as an essential element. Its removal from the diet of experimental animals has been shown to result in reduced growth rate (reversed on silicon supplementation) and changes to bone formation and the synthesis of collagenous connective tissue. However, in spite of much effort, no organic binding (e.g., to proteins) of silicon has been convincingly demonstrated under physiological conditions in which silicon exists as silicic acid, $Si(OH)_4$, and no biochemical rationale has been proposed to account for the effects of silicon deficiency. However, recent research indicates that a major role for silicon (as silicic acid) is to reduce the bioavailability of aluminum, which is toxic when it gains entry into biological systems, but which is normally largely excluded. The formation of subcolloidal hydroxyaluminosilicate species is shown to prevent the absorption of aluminum in fish via gill epithelia. The generality of this effect is discussed. The symptoms of silicon deficiency in experimental animals seem likely to result from aluminum toxicity, so that the environmental balance for the two elements may be critical. This chapter reviews the present position.

IN RALPH K. ILER'S MAGNUM OPUS, *The Chemistry of Silica* (*1*), the final chapter is a review of silica in biological systems. Iler was fascinated by this least understood and most challenging aspect of silica chemistry, perhaps because of his instinctive feel for its fundamental importance. The headings within that last chapter reveal its sweep—from the "Origin of Life" to the "Essential Role of Silica in Mammals". He reviewed the concept of silicates as substrates for the formation of complex molecules

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from simple compounds at the earliest stages in the formation of living organisms, including algae, fungi, insects, plants, mammals, and humans. He discussed the formation of biogenic silica in plants (phytoliths) and in the frustules or exoskeletons of diatoms and the fibrogenic effect of silica and silicates in the lung, the most important manifestation of toxicity. Silica being ubiquitous throughout biological systems, Iler was intrigued by the possibility that it plays a vital role. Silica is used as structural material in diatoms and some sponges, and its deposition in plants can be advantageous in strengthening, stiffening, and hardening leaf surfaces, stalks, or the barbs of nettles. As important as such a "mechanical" role is, it is not a biochemically fundamental one.

The element silicon is the second most abundant element in the earth's crust after oxygen. It is described in modern texts of bioinorganic chemistry as an essential trace element largely as a result of the classical experiments of Carlisle (*2*) and Schwarz and Milne (*3*). These workers, in independent experiments, maintained rats and chicks on a synthetic diet deficient in silicon. Using a similar technique, Schwarz had previously shown the essentiality of selenium and other elements. Silicon deficiency in the experimental animals produced a significant reduction in growth rate, reversed on silicon (as silicate) supplementation, with profound changes to the formation of bone and collagenous connective tissue such as cartilage. Since these experiments were reported (1972), there has been a search for the mechanism of action of silicon. The first hypothesis in explanation was based on the claim that silicon was bound in the biopolymers of connective tissue—collagen and polysaccharides—and acted as a labile cross-link, so influencing tertiary structure and integrity (*4*). However, the reported silicon content of isolated biopolymers declined as isolation and analytical techniques improved, so that this role became increasingly unlikely and the hypothesis untenable (*5*). Essential trace elements such as Fe, Cu, Se, and Zn have defined binding sites, usually within a protein structure, and the metal–protein complex is the functional entity, for example, an enzyme. However, in spite of much searching, no specific binding site for silicon has been found. No evidence exists for the formation of Si–C bonds in biological systems, and such chemistry as exists is that of silicic acid, $Si(OH)_4$. Organic complexes of silicic acid are few and are unstable at physiological pH (e.g., complexes with 1,2-dihydroxyphenols such as catechol). Much speculation (*5*) has occurred as to the possible binding of silicic acid to appropriately spaced hydroxyl groups on minority sugars in polysaccharides, but no convincing experimental evidence for such binding has been presented. (Reference 6 is a review of this topic.) By what mechanism, then, does silicon (as silicic acid) deficiency produce the reported pathological changes?

The Search for Mechanism

A key issue in the mechanism underlying the essentiality of an element is its location at tissue, cellular, and molecular levels, and as noted no *molecular* binding of silicon has been observed. Plasma contains silicic acid in the concentration range 5–10 μm/L, so that all tissue is exposed to it. Noting that osteogenesis was impaired in silicon-deficient experimental animals, Carlisle conducted a microprobe scan across a bone section and found silicon to be concentrated (0.5%) locally at the mineralization front (*7*). A major effect of silicon deficiency was on the synthesis of the preosseous, collagenous matrix that is mineralized to form bone proper. Carlisle noted that the activity of prolylhydroxylase (a key enzyme in collagen synthesis) in tissue cultures of cartilage from silicon-deficient chicks was low but was increased when silicon (silicate) was added to the culture (*8*). The conclusion drawn was that silicon was a cofactor in the proper functioning of this enzyme. The known cofactors for prolylhydroxylase are iron, oxygen, ascorbate, and 2-oxyglutarate, and it is extremely difficult to see how silicic acid can engage in any chemistry with any of these cofactors, or with the enzymic protein. However, the observed increase in activity prompted by silicic acid addition requires explanation.

The first clue to a possible explanation came from an entirely different direction. Hexokinase, with adenosine triphosphate (ATP)-Mg^{2+}, is involved in the first step in the metabolism of glucose, the formation of glucose-6-phosphate. The activity of hexokinase is low and can be raised by the addition of citrate (*9*). The low activity is due to contamination with aluminum, which binds to ATP 10^7 times more strongly than the required Mg^{2+} and blocks phosphate transfer. The role of citrate, a strong complexing agent for aluminum, is to remove aluminum from ATP and so allow Mg^{2+} to bind. Aluminum is almost as ubiquitous as silicon, and the two elements, in Iler's words, "have a unique affinity" (*1*). There appears to be no *organic* chemistry of silicon in biological systems, so the question becomes, Could the effects of its deficiency be related to inorganic chemistry, with aluminum (now known to be toxic) being the interacting metal?

A Test of the Concept: Prolylhydroxylase Activity

Prolylhydroxylase, the collagen synthesis enzyme that has low activity in silicon-deficient tissue, requires iron that cycles between Fe^{3+} and Fe^{2+}. The apoenzyme will bind aluminum (less strongly than iron), and the enzyme is then, of course, inactive. An experiment was conducted (*6*) in which the apoenzyme was presented with iron first and then aluminum, all other essential cofactors being present. Activity, as measured by hydroxyproline production, was reduced by 20% of the control level. When the

apoenzyme was presented with aluminum first and then iron, activity was reduced by 55% of the control levels. Silicic acid alone had no effect on the activity, which remained at the control level (Table I). However, when the "Al first" experiment was repeated in the presence of a sixfold excess of silicic acid (600 μM) over aluminum, the inhibiting effect of aluminum was completely suppressed. Clearly, in the presence of silicic acid, aluminum is removed from competition with iron for binding in prolylhydroxylase.

Table I. Effect of Silicic Acid on Inhibition of Prolylhydroxylase by Aluminum

Addition (100 μM)	*% Inhibition of Control*[a]
$Si(OH)_4$	0
Fe then Al	20
Al then Fe	55
Al + 600 μM ($Si(OH)_4$)	0

[a]Assays were done by measuring the release of ^3H as ^3H_2O from ^3H-prolylprotocollagen, which accompanies the hydroxylation of proline at position 4.

This experiment strongly supported the developing hypothesis that conditions in which silicon levels are (artificially) low allow the manifestation of aluminum toxicity. However, as will be shown later, aluminum challenges Ca^{2+} and Mg^{2+} rather than iron in vivo.

Aluminum in Biological Systems

Aluminum has long been regarded as innocuous. It is not used in biological systems and, strangely, for so ubiquitous an element, is largely excluded; iron, with a very similar charge-to-radius ratio, is essential and actively sought. The perception of aluminum as innocuous has changed over the past 2 decades. Aluminum is indisputably the agent responsible for the disorders observed in patients undergoing hemodialysis for renal insufficiency when aluminum-containing dialysate is used. Plasma aluminum can then rise from <1 μM to >5 μM with three potential consequences (*10*):

1. a microcytic anemia not responding to iron therapy, but responding to reduced plasma aluminum levels
2. a progressive deterioration in cognitive function with eventual dementia (dialysis encephalopathy).
3. a disorder of bone (dialysis osteomalacia) with inactive osteoblasts, bone pain, and spontaneous fracture. In this, aluminum is found at the growth front (Figure 1). (Silicon has been found in the same location).

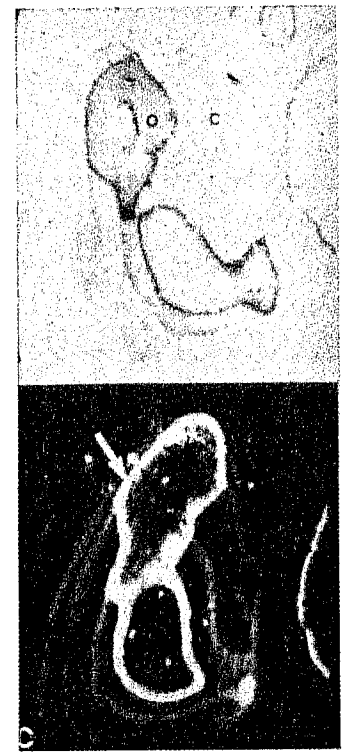

Figure 1. Aluminum (arrowed) at the growth front in bone from patient with dialysis osteomalacia. (Reproduced with permission from reference 35. Copyright 1990.)

Now that aluminum is recognized as the cause of these disorders, levels are carefully monitored, and aluminum is removed from dialysis fluid by reverse osmosis.

Aluminum is the major toxic entity for aquatic life in waters affected by "acid rain" and is the major cause of poor crop yields in acidic soils in which root growth is stunted (*11*, *12*).

The mechanisms underlying these effects are not well-understood, but there is a consensus that, once within the biological milieu, aluminum displaces Mg^{2+} from key sites where this metal is an essential cofactor and is involved in the disturbance of Ca^{2+} manipulation (*see* later).

In dialysis with aluminum-containing water, the metal bypasses the normal exclusion mechanisms, and in acidic waters high in aluminum

(5–10 μM), bioavailable aluminum is adsorbed at fish gill epithelia and then absorbed systemically. The dietary intake of aluminum in humans is of the order of 10–20 mg/day (*13*), but only a small fraction is absorbed in the gut. The exclusion mechanism is unknown. Absorption is increased by citrate and other aluminum-complexing agents.

The facts that aluminum ingress in dialysis gives rise to an encephalopathy, that aluminum levels are raised in the brains of patients with Alzheimer's disease (*14*), and that aluminum, colocalized with silicon, is found at the core of the senile plaques characteristic of Alzheimer's disease (*15*) have prompted concern that dietary aluminum can, in susceptible individuals, provoke or be a cofactor in Alzheimer's disease. In one recent epidemiological study (*16*), a relationship was found between the aluminum content of drinking water and the incidence of Alzheimer's disease. Two criticisms were made of this study: (1) a lack of dose–response correlation with near-maximum increase in Alzheimer's disease incidence at the lowest levels of aluminum concentration, and (2) even at the highest level of aluminum (>111 ppb) included in this study, the daily aluminum intake from water would be <0.5 mg, whereas the intake from food would be 10–20 mg. [In 1982, about 4×10^6 pounds of aluminum compounds were used as food additives in the U.S. (*17*).] This apparent paradox is resolved if the hypothesis that silicon limits aluminum bioavailability is adopted. Aluminum and silicon concentrations in potable water are inversely related. High aluminum and low silicon levels are found in soft waters from high, well-weathered, acidic catchment areas requiring aluminum coagulation treatment for clarification. Conversely, hard, mineralized waters from still-weathering geology are high in silicon, often 10-fold or more than the level in soft water. It has been proposed (*18*) that this epidemiological study in fact revealed a relationship between the silicon content of water and its role in suppressing the absorption of the aluminum contained in food.

A Test of the Al–Si Balance Hypothesis

Fish in acidic waters containing aluminum have high mortality due to gill damage and loss of osmo- and ionoregulatory function. In one experiment (*19*), Atlantic salmon fry were exposed to acidic water (pH 5) containing a toxic level of aluminum (ca. 7 μM) with low (0.60 μM) and high (93 μM) levels of silicon as silicic acid. The "pure", control water (at pH 5) contained low levels of both elements, 0.85 μM aluminum and 0.66 μM silicon. Survival curves are shown in Figure 2. In the 7 μM Al, low-silicon conditions, 50% of fish were dead within 26 h, and all fish were dead within 48 h. Gill damage was obvious, and the fish contained 2 μM Al per gram of dry mass. With the high silicon level, no fish died in the duration of the experiment, gill structure remained normal, and the fish contained

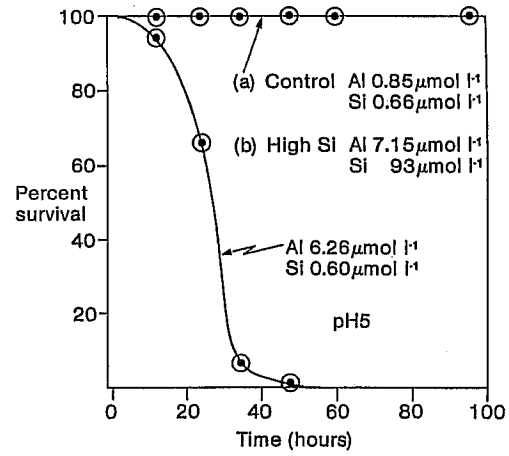

Figure 2. Survival curves for Atlantic salmon fry exposed to control (low Al) water and water containing ca. 7 μM Al with high and low silicic acid levels. The top curve shows both control and high-Si results. (Reproduced with permission from reference 35. Copyright 1990.)

only 0.40 μM Al per gram of dry mass, 10% less than that absorbed from the control water.

Clearly, in the presence of the high level of silicon, aluminum was prevented from binding at gill epithelial surfaces and systemic absorption. This exclusion occurred at the interface between creature and the external environment, and a fundamental question is, Is this a general effect, not only at the fish gill, but also at plant root membranes and in the gastrointestinal tract of mammals and humans?

The Exclusion Mechanism

Iler has remarked (p 193, ref. 1), that "there is a peculiar affinity between the oxides of aluminum and silicon". This affinity results from the isostructural nature of $(SiO_4)^{4-}$ and $(AlO_4)^{5-}$, which is responsible for the vast range of natural aluminosilicates and synthetic zeolites. Synthetic zeolites are synthesized by the reaction of aluminate and silicate anions at high temperature and pH. However, interactions occur between silicic acid and hydroxyaluminum ions in dilute ($<10^{-4}$ M) solution at near-neutral pH, and these interactions are of biological and environmental significance in reducing aluminum bioavailability. Hydroxyaluminum cations were shown (*20*) to react with silicic acid in solutions of pH 4 upwards to form clear solutions containing nondialyzable hydroxyaluminosilicate species with a limiting Si:Al ratio of about 0.5. A concentration of at least 100 μM $Si(OH)_4$ is required. When such solutions are heated, the poorly

crystalline mineral imogolite is precipitated. This unidimensional, tubular structure has the ideal composition $(HO)_3Al_2O_3$ SiOH and can be considered as a single gibbsite sheet with the inner surface hydroxyls replaced by silicic acid. The stable, clear, unheated solutions appear to contain fragments of this structure. The species have been detected by the infrared examination of solids recovered by freeze-drying solutions (*20*) and by ion-exchange experiments (*21*, *22*). Although the apparent solubility of aluminum is raised at the pH of normally minimum solubility in the presence of silicic acid (Figure 3), the hydroxyaluminosilicate species present limit the bioavailability of aluminum. The interaction of aluminum with various binding groups is reduced when silicic acid is present, as is illustrated by ion-exchange experiments using an iminodiacetate functional resin (Figure 4) (*22*). The fall in aluminum retention (Figure 4a) from about pH 7 is seen to correspond to the formation of hydroxyaluminosilicate species (Figure 4b). Similar results (*21*) were obtained with sulfonate and phosphonate functional resins with the pH of onset of reduced aluminum binding being >5 and >6.6, respectively. Such experiments reflect the stability of the hydroxyaluminosilicate species with respect to ligand–Al binding.

Fish gill epithelia and associated mucus contain such binding groups and, as in ion-exchange resins, aluminum binding is similarly reduced in the presence of silicic acid. This reduction is possibly aided by a pH more

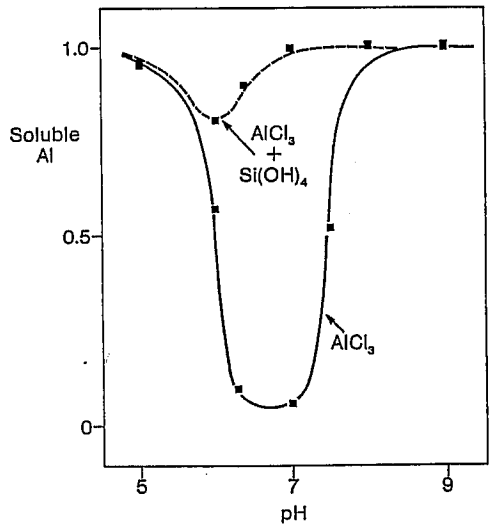

Figure 3. Fraction of aluminum remaining in 20-h-old solution after filtration through a 0.2-μM membrane as a function of pH. Solutions contained 0.1 mM $AlCl_3$ with and without 0.5 mM $Si(OH)_4$. (Reproduced with permission from reference 35. Copyright 1990.)

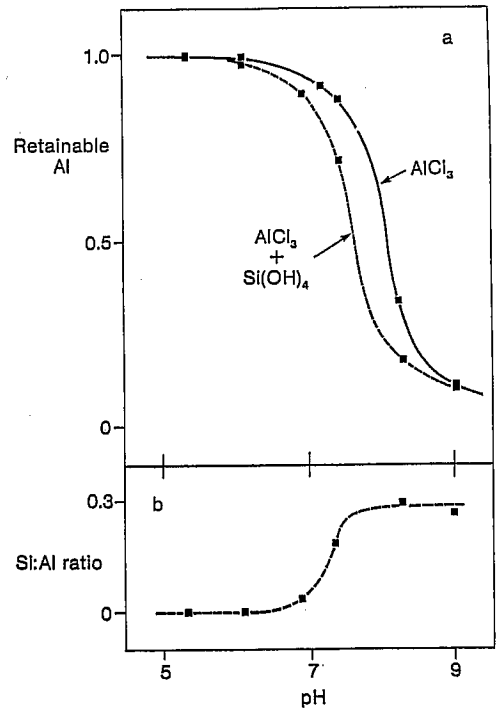

Figure 4. Part a: Fraction of aluminum retained on iminodiacetate functional resin as a function of pH. Solutions contained 0.1 mM $AlCl_3$ with and without 0.5 mM $Si(OH)_2$. Part b: The Si:Al ratio of the retained species. (Reproduced with permission from reference 35. Copyright 1990.)

alkaline than that of the bulk water within a boundary layer proximate to the gill surface and resulting from NH_3 and CO_2 excretion.

At pH 6.2, the formation of the solid hydroxide phase gibbsite limits the level of dissolved aluminum to about 10^{-7} M. The formation of imogolite reduces this level to 10^{-11} M, so that the formation of hydroxyaluminosilicate phases reduces the concentration of biologically available aluminum to levels well below those producing toxic effects.

The formation of hydroxyaluminosilicate species at near-neutral pH is unique. No interactions occur between silicic acid and Ca^{2+} or Mg^{2+} at less than pH 10, so that the transport and binding of these cations is unhindered. The interactions of Fe^{3+} with silicic acid at near-neutral pH are very different from those of aluminum. Acidic solutions containing Fe^{3+} (10^{-4} M) with a threefold molar excess of silicic acid remain clear on neutralization: no visible precipitate forms. Instead, Fe–O polymers are formed as spherical hydrated ferric oxide particles 10–15 nm in diameter,

stabilized against growth, aggregation, and precipitation by an adsorbed layer of silicic acid (*23*).

Such sols present iron in a readily available form to chlorotic plants, probably because the minute particles are easily reduced to Fe^{2+} and solubilized by root exudates (*24*). Thus, silicic acid distinguishes between aluminum and iron as regards biological availability. This ability to distinguish may have been important in primitive biological systems.

The Significance of the Environmental Si:Al Balance

Biological systems are not tolerant of internalized aluminum, which normally is excluded or, as in some plants, rendered immobile, possibly by binding to phytate. In mammals and humans, once internalized, aluminum is bound and carried in the iron-transport protein transferrin (*25*), which can bind two M^{3+} ions per molecule. Although aluminum is bound much less strongly than iron, (log K ca. 12 for Al^{3+} and log K ca. 20 for Fe^{3+}, where K is the stability constant) there is normally an abundance of transferrin with empty sites. Aluminum appears to be concentrated in cells and tissue with high transferrin receptor density, a conclusion supported by experiments using ^{67}Ga-loaded transferrin, in which the marker is found in areas of the rat brain with high receptor density (cerebral cortex, hippocampus, septum, and amygdala) (*26*). These areas are selectively vulnerable in Alzheimer's disease. Aluminum-loaded transferrin is internalized by cultured neuroblastoma cells (*27*) and, presumably, by cerebrovascular endothelial cells because aluminum crosses the blood–brain barrier. Aluminum has also been detected within osteocytes at the junction of osteoid and mineralized bone in patients with dialysis osteomalacia (*28*) and is almost certainly responsible for the low level of cellular activity. A key point is that ferritin is inefficient at loading with aluminum, so that there is no safe "sink" for the element. Events at the intracellular level ultimately responsible for toxicity remain unclear, but aluminum impairs glucose utilization and cholinergic activity in the rat brain (*29*). GTP–GDP (guanosine 5′-triphosphate–guanosine diphosphate) nucleotide exchange is inhibited by aluminum (*30*) and, in vitro, aluminum stimulates phosphatidylinositol (PtdIns) hydrolysis and inhibits PtdIns(4,5)P_2 (where (4,5)P_2 is inositol 4,5-bisphosphate) hydrolysis (*31*). In vitro, aluminum inhibits tetrahydrobiopterin synthesis (*32*). Significantly, aluminum has been reported to increase the permeability of the blood–brain barrier (*33*), and indeed, endothelial "leakiness" is a constant theme, as is alteration in the manipulation of Ca^{2+}. Recent experiments (*34*) suggest that this latter alteration may result from interference in the phosphatidylinositol-derived Ca^{2+} intracellular second messenger system. In rat pancreatic acinar cells, the microinjection of aluminum eliminated the acetylcholine-evoked mobilization of Ca^{2+} from cytoplasmic stores. Early experiments indicated

that this inhibitory effect of aluminum is absent in the presence of silicic acid. This Ca^{2+}-mobilizing system is ubiquitous in biological systems, and its alteration may account for many of the toxic effects of aluminum in plants, animals, and humans.

In view of these various effects of internalized aluminum, the exclusion of the element from biological systems is fundamentally important (*35*). The low solubility of aluminum at neutral pH is one mechanism, but acidity increases availability. Citrate (*36*) and other chelators [e.g. maltol (*37*)] appear to increase absorption in the gastrointestinal tract. An important question is, How general throughout biological systems is the observed effect of silicic acid in excluding aluminum from fish? Is this mechanism operating at plant root membranes and within the gastrointestinal tract?

Silicic Acid: Geochemistry and Health

The essential trace elements (and the toxic elements) are ultimately obtained from the earth's crust via crops and water, although human activity can modify occurrence and availability. The multidisciplinary subject of environmental geochemistry and health studies the relationship between disease epidemiology and geochemistry. Most success has come in understanding the relationship between trace-element deficiency in farm animals and local geochemistry, for example, the effects of Cu deficiency in cattle. The recognition of the goiter of iodine deficiency and the effects of fluorine on the incidence of dental caries are examples of success, as is the recognition of selenium deficiency as the cause of endemic cardiac myopathy in the Keshan district of China (*38*).

A negative association between silica concentration and the incidence of ischemic heart disease (IHD) has been reported (*39*, *40*) and is associated with the lower incidence of IHD in hard-water areas (*41*, *42*). Silicon is associated negatively with IHD mortality (correlation coefficient $r = 0.66$) and positively ($r = +0.68$) with water hardness (*42*). However, no explanation for this observation has been possible. A marked geographical variation occurs in the incidence of ischemic heart disease in the British Isles. A high incidence occurs in the north and west, and a low incidence in the south and east, the relative odds of a major IHD event in males changing from 1.0 in the south of England to 3.03 in Scotland (*43*). This difference reflects, inter alia, a difference in geology between the regions with hard water in the south and east and soft, peaty water from upland areas in the north and west. Silica concentration can differ by an order of magnitude (<10 to >200 μM). The water from upland catchment areas is frequently treated with aluminum for clarification, and with very low silicic acid levels, residual aluminum is likely to be biologically available.

However, with the major part of the intake of aluminum being food (and antacid medication), the important question is the effect of *silicic acid* in water on the absorption of the aluminum in food (*18*). The extent of exclusion would not then be a linear function of silicic acid concentration, because a minimum level of about 100 μM Si is required for the formation of stable hydroxyaluminosilicates, in which the Si:Al ratio is about 0.5 and which have minimum solubility (Figure 5).

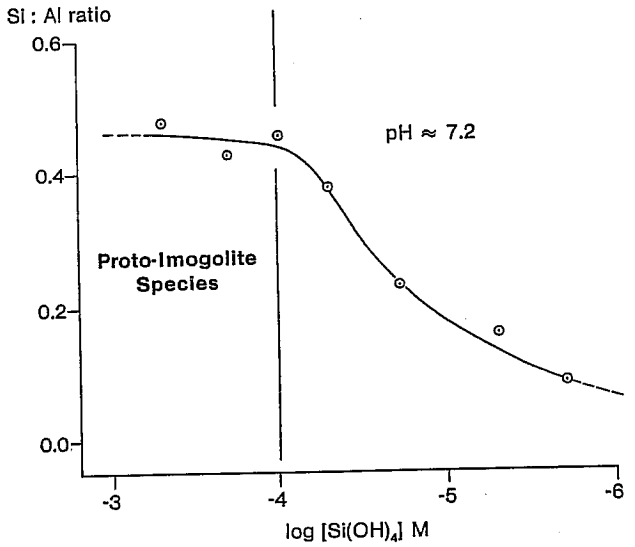

Figure 5. The Si:Al ratio of hydroxyaluminosilicate species formed in solutions containing 10 μM Al^{3+} at pH 7.2. All solutions were aged 20 h and held at 20 °C. (Private communication, J. S. Chappell).

Silicic acid is readily absorbed, and plasma levels rise rapidly following intake. In normal subjects excretion is rapid, average plasma levels are 5–10 μM, and all cells and tissues contain silicon, which may be concentrated in some cells or cellular compartments, for example, in the osteoblast. Little is known of the interactions between this silicic acid and internalized aluminum. With aluminum bound strongly to transferrin and the low plasma silicic acid levels, interaction is unlikely except at sites of local concentration. Codeposited aluminum and silicon (as amorphous aluminosilicate) has, so far as is known, been reported only at the core of senile plaques. Separate groups of workers report silicon in artery walls (*44*) and aluminum (*45*) in artery walls, but no studies have been made of the association and balance of the two elements in tissue. Such studies will be required if progress is to be made. Some workers have reported an

inverse relationship between the level of silicon in arterial tissue and the degree of sclerotic damage and calcification (*46*). The link between all these various observations may be the ability of internalized aluminum to increase the permeability of endo- and epithelial membranes and to alter intracellular Ca^{2+} manipulation and the ability of silicic acid to exclude aluminum from entry in biological systems and, possibly, its ability to modify the effects of internalized aluminum.

Conclusions

The most recent research indicates that in its biological effects, silicon (always as silicic acid) is inextricably linked with aluminum. Good evidence suggests that silicic acid reduces the absorption of manganese in plants and thereby moderates the toxicity associated with excess manganese (*47*, *48*). However, the predominant association is with aluminum because of the prevalence of the two elements and the unique affinity of one for the other. The need in primeval biological systems to "select out" aluminum thus probably involved high silicic acid levels at near-neutral pH, and it will be important to understand the anthropogenic disturbance of the interactions of these two elements that, with oxygen, constitute 80% of the earth's crust. This area is one of the most exciting in bioinorganic chemistry.

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