ALUMINIUM IN BIOLOGY AND MEDICINE
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Symposium on Aluminium in Biology and Medicine, held at the Ciba Foundation, London, 19–21 November 1991

The topic of this symposium was proposed independently by Professor D. N. S. Kerr and by Professor J. D. Birchall

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Aluminium in biology: an introduction
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The easiest way to an understanding of the roles played by an element in the chemistry of living systems is to start from the periodic table:

<table>
<thead>
<tr>
<th>IA</th>
<th>IIA</th>
<th>IIIA</th>
<th>IVA</th>
<th>V</th>
<th>Transition metals</th>
<th>IIIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li</td>
<td>Be</td>
<td>B</td>
<td>C</td>
<td></td>
<td>......</td>
<td>......</td>
</tr>
<tr>
<td>Na</td>
<td>Mg</td>
<td>Al</td>
<td>Si</td>
<td>P</td>
<td>..........</td>
<td>Cr</td>
</tr>
</tbody>
</table>

where M stands for a great number of elements including scandium (Sc), yttrium (Y) and the fourteen lanthanides (Da Silva & Williams 1991). Of this group of elements, Li, Be and B are rare elements in the cosmos, because of the mode of nuclear synthesis and the stability of the nucleus of carbon. Even so, boron is essential for plant life. All the other elements shown above are more abundant and, with the exception of Al, M, Cr and gallium (Ga), are used extensively by biology and are in fact essential for all life. In chemical terms this means that biological systems have created a strong artificial divide between cationic elements, metals, and anionic, non-metal elements by ignoring the elements which exist only as $M^{3+}$ ions in water (Fig. 1). Iron and manganese escape exclusion through the switch to Fe$^{2+}$ and Mn$^{2+}$. A similar restriction of acceptability applies in Group IV to elements such as germanium (Ge) and titanium (Ti), which widens the gap between biologically useful metals and useful non-metals. What is wrong with $M^{3+}$, and especially $Al^{3+}$, as far as biology is concerned?

Many points will be highlighted in the following chapters. Some of them will be introduced here so that the flow of the symposium will be apparent.

The first point to make is that aluminium is not easily available, and this is generally true of all $M^{3+}$ ions. Hydrolysis at pH=7 ensures that while virtually all Groups IA, IIA and divalent ions of transition metals from Mn to Zn are available and soluble, and the elements from Group V onwards are hydrolysed to anions and so become soluble and available (Fig. 1), the elements
from Groups III and IV are lost as oxide precipitates. In addition, iron, as Fe$^{3+}$, is heavily hydrolysed and is not readily available, so that biology has had to devise siderophores and proteins (transferrins) to obtain it. Now, the fact that biology could learn to handle the uptake of Fe$^{3+}$ means that it has always had the capability to devise means of obtaining Al$^{3+}$ and M$^{3+}$ generally. However, it did not do so and does not do so. Why?

The parallel chemistries of Fe$^{3+}$ and Al$^{3+}$ (M$^{3+}$) raise other problems, because Al$^{3+}$ could perhaps utilize Fe$^{3+}$ systems of uptake and transport. Is this a problem? Similarly, methods for removing Al$^{3+}$ in biology, if they exist, must run into the problem of protecting Fe$^{3+}$, unless there are selectivity factors. Notice, for example, that most of the insoluble minerals of the earth undergo easy isomorphous substitution of Al and Fe—for example, in asbestos. We have to look for subtle chemical differences to see where iron and aluminium differ in order to understand how nature has avoided aluminium and can manage to do this in the presence of iron.

A suggestion may not be out of order. Al$^{3+}$ is exceedingly small, with a radius of 0.54 Å, while Fe$^{3+}$ has a radius of 0.65 Å. There are always likely to be heavy steric constraints around Al$^{3+}$. However, we also know that Fe$^{3+}$ has a preference for nitrogen-donor ligands which exceeds that of Al$^{3+}$. Taking these two factors together, we should not be too surprised that the difference between the hydrolysis constants giving hydroxides and the binding constants for ligands such as EDTA$^{4-}$ favours Fe$^{3+}$ binding to EDTA$^{4-}$, while
TABLE 1 Some thermodynamic binding data for aluminium and closely related elements

<table>
<thead>
<tr>
<th>Property</th>
<th>Al$^{3+}$</th>
<th>Ga$^{3+}$</th>
<th>Fe$^{3+}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility product (OH$^-$)</td>
<td>32.0</td>
<td>38.0</td>
<td>38.8</td>
</tr>
<tr>
<td>log $K$ (EDTA$^{4-}$)</td>
<td>16.3</td>
<td>21.7</td>
<td>25.8</td>
</tr>
<tr>
<td>log $K$ (F$^-$)</td>
<td>6.4</td>
<td>5.5</td>
<td>5.3</td>
</tr>
<tr>
<td>log $K$ (OH$^-$)</td>
<td>9.0</td>
<td>11.1</td>
<td>11.4</td>
</tr>
</tbody>
</table>

For more extensive data on Al$^{3+}$ (and on Ca$^{2+}$) see Tam & Williams (1985).

aluminium is more likely to be found as the hydroxide (Table 1). Even Ga$^{3+}$, which has a somewhat similar affinity for EDTA$^{4-}$, is weaker in its binding than Fe$^{3+}$, although Ga$^{3+}$ is intermediate between Fe$^{3+}$ and Al$^{3+}$ in size. We find that transferrin binds to Ga$^{3+}$ some 100-fold less tightly than does Fe$^{3+}$. We may wonder if Ga$^{3+}$ is a better marker for Fe$^{3+}$ or for Al$^{3+}$.

The above considerations concern thermodynamic binding properties, but we should also consider rates of reaction of $M^{3+}$. It has been known for long enough that the on/off reactions of $M^{3+}$ ions, even removal of water from them, are slow. Their reactions are very sticky so that (unlike $M^+$ and $M^{2+}$ ions) they are of little value in message transmission which demands exchange (compare K$^+$, Na$^+$ and Ca$^{2+}$ and the lesser value of the slower Mg$^{2+}$). Even in acid/base catalysis (compare the relatively fast acting Mg$^{2+}$, Mn$^{2+}$ and Zn$^{2+}$ but the lesser value of the slower Ni$^{2+}$) and gene control (as for example by the faster Fe$^{2+}$, Mn$^{2+}$, Zn$^{2+}$) the trivalent ions may be unsuitable because of slowness of exchange. All such factors influence the way in which evolution 'assesses' the value of an element. In a comparative sense, does Al$^{3+}$ have no positive advantage and therefore can it only inhibit useful functions of other elements?

Only when we have this chemistry in mind can we turn to the potentially hazardous influence of $M^{3+}$ and especially Al$^{3+}$ in biology—once it is admitted. Here, we divide the effects of Al$^{3+}$ in the environment (problems generated by acid rain) from those in biological fluids. Clearly, in acidic water Al$^{3+}$ is damaging to aquatic life, especially fish gills and probably plant root systems. We must ask why this is so. We may suspect that Al$^{3+}$ is displacing Ca$^{2+}$ and Mg$^{2+}$ at external sites, such as the root cell wall and the extracellular structures of fish gills (Tam & Williams 1986). Does the same logic apply in the digestive system? We know that Al$^{3+}$ salts are used to remove excess phosphate by precipitation in patients on dialysis, but this leads to high Al$^{3+}$ concentrations elsewhere and consequent hazards.

When we come to the inside of the cell, we approach a new milieu. There is virtually no calcium, but much Mg$^{2+}$ and a variety of phosphate compounds. Al$^{3+}$ ($M^{3+}$) has a high affinity for phosphate. This consideration (and a similar one arises through the affinity of Al$^{3+}$ for fluoride) leads to
obvious thoughts about the possible problems of $\text{Al}^{3+}$ poisoning, but (and there are many buts) how could $\text{Al}^{3+}$ ever come to be in the cell?

One of the possible modes is through the carriers of iron. In bacteria these are siderophores, in plants maybe citrate, and in animals, transferrins. We shall need to know if $\text{Al}^{3+}$ binding to these molecules is strong enough and if the shapes of its complexes are sufficiently similar to those of $\text{Fe}^{3+}$ for it to be carried into the cell by these carriers. Of course, this is not enough. It must also be released from the internalized carrier. Assuming that a step in the uptake of $\text{Fe}^{3+}$ by these carriers is reduction to $\text{Fe}^{2+}$, this path is not open to $\text{Al}^{3+}$, but what if the step is just acidification?

There are, then, many chemical and biochemical issues before we come to the problems which could be related to Alzheimer’s disease. It is here we must be more cautious, because while aluminium may be a problem, it is clear that there may well be genetic factors and (resultant) proteins or glycoproteins generated through ‘mistaken’ syntheses. These aspects will be discussed in several chapters and they introduce new points for consideration. How good are the analytical methods for measuring aluminium levels inside cells? How well characterized is aluminium’s association with target proteins, and with early signs of Alzheimer’s disease? To what degree is Alzheimer’s disease inherited?

Let us go so far as to say that maybe aluminium is not yet known to be the cause of any known disease of those who live on a normal diet (Sherrard 1991). This must not stop us asking whether it exacerbates any diseases. At the same time, it must not hide from us the fact that $\text{Al}^{3+}$ is often found associated with plaques outside cells within damaged nervous tissue of brain. We know, in fact, that this association is diagnostic in many cases of the diseased state in post mortem analysis. Why has $\text{Al}^{3+}$ become selectively bound in plaques? This must tell us the nature of the specific lesion. Other trivalent ions are purposefully introduced to be used in diagnostics—$\text{Ga}^{3+}$, $\text{Gd}^{3+}$, $\text{In}^{3+}$ and so on. What do we understand about their relative chemistries? Will a combination of the use of high valent ions lead us to a set of diagnostic tools for disclosing what $\text{Al}^{3+}$ is indicating to us?

I close leaving the problems as they were. Let us see what light can be shed upon them in the next few days.

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Aluminium speciation in biology

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Abstract. Before we can understand the role of Al$^{3+}$ in living organisms we need to learn how it interacts with molecules found in biological systems. The only aluminium oxidation state in biology is $3^+$. In aqueous solutions there are only two main Al(III) species: the hexahydrate Al$^{3+}$ at pH < 5.5 and the tetrahedral aluminate at pH > 6.2. In the blood plasma, citrate is the main small molecule carrier and transferrin the main protein carrier of Al$^{3+}$. In fluids where the concentrations of these two ligands are low, nucleoside di- and triphosphates become Al$^{3+}$ binders. Under these conditions Al$^{3+}$ easily displaces Mg$^{2+}$ from nucleotides. When all three classes of ligands are at low concentrations, catecholamines become likely Al$^{3+}$ binders. Double-helical DNA binds Al$^{3+}$ weakly and under no conditions should it compete with other ligands. Al(III) in the cell nucleus probably binds to nucleotides or phosphorylated proteins. Al$^{3+}$ undergoes ligand exchange much more slowly than most metal ions: $10^3$ times slower than Mg$^{2+}$.


To understand the roles of an element in an organism we need to know not only the gross amount present, but also the locale and species—valence state and complexes or compounds—into which the element enters. In the case of Al$^{3+}$, strong complexing by citrate or transferrin prevents Al$^{3+}$ from acting as a surrogate for Mg$^{2+}$ in reactions with nucleotide. The chemistry of aluminium is relatively simple. It reacts $10^7$ times faster than Cr$^{3+}$, its hydroxide is much more soluble than that of Fe$^{3+}$, and it exhibits only one oxidation state in biological systems, Al$^{3+}$. Metallic aluminium is too reactive to be found free in Nature, and the metal is won from its ores only with difficulty. Thus there is no oxidation-reduction chemistry to Al$^{3+}$ in biology.

We begin our evaluation of Al$^{3+}$ by considering its ionic radius. In both mineralogy and biology, comparable ionic radii are frequently more important than charge in determining behaviour. The effective ionic radius of Al$^{3+}$ in six-fold coordination is 54 pm. By way of comparison, other values are Ga$^{3+}$, 62; Fe$^{3+}$, 65; Mg$^{2+}$, 72; Zn$^{2+}$, 74; Fe$^{2+}$, 78; and Ca$^{2+}$, 100 pm (Martin 1986a). On the basis of the radii, though quite small, Al$^{3+}$ is closest in size to Fe$^{3+}$ and Mg$^{2+}$, and it is to these ions that we compare Al$^{3+}$. Ca$^{2+}$ is much larger,
and in its favoured eight-fold coordination exhibits a radius of 112 pm, yielding a volume nine times greater than Al\(^{3+}\). For this and other reasons we have argued that in biological systems Al\(^{3+}\) will be competitive with Mg\(^{2+}\), rather than Ca\(^{2+}\) (Macdonald & Martin 1988, Martin 1988a). Both Al\(^{3+}\) and Mg\(^{2+}\) favour oxygen donor ligands, especially phosphate groups (Martin 1990b). Al\(^{3+}\) is 10\(^7\) times more effective than Mg\(^{2+}\) in promoting the polymerization of tubulin to microtubules (Macdonald et al 1987). Wherever there is a process involving Mg\(^{2+}\), seek there an opportunity for interference by Al\(^{3+}\).

**Al\(^{3+}\) hydrolysis**

Whatever ligands may be present, understanding the state of Al(III) in any aqueous system demands awareness of the species that Al(III) forms with the components of water at different pH values. (We use Al(III) as a generic term for the 3\(^+\) ion when a specific form is not indicated.) In solutions more acid than pH 5, Al(III) exists as an octahedral hexahydrate, Al(H\(_2\)O\(_6\))\(^{3+}\), usually abbreviated as Al\(^{3+}\). As a solution becomes less acidic, Al(H\(_2\)O\(_a\))\(^{3+}\) undergoes successive deprotonations to yield Al(OH)\(^2+\), Al(OH)\(^+\) and soluble Al(OH)\(_3\), with a decreasing and variable number of water molecules (Martin 1988a, 1991b). Neutral solutions give an Al(OH)\(_3\) precipitate that redissolves, owing to the formation of tetrahedral aluminate, Al(OH)\(_4^-\), the primary soluble Al(III) species at pH > 6.2.

The four successive deprotonations from Al(H\(_2\)O)\(_6\))\(^{3+}\) to yield Al(OH)\(_4^-\) squeeze into an unusually narrow pH range of less than one log unit with pK\(_a\) values of 5.5, 5.8, 6.0 and 6.2 (Ohman 1988). In contrast, the corresponding four normal deprotonations from Fe(H\(_2\)O)\(_6\))\(^{3+}\) span 6.6 log units with pK\(_a\) values of 2.7, 3.8, 6.6 and 9.3. The narrow span for Al\(^{3+}\) is explained by the cooperative nature of the successive deprotonations resulting from a concomitant decrease in coordination number (Martin 1991b).

The upper half of Fig. 1 shows the distribution of free metal ion and mononuclear hydrolysed species based on the four successive pK\(_a\) values given above. Thus only two species dominate over the entire pH range, the octahedral hexahydrate Al(H\(_2\)O\(_6\))\(^{3+}\) at pH < 5.5, and the tetrahedral Al(OH)\(_4^-\) at pH > 6.2, while there is a mixture of hydrolysed species and coordination numbers between 5.5 < pH < 6.2 (Martin 1988a, 1991b). These equilibria must be considered in all solutions containing Al(III). If in addition other ligands are incapable of holding Al(III) in solution, it becomes necessary to include the solubility equilibrium.

The lower half of Fig. 1 applies to solutions saturated with amorphous Al(OH)\(_3\). The dashed straight line of slope 3 in the lower half of the figure gives the molar concentration of the free metal ion, [Al\(^{3+}\)]. The solid curve represents the total concentration of the free metal ion and all mononuclear hydrolysed forms, T\(_{Al}\), with the distribution shown in the upper half of the figure. From the lower part of Fig. 1 we learn that large amounts of Al(OH)\(_3\) dissolve in acidic stomachs.
Aluminium speciation in biology

**FIG. 1.** $\text{Al}^{3+}$ hydrolysis. Upper half: Mole fraction of soluble species as a function of pH. Lower half: For saturated solutions of amorphous Al(OH)$_3$, the negative logarithm of molar concentration of the free ion, $[\text{Al}^{3+}]$, is shown as a straight dashed line; and the sum over all species present, $T_{\text{Al}}$, as a curved solid line. The straight dotted line represents the concentration of tetrahedral aluminate ion, $[\text{Al(OH)}_4^-]$. (From Martin 1991b by permission of the publisher. ©1991 Elsevier Science Publishing Co. Inc.)

Figure 1 also shows as a dotted line the molar concentration of aluminate, $[\text{Al(OH)}_4^-]$, the main species at pH $> 6.2$. At any pH the ordinate distance between the straight lines for $[\text{Al(OH)}_4^-]$ and $[\text{Al}^{3+}]$ gives the logarithm of their concentration ratio. Thus at pH 7.0 the molar ratio of $[\text{Al(OH)}_4^-]/[\text{Al}^{3+}]$ is given by $10^{4.5} = 3 \times 10^4$. Therefore, Al(OH)$_4^-$ (aluminate) should be the starting point for thinking about aluminium in biological systems.

What happens when an AlCl$_3$ solution is administered at a local concentration of 0.01 M Al(III) to a tissue at pH 7? Ascent of the dashed pH 7 line in Fig. 1 indicates that the permissible free $\text{Al}^{3+}$ is only $10^{-10.3}$ M and that...
of all soluble forms is $10^{-5.7} \text{M} = 2 \mu \text{M}$. Unless the remainder of the added Al(III) has been complexed by other ligands, it will form insoluble Al(OH)$_3$. From the upper part of Fig. 1 we see that of the soluble forms, 85% is Al(OH)$_4^-$ and 14% Al(OH)$_3$. Of the Al(III) administered at pH 7, only 2 μM appears in soluble forms, most of which is Al(OH)$_4^-$, since most of the added Al(III) precipitates or coordinates to nearby ligands. To keep Al(III) in solution, we can administer it as a complex.

$$pAl = -\log [\text{Al}^{3+}]$$

In addition to the hydrolysis features already considered, the amount of free, aqueous Al$^{3+}$ in solution depends upon several variables: ligands present, their stability constants with Al$^{3+}$, and the mole ratio of total Al(III) to total ligand. For ligands with protons competing with metal ion for binding sites in the pH range of interest, the pH is also a variable. Thus, instead of simple association of metal ion and basic ligand, Al$^{3+}$ + L → AlL, the relevant reaction may become displacement of a proton from the acidic ligand by the metal ion, Al$^{3+}$ + HL → AlL + H$^+$. For ligands containing amino, phenolate and catecholate groups, the amount of free, aqueous Al$^{3+}$ in neutral solutions becomes pH dependent. Thus, for these ligands, the listed stability constants overstate effective binding strengths and need to be lowered to reflect competition of the proton with the metal ion for basic binding sites. The most practical method to allow for proton–metal ion competition at a ligand is to calculate conditional stability constants applicable to a single pH (Martin 1986c, 1988a, 1991a). Conditional stability constants may also allow for the deprotonation of metal ion-coordinated water that yields more stable complexes with increasing pH in some Al$^{3+}$ complexes, such as with citrate, nitrilotriacetate and EDTA.

Results from the quantitative evaluation of conditional stability constants are revealingly expressed as the negative logarithm of the free Al$^{3+}$ concentration, $-\log [\text{Al}^{3+}] = pAl$. By analogy with pH, higher pAl values represent smaller amounts of free Al$^{3+}$. Table 1 and Figs. 2 and 3 show the conclusions. Table 1 lists conditional stability constants and pAl values at pH 6.6 and 7.4 for several systems with 1 μM total Al(III) under the conditions indicated in the table (Martin 1991a). Weak Al$^{3+}$ binders appear at the top and strong binders at the bottom of Table 1. The increasing pAl values as one goes down the table indicate decreasing free Al$^{3+}$ concentrations. Thus, since 0.1 mM citrate lies lower in Table 1 then does 1 mM ATP$^4^-$, we predict that citrate will withdraw Al$^{3+}$ from ATP$^4^-$, and experimentally citrate has been used for this purpose (Womack & Colowick 1979). Despite high normal stability constants as indicated in the second column, salicylate (Ohman & Sjoberg 1983) and catecholamines (Kiss et al 1989) bind Al$^{3+}$ relatively weakly because competition from the proton in the strongly basic ligands leads to the low conditional stability.
TABLE 1 Negative logarithm of free Al$^{3+}$ concentration (pAl)$^a$

<table>
<thead>
<tr>
<th>Complex or ligand$^b$</th>
<th>Log $K_5$</th>
<th>Log $K_{6.6}$</th>
<th>pAl</th>
<th>Log $K_{7.4}$</th>
<th>pAl</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>&lt;5.6</td>
<td>&lt;5.6</td>
<td>&lt;7.3</td>
<td>&lt;5.6</td>
<td>&lt;7.3</td>
</tr>
<tr>
<td>Salicylate, 0.2 mM</td>
<td>12.9, 10.6</td>
<td>6.3, 4.0</td>
<td>9.1</td>
<td>7.1, 4.8</td>
<td>10.7</td>
</tr>
<tr>
<td>Amorphous Al(OH)$_3$</td>
<td>Insoluble</td>
<td>9.1</td>
<td></td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>Al$^{3+}$ to Al(OH)$_4^-$</td>
<td>9.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catecholamines</td>
<td>15.6, 13.0</td>
<td>7.4, 4.8</td>
<td>9.7</td>
<td>9.0, 6.4</td>
<td>12.8</td>
</tr>
<tr>
<td>Kaolinite$^c$</td>
<td>Insoluble</td>
<td>10.2</td>
<td></td>
<td>12.6</td>
<td></td>
</tr>
<tr>
<td>AlPO$_4$</td>
<td>Insoluble</td>
<td>11.7$^c$</td>
<td></td>
<td>12.1$^d$</td>
<td></td>
</tr>
<tr>
<td>(HO)$_2$AlO$_3$POH$^-$(see text)</td>
<td>11.7$^c$</td>
<td>12.9$^d$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrilotriacetate (NTA)</td>
<td>11.1</td>
<td>10.0</td>
<td>11.7</td>
<td>11.6</td>
<td>13.3</td>
</tr>
<tr>
<td>2,3-DPG, 3 mM</td>
<td>12.5</td>
<td>11.6</td>
<td>12.2</td>
<td>12.2</td>
<td>13.1</td>
</tr>
<tr>
<td>ATP, 1 mM</td>
<td>7.9, 4.6</td>
<td>8.9</td>
<td>12.3</td>
<td>9.8</td>
<td>13.0</td>
</tr>
<tr>
<td>Citrate, 0.1 mM</td>
<td>8.1</td>
<td>11.3</td>
<td>13.3</td>
<td>12.7</td>
<td>14.7</td>
</tr>
<tr>
<td>Transferrin</td>
<td></td>
<td></td>
<td>13.6, 12.8</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>F$^-$, 5 mM, with OH$^-$</td>
<td></td>
<td></td>
<td>14.9</td>
<td>15.1</td>
<td></td>
</tr>
<tr>
<td>EDTA</td>
<td>16.2</td>
<td>13.1</td>
<td>14.8</td>
<td>14.7</td>
<td>16.4</td>
</tr>
<tr>
<td>Desferrioxamine</td>
<td>24.1</td>
<td>16.8</td>
<td>18.4</td>
<td>19.2</td>
<td>20.8</td>
</tr>
</tbody>
</table>

$^a$1 μM total Al(III) except for insoluble salts. Equilibria in addition to those related to listed log $K_c$ values often required to calculate pAl.

$^b$50 μM ligand unless otherwise noted.

$^c$10 mM total phosphate.

$^d$2 mM total phosphate.

$^e$Al$_2$(OH)$_3$Si$_2$O$_5$ with 5 μM Si(OH)$_4$, typical of plasma.

constants listed in the third and fifth columns. Kaolinite is the least soluble aluminium silicate (Martin 1990a).

Figures 2 and 3 show for several ligands pAl as a function of pH. A 1 μM total Al(III) is assumed, as indicated by the left pAl = 6 intercept of the curves on the ordinate at low pH, where in all cases the aluminium appears unbound as Al$^{3+}$. As the pH increases, strong differentiation in binding strength occurs, with maltol the weakest and desferrioxamine the strongest Al$^{3+}$ binder. The rectangle at pH 7.4 labelled Tf represents a range of reported values for transferrin under blood plasma conditions (Harris & Sheldon 1990, Martin et al 1987).

The dashed curve labelled Al(OH)$_4^-$ near pH 9 in Figs. 2 and 3 represents the pAl of 1 μM total Al(III) allowed by the hydrolysis depicted in the upper
FIG. 2. Negative logarithm of free aqueous Al\(^{3+}\) concentration (pAl) versus pH allowed by several introduced Al(III) complexes and solids. The dotted straight line of slope 3 represents amorphous Al(OH)\(_3\)\(\text{aq}\) and the dotted curve, 4.5 mM inorganic phosphate. Dashed and all solid curves refer to 1 \(\mu\)M total Al(III), beginning as Al\(^{3+}\) at pAl=6 at low pH on the left-hand ordinate. The dashed curve shows the decrease of free Al\(^{3+}\) due to metal ion hydrolysis leading to Al(OH)\(_4^-\) at bottom right. Solid curves (with mole ratios) represent maltol (3:1), nitrilotriacetate (NTA) (2:1), citrate (4:1), EDTA (2:1) and desferrioxamine, dfo (2:1). The rectangle labelled Tf refers to 50 \(\mu\)M transferrin under blood plasma conditions. (From Martin 1991a by permission of the publisher.)

Phosphate binding

In the human body, extracellular fluids contain about 2 mM total phosphate at pH 7.4 and intracellular fluids about 10 mM total phosphate at pH 6.6. Al\(^{3+}\) forms an insoluble salt with phosphate, often designated as AlPO\(_4\) or sometimes as AlPO\(_4\)•2H\(_2\)O, corresponding to the composition of the mineral...
Aluminium speciation in biology

FIG. 3. Negative logarithm of free aqueous Al\(^{3+}\) concentration (pAl) versus pH allowed by several natural Al(III) complexes and solids. The dotted straight line of slope 3 represents amorphous Al(OH)\(_3\)(s), and the dotted curve, 4.5 mM inorganic phosphate. Dashed and all solid curves refer to 1 \(\mu\)M total Al(III) beginning as Al\(^{3+}\) at pAl = 6 at low pH on the left-hand ordinate. The dashed curve shows the decrease of free Al\(^{3+}\) due to metal ion hydrolysis leading to Al(OH)\(_2\)- at bottom right. Solid curves (with mole ratios) represent adrenaline (epinephrine), epi (10:1), 2,3-diphosphoglycerate, DPG (3000:1), ATP (dashed curve, 1000:1), citrate (100:1) and desferrioxamine, dfo (2:1). The rectangle labelled Tf refers to 50 \(\mu\)M transferrin under blood plasma conditions.

For intracellular fluids at pH 6.6 containing 10 mM total phosphate we find \(-\log [\text{Al}^{3+}] = \text{pAl} = 11.7\), while for extracellular fluids at pH 7.4 containing 2 mM total phosphate, pAl = 12.1 (Martin 1991a). This pair of values appears in the seventh row of Table 1 and represents extremely low maximum free Al\(^{3+}\) concentrations.

The dotted curve labelled Pi in Figs. 2 and 3 shows the pAl permitted by the solubility of AlPO\(_4\) in the presence of an inorganic phosphate concentration of 4.5 mM, the geometric mean of extra- and intracellular concentrations. The curve therefore lies within 0.35 log units of the 2 and 10 mM concentrations for extra- and intracellular phosphate. Near pH 8.3 the free Al\(^{3+}\) permitted by 4.5 mM inorganic phosphate exceeds that allowed by the solubility of an amorphous Al(OH)\(_3\). The two dotted curves in Figs. 2 and 3 are not limited by the 1 \(\mu\)M total Al(III) concentration assumed for all the other curves.
**TABLE 2**  \( \text{Al}^{3+} \) binding to phosphate ligands

<table>
<thead>
<tr>
<th>Ligand</th>
<th>( pK_a^a )</th>
<th>( \log K_1 )</th>
<th>( \log K_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP</td>
<td>6.4</td>
<td>7.9</td>
<td>4.6</td>
</tr>
<tr>
<td>ADP</td>
<td>6.3</td>
<td>7.8</td>
<td>4.3</td>
</tr>
<tr>
<td>AMP</td>
<td>6.1</td>
<td>6.2</td>
<td>4.2</td>
</tr>
<tr>
<td>2,3-DPG</td>
<td>6.1, 7.2</td>
<td>6.0 (AILH(^+))</td>
<td>4.2 (AIL(_2)H(_2)(^-))(^b)</td>
</tr>
<tr>
<td>HOPO(_3)(^2-)</td>
<td>6.77</td>
<td>6.3(^c)</td>
<td>4.4(^c)</td>
</tr>
</tbody>
</table>

\(^a\)Phosphate group values adjusted to usual activity pH scale.

\(^b\)2,3-DPG (2,3-diphosphoglycerate) 2:1 complex loses protons with \( pK_a = 5.7 \) and 6.4, so the main species in neutral solutions is AIL\(_2\)H\(_2\)\(^-\).

\(^c\)Estimated.

\( \text{Al}^{3+} \) will frequently form soluble complexes with phosphate groups in biological systems. We compare the binding strengths of various phosphate-containing ligands. Stability constant logarithms recently determined for \( \text{Al}^{3+} \) binding to adenosine 5'-nucleotides (Kiss et al 1991a) and 2,3-diphosphoglycerate (DPG) (Sovago et al 1990) appear in Table 2. The strongest stability constants occur for ADP and ATP, where chelation occurs. At about 3 mM there is three times as much DPG as ATP in the red blood cell but, since ATP binds \( \text{Al}^{3+} \) 80 times more strongly, most \( \text{Al}^{3+} \) binds to ATP rather than to DPG. For comparison, the stability constant for Mg\(^{2+} \) binding to ATP and other nucleoside triphosphates is \( \log K_1 = 4.3 \) (Sigel et al 1987), 4000 times weaker than for \( \text{Al}^{3+} \). Thus, 0.2 \( \mu \text{M} \) \( \text{Al}^{3+} \) competes with 1 mM Mg\(^{2+} \) for ATP.

Because of the insolubility of \( \text{AlPO}_4 \), the soluble monophosphate complexes are difficult to study. We have used the \( pK_a \) and \( \log K_1 \) results in Table 2 to predict \( \log K_1 = 6.3 \) for \( \text{Al}^{3+} \) binding to inorganic phosphate, HOPO\(_3\)\(^2-\), in the last row of Table 2. This complex dominates in acidic solutions, mainly as AlO\(_3\)POH\(^+\). It loses a proton to give either AlO\(_3\)PO (AlPO\(_4\)), or more likely an alternative microform, HOAlO\(_3\)POH. The latter in turn may lose a proton to yield HOAlO\(_3\)PO\(^-\) or the more likely microform (HO\(_2\))AlO\(_3\)POH\(^-\). Water molecules occupy the other coordination positions. The extent to which cooperativity (Martin 1991b) might favour \( \text{Al}^{3+} \)-bound OH\(^-\) in this system is unknown. The net negatively charged microforms probably predominate in neutral solutions. By assigning \( pK_a = 5.5 \) and 6.0 to the successive deprotonations, we obtain the pAl values listed in the eighth row of Table 1. At pH 6.6 the pAl value compares with that allowed by insoluble AlPO\(_4\). The estimates suggest that though inorganic phosphate is an effective \( \text{Al}^{3+} \) binder, its middle position in Table 1 indicates that it is less effective than other ligands found in a cell and the plasma.

Many suppose that \( \text{Al}^{3+} \) binds to DNA in the cell nucleus. However, \( \text{Al}^{3+} \) binding to DNA is so weak that a quantitative study was limited to a high pH = 5.5, because of metal ion hydrolysis and precipitation (Dyrssen et al 1987).
Therefore, DNA cannot compete with ATP, HOPO$_2^{2-}$ and other ligands in Table 1 for Al$^{3+}$. With very weakly basic phosphates of $pK_a \approx 1$, DNA serves merely as a polyelectrolyte interacting with Al$^{3+}$ weakly and non-specifically. Residing at the very top of Table 1 with the lowest pAl values or highest allowed free Al$^{3+}$ concentrations, DNA loses Al$^{3+}$ to all other entries in the table. We deduce that Al$^{3+}$ binding to double-helical DNA is so weak under intracellular conditions that it fails by several orders of magnitude to compete with either metal ion hydrolysis or insolubility of even an amorphous Al(OH)$_3$. No matter what other ligands are present, this competition with aqueous solvent components remains. Therefore, we conclude that the observation of aluminium with nuclear chromatin is due to its coordination not to DNA but to other ligands.

What ligands might bind Al$^{3+}$ in the cell, especially in the nuclear chromatin region? ATP and ADP are comparably strong Al$^{3+}$ binders (Table 2). A crucial Al$^{3+}$ binding site in chromatin promises to be phosphorylated proteins, perhaps phosphorylated histones. Phosphorylation and dephosphorylation reactions normally accompany cellular processes. The phosphate groups of any phosphorylated protein provide the requisite basicity, and, in conjunction with juxtaposed carboxylate or other phosphate groups, become strong Al$^{3+}$-binding sites. Abnormally phosphorylated proteins have been found in brains of patients with Alzheimer's disease (Grundke-Iqbal et al 1986, Sternberger et al 1985). Al$^{3+}$ aggregates highly phosphorylated brain cytoskeletal proteins (Diaz-Nido & Avila 1990). Ternary Al$^{3+}$ complexes have received little study, and Al$^{3+}$ has been used as a tanning or cross-linking reagent. Very possibly, Al$^{3+}$ cross-links proteins, and proteins and nucleic acids in the nucleus.

**Ligands for Al$^{3+}$**

The most likely Al$^{3+}$ binding sites are oxygen atoms, especially if they are negatively charged. Carboxylate, catecholate and phosphate groups are the strongest Al$^{3+}$ binders. Even when part of a potential chelate ring, sulphhydryl groups do not bind Al$^{3+}$ (Toth et al 1984). Amines do not bind Al$^{3+}$ strongly except as part of multidentate ligand systems such as nitrilotriacetate (NTA) and EDTA. The nitrogenous bases of DNA and RNA do not bind Al$^{3+}$ (Martin 1986b, 1988a). Fluoride binds Al$^{3+}$ avidly, and, at the 1 p.p.m. level at which fluoride is added to acidic drinking water, most Al(III) appears as AlF$_2^{+}$ and neutral AlF$_3$ (Martin 1988b). In mixed complexes of ADP and F$^-$, the ternary complex appears with the frequency expected statistically on the basis of binary complex stabilities (Nelson & Martin 1991).

Reported observations of facilitated transfer of Al(III) into erythrocytes when whole blood is made 10 mM in glutamate, and into rat brains by the subcutaneous injection of glutamate, have been interpreted as the passage of
a neutral Al(III)–glutamate complex across the erythrocyte membrane and blood–brain barrier (Deloncle et al 1990). It is also argued that glutamate and aspartate complexes of Al\(^{3+}\) play roles in Alzheimer’s disease and other Al(III)-related conditions (Deloncle & Guillard 1990). From the stability constants, these ideas are not tenable. The quoted stability constants are unreliable; because of the weakness of binding, mainly Al\(^{3+}\) hydrolysis is being measured. Careful allowance for the highly competitive hydrolysis yields only weak stability constants of \(\log K_s = 7.69\) for glutamate and 7.77 for aspartate, with no 2:1 nor 3:1 complexes (Dayde 1990). With ligand pK\(_a\) values of 9.18 and 9.27, the conditional stability constants for pH 6.6 become \(\log K_{6.6} = 5.1\) for both amino acids. This value is less than that for all other ligands in Table 1. We conclude that glutamate and aspartate are not competitive with numerous other ligands for Al\(^{3+}\) in physiological systems. Any role for glutamate must be indirect and not as a non-competitive Al\(^{3+}\) complex.

There is ample proof that citrate facilitates the incorporation of Al(III) into mammalian tissues. Al(III) levels were elevated in both the brain and bones of rats fed a diet containing aluminium citrate, or even just citrate (Domingo et al 1991, Slanina et al 1984, 1985). Evidently citrate alone chelates trace Al(III) in the diet. Dosing lambs with aluminium citrate promotes the absorption of Al(III) and alters the balance of other minerals (Allen et al 1990, 1991). Increased levels of serum Al(III) were found in patients with chronic renal failure who were taking an Al(III)-containing phosphate binder with citrate (Hewitt et al 1988). A rapidly fatal encephalopathy in human patients with chronic renal failure has been attributed to concomitant ingestion of Al(OH)\(_3\) and citrate (Bakir et al 1986, Kirschbaum & Schoolwerth 1989). Moreover, healthy adults taking Al(OH)\(_3\)-based antacids along with citric acid, citrate salts or citrus fruits showed substantial increases in Al(III) levels in blood (Slanina et al 1986, Weberg & Berstad 1986) and urine (Bakir et al 1989, Coburn et al 1991, Walker et al 1990).

Citrate exists mainly in the form of the tricarboxylate anion (L\(_3^-\)) at pH > 6, and at 0.1 mM in the blood plasma it is the leading small molecule Al\(^{3+}\) binder (Martin 1986b,c). In neutral solutions the main species is HOAIH\(_{12^-}\), followed by AIH\(_{10^-}\) with pK\(_a\) = 6.5 for the loss of a proton from metal ion-bound water (Martin 1988a). Even though much of the citrate in plasma occurs as a Ca\(^{2+}\) complex, Al\(^{3+}\) easily displaces Ca\(^{2+}\) from citrate. Even when alkaline earth cations in the plasma are taken into consideration, there is an almost 10\(^8\) mole ratio of citrate-bound to unbound Al\(^{3+}\) (Martin 1991a). Because of the citrate binding of Al\(^{3+}\), calcium citrate increases intestinal Al(III) absorption (Nolan et al 1990) and should not be given to uraemic patients; calcium acetate appears to be a better choice (Emnett et al 1991).

As indicated in Table 1 and Fig. 3 and previously (Martin 1986b,c, 1988a), citrate solubilizes Al\(^{3+}\) from both insoluble Al(OH)\(_3\) and AlPO\(_4\). On the basis of information from equilibrium constants, it was strongly urged in 1986 that
people should not take Al(III) and citrate together (Martin 1986b,c). A more recent warning suggests that uraemic patients should avoid citrate compounds (Molitoris et al 1989). However, since a healthy diet always contains citrate, all deliberate ingestion of Al(III) compounds might be better avoided. The amount of citrate present should always be considered as a variable in Al(III) ingestion studies.

Transferrin is the main protein carrier of Al$^{3+}$ in the plasma. Displacement of the $10^9$ times stronger binding Fe$^{3+}$ is unnecessary because plasma transferrin is about 50 $\mu$M in unoccupied sites. Recent experiments confirm the conclusion based on stability constants (Martin 1986b, Martin et al 1987) that citrate is the low molecular weight and transferrin the high molecular weight carrier of Al$^{3+}$ in rat serum (Van Ginkel et al 1990). We emphasize again, however, that albumin does not bind Al$^{3+}$ with anywhere near the strength of transferrin or citrate.

Upon binding of Al$^{3+}$ to transferrin there are two scenarios. First, by removing Al(III) from the bloodstream and tightly complexing it, transferrin binding may be detoxifying and favourable to the body, though the final disposition of the Al(III) remains a source of concern. Second, transferrin binding may be dangerous if it results in incorporation of Al(III) at transferrin receptors. In this case it might be possible to detoxify the Al(III) by adding Fe(III) and saturating transferrin with this much more strongly binding metal ion to displace Al(III). The displaced Al(III) would be picked up by citrate and eliminated in the urine. In this scenario the antidote for Al(III) poisoning is Fe(III).

In body fluids low in citrate, transferrin and nucleotides, the catecholamines may well become important Al$^{3+}$ binders (Kiss et al 1989). While dopa and noradrenaline (epinephrine) fail to bind Mg$^{2+}$ at pH 7.4, they bind Al$^{3+}$ at picomolar levels (Table 1). In neutral solutions the main species is a 3:1 complex with the catechol moiety chelating the Al$^{3+}$ and the ammonium group remaining protonated (Kiss et al 1989, 1991b). The noradrenaline-Al$^{3+}$ complex inhibits enzymic O-methylation but not N-methylation by catechol-O-methyltransferase (Mason & Weinkove 1983). This result conforms to that expected if Al$^{3+}$ binds only to the catechol moiety of noradrenaline. When other metal ions are deficient, Al(III) decreases catecholamine levels in the rat brain (Wenk & Stemmer 1981). By binding to the catechol moiety of catecholamines, trace amounts of Al$^{3+}$ may disrupt neurochemical processes.

**Ligand exchange**

In addition to the stability of metal ion complexes, an important and often overlooked feature is the rate of ligand exchange out of and into the metal ion coordination sphere. Ligand exchange rates take on special importance for Al$^{3+}$ because they are slow, and systems may not be at equilibrium. The rate
for the exchange of inner sphere water with solvent water is known for many metal ions, and the order of increasing rate constants in acidic solutions is given by

\[ \text{Al}^{3+} \ll \text{Fe}^{3+} < \text{Ga}^{3+}, \text{Be}^{2+} \ll \text{Mg}^{2+} < \text{Fe}^{2+} < \text{Zn}^{2+} < \text{Ca}^{2+} \]

Each inequality sign indicates an approximate 10-fold increase in rate constant from 1.3 s\(^{-1}\) for \(\text{Al}^{3+}\) and increasing through eight powers of 10 to 10\(^8\) s\(^{-1}\) for \(\text{Ca}^{2+}\) at 25 °C (Martin 1991a). Though these specific rate constants refer to water exchange in aquo metal ions, they also reflect relative rates of exchange of other unidentate ligands. Reducing \(\text{Fe}^{3+}\) to \(\text{Fe}^{2+}\) gains a 10\(^4\)-fold increase in rate. Chelated ligands exchange more slowly, but the order remains. The slow ligand exchange rate for \(\text{Al}^{3+}\) makes it useless as a metal ion engaged in reactions at enzyme active sites. The 10\(^5\) times faster rate for \(\text{Mg}^{2+}\) furnishes enough reason for the \(\text{Al}^{3+}\) inhibition of enzymes with \(\text{Mg}^{2+}\) cofactors. Processes involving rapid \(\text{Ca}^{2+}\) exchange would be thwarted by substitution of the 10\(^8\)-fold slower \(\text{Al}^{3+}\).

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DISCUSSION

Kerr: If I have understood your pAl data, one would expect desferrioxamine to take aluminium off transferrin. Is that correct?

Martin: Yes, you would expect removal thermodynamically, but maybe not clinically. It’s possible that it will be hard to get aluminium out of transferrin in a reasonable time.

Kerr: We generated conflicting results on the competition between desferrioxamine and transferrin for bound aluminium in Newcastle. In one series of unpublished studies by Dr Habibur Rahman, no aluminium was leached from transferrin during prolonged incubation against therapeutic concentrations of desferrioxamine. However, in a later study by Skillen & Moshtaghie (1986), substantial amounts of Al were removed during dialysis for 24 hours or more against Earle’s medium at pH 7.4 containing 200 mg/l desferrioxamine. Certainly the binding to transferrin is tight and can only be broken by desferrioxamine under specific conditions of pH and bicarbonate concentration.