

Chapter 3

ALUMINIUM AND MEDICINE

Christopher Exley

Birchall Centre for Inorganic Chemistry and Materials Science,
Lennard-Jones Laboratories, Keele University, Staffordshire, UK

1. AN APOLOGY

I have been asked to communicate my personal view on the increasingly broad subject area of aluminium and medicine. I have taken this as an opportunity to put my thoughts into print so that they might be widely shared with an interested and informed community. These thoughts concern only humans and little if any reference will be made to the impact of aluminium in other biota including so-called animal models of human disease. I have not reviewed the vast subject area of aluminium and medicine. I have not attempted to write a reference source for this field. You should not be upset if your research is not specifically cited herein. You might accept my word that I am widely read in this subject and that your research will have contributed to my personal view of aluminium and medicine. I will take this opportunity to thank you in advance for helping in forming my opinions. I am hopeful that these opinions on current understanding of aluminium and medicine will raise awareness of that which is dogma, that which is actually known and that which remains to be investigated and understood. It is my considered and concluding opinion that while the former of these three (ie. the dogma) continues to dominate popular as well as academic thinking in the field of aluminium and human health we will neither understand nor be able to react to the consequences for modern life of living in *The Aluminium Age*.

2. A PERSONAL VIEW

It is not difficult to argue the case for at least a few atoms of biologically reactive aluminium being present in every space or compartment of the human body. Every organelle, cell cytoplasm, systemic fluid, epithelial secretion and surface of the human body will be experiencing some biological chemistry with aluminium. The majority of these atoms of

aluminium will not be *biologically available* in that the sum of their reactions will not result in any net biological effect. Though biologically reactive they will only become biologically available when the sum of their reactions is sufficient to overwhelm a particular biochemical system and to elicit a biological response from that system. The latter is a paraphrase of my, though perhaps not the generally accepted, definition of *biological availability* [1].

I have also argued that the greater majority of these aluminium atoms are where they are as the direct result of the activities of modern human beings [2]. We are the perpetrators of a burgeoning body burden of aluminium. This is primarily because we live in *The Aluminium Age* and, subsequently we are no longer able to avoid exposure to aluminium. However, it is also because of human activities on a global scale, such as the burning of fossil fuels and the widespread application of intensive agricultural practices, which are resulting in the acidification of the environment to the extent that aluminium is continuously leached from inert edaphic stores to aqueous environments and hence is available to be taken up by living things. The emergence of an aluminium burden amongst the primary producers must inevitably result in its transfer through the food chain and ultimately to human beings. I would continue my argument in declaring that the evolution of human biochemistry in the presence of biologically available aluminium, the natural selection of aluminium as an element of biological essentiality, is very much in a primordial state. Furthermore it is the chemistry which underlies the processes which define the present and future state of this co-evolution which we will need to address if we are to understand and predict the potential impacts of human exposure to aluminium and its relationship to medicine.

Living in *The Aluminium Age* has the inevitable consequence of an increased everyday exposure to aluminium and this increase in exposure will result in a burgeoning body burden. The accumulation of aluminium in the body will directly or indirectly define the impact of aluminium on human health and, I would argue, has yet to become a subject of serious investigation and consideration in medicine. There exists a remarkable and difficult to explain complacency in respect of our relationship with the non-biologically essential aluminium. It would appear that we have been and that we remain happy to accept dogma which continues to purport such experimentally unproven concepts as; (i) aluminium's chemical inertia prevents its significant entry into the body, (Only recently was I informed by a manufacturer of sunscreens that the form of aluminium in their product cannot enter the skin and they are happy to continue to give such advice without having any experimental evidence to support their claim.) and (ii) that if (unusually!) a small amount of aluminium did gain entry to the systemic circulation then it will all be rapidly excreted in the urine, and finally (iii) that any aluminium which (incredibly!) was not rapidly excreted from the body would be deposited in biologically inert stores such as bone. These are the three commandments which heralded the onset of *The Aluminium Age* and which continue today to serve to obscure any precautionary opinions concerning human exposure to aluminium. We seem to have readily accepted the idea, without serious questioning of what or whom might have put such an idea into our minds, that there exists on Earth an inherent mechanism of protection of the human body against exposure to biologically available aluminium. In fact there is no direct evidence that the pathways which describe human evolution and biologically available aluminium have coincided in the natural selection of the elements of life. This surprising, since aluminium is the most abundant metal in the Earth's crust and the third most abundant element after oxygen and silicon, though evidentially supported thesis must then raise the possibility that it is only now that we are experiencing indirect evidence, or effects, of such a coincidence?

Thus, if we now proceed to examine the myriad associations between aluminium and human health which have already been documented in the scientific and medical literature do we conclude with, (i) the recognition that the ‘symptoms’ of these associations are simply the manifestations of the over active imaginations of those whom display an ignorance of the aforementioned three commandments, or (ii) might we proffer the heretical suggestion that they are plausible indications of physiological responses to biologically available aluminium as the result of living in *The Aluminium Age*? Which of these two views will improve in its focus and clarity as we apply Occam’s razor to what we think we know about aluminium and medicine?

3. THE SCIENTIFIC VIEW

3.1. The Body Is an Effective Barrier to Exposure to Aluminium?

There are probably only a few serious scientists who would even attempt to dispute the observation that humans in their everyday lives are experiencing a burgeoning exposure to aluminium. The phenomenal successes of aluminium and aluminium salts as effective materials in myriad applications will continue to ensure that the human body will be challenged by aluminium. However, while there may be a general, if not sometimes reluctant, admission that humans are in contact on a daily basis with potentially biologically available aluminium there cannot be an informed consensus as to the relative significances of the different routes of human exposure. I am saying that there cannot be such a consensus, and I will explain why, even though this might not necessarily be the obvious conclusion which would be drawn from recent reviews of this field. For example, the published literature often identifies the diet as the primary *source* of exposure and gastrointestinal absorption as the primary *route* of exposure to aluminium in everyday life. Indeed this is the conclusion of a recent review of aluminium and human health which was sponsored by the International Aluminium Institute, a forum which represents the global aluminium industry. While at one time this was certainly also the view of the ‘non-aligned’ academic community it is now simply a view of convenience and is representative of only what the global aluminium industry would wish to concede to the scientific community and interested other persons. It is a convenient viewpoint in, (i) it serves to distract attention away from other potential significant sources of exposure to environmental aluminium, and (ii) it equates the significance of exposure to the amount of aluminium which is involved rather than the potential for that aluminium to participate in biochemical reactions. It is also a convenient conclusion in that while it is an accurate summary of that which can be fully supported in the scientific literature the latter is, in reality, extremely limited in respect of human exposure to aluminium. In fact it is the paucity of volume of research in this field which is being used to support such a convenient view.

There are, of course, examples of excellent research in this field. A significant stumbling block for research with the specific aim of investigating human exposure to aluminium has been the provision of unequivocal evidence that the aluminium to which an individual has been exposed was also the aluminium which thereafter could be identified systemically, for example, in the individual’s blood or urine. This is a particular problem in studies concerned

with everyday or normal exposures to aluminium since any consequent changes in the concentration of aluminium in body fluids or tissues would be expected to be very small and therefore, difficult to confirm by experimental methods. This problem of 'provenance' has become accessible to experiment through the relatively recent availability of an isotope of aluminium, ^{26}Al , which has both a long half life and is not naturally occurring in the environment. The use of this isotope and access to accelerator mass spectrometry (AMS) enabled the pioneering research of JP Day and colleagues [3] to demonstrate unequivocally that aluminium ingested in the diet is absorbed across the gastrointestinal tract as it could be identified subsequently in blood and urine. These data are very powerful in that they confirm the absorption of aluminium into the body though caution is required in their extrapolation to provide accurate estimates of the fraction of the total ingested aluminium which is actually absorbed. In my opinion data obtained using ^{26}Al has been used erroneously to provide estimates of the percentage of a bolus of ingested aluminium which is absorbed across the gut. There are a number of reasons why the estimates obtained are misleading not the least of which are directly concerned with the plethora of assumptions which are associated with the use of serum aluminium concentrations as indicators of systemic aluminium. Measurements of total aluminium in samples of plasma or serum are rarely representative of the systemic body burden of aluminium. The concentration of aluminium in, for example, plasma will change following a change in an individual's exposure to aluminium but, there is little evidence that the changes are ever proportionate to the change in conditions of exposure. There are many barriers to obtaining reliable quantitative estimates of the gastrointestinal absorption of aluminium and in overcoming such we will need a full mass balance of ^{26}Al into and out of (excretion) the body during a period of time in which the physiology/metabolism of the experimental participants is controlled or at least closely monitored. Of course, experiments of this nature will only provide data which are immediately relevant to the experimental conditions and these will not necessarily be representative of the absorption of dietary aluminium as it occurs in everyday life. In addition they would also need to be carried out on a sufficient number of subjects so as to accurately reflect the potential inherent differences which exist between individuals. In the only example of the use of ^{26}Al to estimate the dietary absorption of aluminium in a small group of individuals (five) the results, taking into account all of the personal misgivings highlighted previously, showed that the highest individual absorbance value was more than three times that of the lowest individual absorbance value [4]. One is left to speculate upon how a three-fold difference in the so-called percentage absorbance of aluminium across only five individuals would be manifested within a non-experimental population of individuals who were affected by all of the potential confounding factors of, for example, dietary differences, gender, age and general and specific health-related effects. While diet clearly is an important factor in human exposure to aluminium we should not allow ourselves to be lulled into the state of mind which suggests to us that it is the only important factor. We should avoid such a conclusion for two main reasons, the first being, as I have already tried to explain, that we do not know enough about the absorption of aluminium across the gut and the second being that we know almost nothing about other potential routes of exposure to aluminium. We need to ensure that we are not hoodwinked into equating a lack of information about a subject area with a lack of interest or importance of that area. This remains a successful ploy of those with a vested interest in maintaining a high level of ignorance of human exposure to aluminium.

There has been much ambiguity concerning the skin as a barrier to the absorption of aluminium. The apparent confusion has reconciled individuals to the potentially erroneous opinion that the topical application of aluminium salts contained within, for example, antiperspirants, sunblocks/sunscreens and other cosmetics will not result in any of the aluminium being absorbed into or across the skin. Once again, the convenient view point, that aluminium compounds found in such cosmetic preparations will not cross the skin, has been perpetuated by both suppliers and users alike without any scientific evidence to support such a claim. In fact, in a seminal piece of research using an antiperspirant formulation which included ^{26}Al , Flarend and colleagues demonstrated the unequivocal absorption of aluminium across the skin and its excretion in urine [5]. The skin is not a barrier to aluminium and we now need urgent investigation of the absorption of aluminium into and across skin when it is applied in a range of different, primarily cosmetic, preparations. For example, we recently showed that we apply up to one gramme of aluminium to our body surface in sunscreen during an average day on the beach! Only two subjects were used in the seminal experiment on aluminium absorption from antiperspirant and it was of note that these two individuals showed significantly different rates of urinary excretion of topically applied ^{26}Al . This, in a similar way to what was found for the gastrointestinal absorption of aluminium, may be indicative of inter-individual differences in the absorption of aluminium across the skin and/or the way in which the body stores and excretes aluminium. That there are significant differences in the absorption of aluminium both across different skin surfaces on the same individual and between individuals was supported by an unusual clinical observation which concerned the admission of a woman to hospital with symptoms of aluminium overload [6,7]. The woman had been using an aluminium-based antiperspirant for four years prior to her admission but had not used an antiperspirant for the preceding thirty-nine years. Cessation of use of the antiperspirant reduced the individual's plasma aluminium concentration from *ca* 4 μM to within the 'normal' range and resulted in the disappearance of her symptoms of aluminium overload. It should be clear to all that the skin cannot be considered as an effective barrier to topically applied aluminium. However, we know nothing about the forms of aluminium which are entering the skin or how differences in skin structure or integrity might influence its permeability to aluminium. We also know nothing about how pre-exposure to aluminium either of the skin itself or another target site might subsequently influence the permeability of skin to aluminium. The significant absorption of aluminium from an antiperspirant which was just highlighted might be an example of an individual's hypersensitivity to aluminium or it may be related to the fact that the woman had not previously used aluminium-based antiperspirant. The latter raises the possibility that regular application of aluminium to the skin surface predisposes (or conditions) the affected skin to a reduction in its permeability to subsequent applications of aluminium. The skin being made less permeable in a similar manner to the way that aluminium salts are used to 'cure' leather. If this were true then skin which does not receive regular applications of aluminium may be more permeable to aluminium when applied on a more occasional basis. This has important implications for future research on the absorption of aluminium across skin and in particular for aluminium absorption from other products which include aluminium and are applied to the whole skin surface.

An example of how pre-exposure to aluminium at an alternative target site might then influence how the skin responds to a subsequent aluminium challenge can be found where muscle tissue is exposed to aluminium as an adjuvant in vaccination. We know from research

in rabbits that while aluminium, in this case labelled with ^{26}Al , when injected into muscle as an adjuvant, usually a preparation of aluminium hydroxide or aluminium hydroxyphosphate, does persist at the site of injection it also migrates away from the site and can subsequently be identified in urine [8]. Adjuvant aluminium is now implicated in a wide spectrum of human diseases, including adverse skin reactions, by as yet unknown mechanisms which will be discussed at a later point in this chapter.

The gut and skin are the only routes of uptake of aluminium into the human body for which there exists unequivocal scientific support. There are animal studies which have shown that both respiratory and olfactory surfaces are also routes of uptake of aluminium and these are supported by myriad related data for humans which provide circumstantial evidence that aluminium gains entry to the systemic circulation via both the lung and the nose. These studies include evidence of enhanced urinary excretion of aluminium in, for example, tobacco smokers and users of illicit heroin [9,10] and unusual observations such as the immediate and significant increases in the urinary excretion of aluminium which followed brief exposure of individuals to aluminium-rich plumes of volcanic smoke [11]! While we can be confident that all mucosal surfaces are likely routes for the uptake of aluminium we have more or less no information on the mechanisms by which aluminium permeates such surfaces. There are clearly rapid mechanisms, as evidenced by the early appearance of aluminium in urine, which probably involve the transmembrane passage of lipophilic aluminium complexes as well as slower mechanisms perhaps involving the phagocytosis of aluminium particles by, for example, dendritic cells. The latter, in particular, may have a central role in aluminium as a factor in auto-immunogenic disease?

I hope that if only one thing is clear at this juncture it is that we understand very little about human exposure to aluminium and even less about the relationship between human exposure and biological availability. Of course, part one of the international aluminium industry's defence of why aluminium is actually good for you, that is, the opinion just discussed that *'aluminium doesn't really gain entry into the human body in significant amounts'* is, as a precaution always seamlessly followed by part two of its defence namely the reassurance that *'even if aluminium does enter the systemic circulation it will be rapidly excreted from the body in the urine'*.

3.2. Urinary Excretion of Aluminium Protects against an Aluminium Body Burden?

There can be no question that the urinary excretion of aluminium is a significant route of removal of systemic aluminium from the body. It may also be the most rapid route for excretion of systemic aluminium but is the urinary excretion of aluminium effective protection against the build up of aluminium in the body? Does it prevent a burgeoning body burden of aluminium? How confident should we be in the view that following an exposure to aluminium the aluminium which enters the blood will be rapidly, indeed almost instantaneously, filtered out of the blood by the kidney and irreversibly stored in the bladder prior to being excreted in the urine. What is actually known from the scientific literature is that the kidney is a route of excretion of systemic aluminium and that a proportion of aluminium in the blood is continually removed by the kidney. We know this since we always measure some aluminium in urine. In addition, there is evidence that following an abnormally

elevated exposure to aluminium, such as, for example, from volcanic plumes, the urinary excretion of aluminium, when normalised for changes in the glomerular filtration rate of the kidney, will be increased transiently. The increase might be interpreted as either an increase in the total concentration of aluminium in the blood or as an increase in the proportion of the blood aluminium which is available to be rapidly filtered by the kidney. An additional or alternative interpretation might be that urinary excretion is influenced by factors associated with the reabsorption of filtered aluminium back into the systemic circulation. In truth we only actually know that following the exposure more aluminium was excreted than previous to the exposure. We know virtually nothing about the mechanisms which underlie this effect or indeed, and importantly, the proportion of the aluminium which was absorbed following the exposure which would subsequently be excreted in the urine. In other words does the efficiency with which aluminium is excreted in the urine change with the nature of the aluminium challenge. Do we excrete proportionately more aluminium when there is more aluminium to excrete? Clearly it would be an ill-informed decision which assumed that the urinary excretion of aluminium provided a robust defence against the presence of aluminium in blood and its distribution throughout the body in the systemic circulation. We do know that the urinary excretion of aluminium does not prevent aluminium from accumulating in the body since both medical practice and experimental research have shown that aluminium is actively titrated from the body via the urine during various forms of chemical chelation therapy [12]. For example, anyone, regardless of their aluminium status, who is given an intramuscular injection of the iron chelator desferrioxamine, DFO, will subsequently show an increase in their urinary excretion of aluminium. DFO binds aluminium with significant avidity to form a stable and presumably ultrafilterable DFO-aluminium complex (MW *ca* 700Da). While we do not understand exactly how DFO promotes the urinary excretion of aluminium it can be assumed that its presence in the blood and the formation of the DFO-aluminium complex will influence the competitive equilibria which normally define the ultrafilterable fraction of aluminium such that they support a higher proportion of ultrafilterable aluminium than before. What chelation studies show is that there are non-ultrafilterable stores of aluminium in the body which can be converted to a form which can subsequently be removed from the blood by the kidney. The data from such studies do not give any indication as to the source of the additional aluminium only that it is relatively rapidly accessible via equilibrium shifts in the distribution of aluminium in blood. The observation that multiple administrations of DFO over several days or even months are often required to treat an aluminium overload and thereby to reduce the urinary excretion of aluminium to more usual levels does suggest that it works by the titration of aluminium from body stores into the blood where, presumably, the formation of the DFO-aluminium complex will allow its filtration by the kidney and subsequent excretion in the urine. I write, presumably, since there has not as yet been a direct confirmation of such a mechanism of action only the observation of a peak in urinary aluminium following the administration of DFO. While there is evidence of the DFO-aluminium complex in blood it is unknown if it is stable in urine. The latter may be of significance for the potential reabsorption of aluminium following its passage across the glomerulus as a complex of DFO. What should now be abundantly clear is that while a proportion of aluminium in blood is effectively filtered out by the kidney this mechanism of elimination of systemic aluminium cannot alone prevent its build up throughout the body. However, is, as we are once again asked to believe, the majority of the body burden of aluminium 'safely' locked up in bone stores? Are we

confident that even though some aluminium will be absorbed and thereafter not necessarily rapidly excreted in the urine that the remainder will pose no health risk '*as it will be deposited as an inert store in bone*'? This is the third tenet of the international aluminium industry's defence of the safety of their product in humans!

3.3. The Majority of the Body Burden of Aluminium Is “Safely” Deposited in Bone?

There is an abundance of direct evidence, such as bone biopsies, and indirect evidence, including the known links to adynamic bone disease, that bone is a sink for systemic aluminium. There is also good indirect evidence, for example from chelation studies using DFO, that some of the aluminium which is deposited in bone will only be very slowly exchanged with other body compartments such as the blood. The known association with bone combined with a slow dissociation from bone define a time-dependent accumulation of aluminium in this tissue. Bone is a long term sink for systemic aluminium. However, bone in acting as a slowly exchanged reservoir of biologically reactive aluminium should not be equated with bone as affording protection against possible aluminium toxicity. This is common sense as in the first instance we already know that aluminium is a contributor to if not a cause of bone disease and in the second instance we know that bone can act as a source of aluminium and under certain physiological conditions will enable the redistribution of aluminium between other tissues and organs. In addition, while we know that aluminium is in bone there is very little direct evidence that bone has a higher content of aluminium per weight of tissue than other possible sinks for systemic aluminium. Of course, the skeleton could be considered as the body's most massive organ or collection of tissues and so it clearly has the potential to accommodate a significant proportion of the body burden of aluminium. However, none of the aforementioned analysis of what we know about aluminium in bone would support the contention that most systemic aluminium which is not immediately excreted in the urine will be 'safely' locked away in bone.

In fact what is highlighted by such an Occam's razor-like approach to the literature is the general lack of understanding that persists of what happens to aluminium upon its entry into blood. The 'behaviour' of aluminium in blood will be critical to its subsequent distribution throughout the body. Aluminium in blood is another area of our understanding of aluminium toxicokinetics which is mainly informed by dogma and principally by the view that the majority of aluminium entering the blood will be bound and transported around the body by the iron transport protein transferrin. This view is based upon the best available data to describe the chemical fractionation of aluminium in plasma but it is dogmatic in that it is actually an interpretation of scientific evidence which does not by itself address the fundamental question of the pre-eminence of this route as a mechanism for the transport and distribution of all aluminium entering the blood. We have called this dilemma '*the blood-aluminium problem*' and we are currently applying a combination of systems biology and computation to explore *in silico* the role played by transferrin in the transport and distribution of aluminium [13,14]. This is fundamental in that our understanding of the 'transferrin route', it being of such importance to the transport and distribution of iron, has already been well established and if it was also the pre-eminent route for aluminium then it should be possible to accurately predict the fate of systemic aluminium. However, in spite of the paucity of

information which concerns the distribution of aluminium throughout the human body it can still be safely assumed that it is not adequately predicted by the transferrin route. There is no evidence, for example, that those cells or tissues which express the highest density of transferrin receptors also accumulate more aluminium. An example of why the transferrin-route may not be the best indicator of the distribution of aluminium is conveyed in studies of the urinary excretion of aluminium. If one keeps to the back of one's mind that the transferrin-aluminium complex has a molecular weight (ca 78K Da) which is several fold higher than the molecular weight cut-off (ca 18K Da) of the glomerulus of the kidney, then the rapid changes in the urinary excretion of aluminium which are observed following environmental exposure, cannot be easily accounted for by ca 90% of all blood-borne aluminium being bound and transported by transferrin. The form in which aluminium is present in blood will be significant in respect of its fate such that it will influence its association with myriad compartments, both physical and chemical, and importantly it will influence the rates at which such associations can take place. Kinetic constraints under the direction of thermodynamic forces are driving the complexation, transport and subsequent tissue distribution of blood-borne aluminium. These are neither defined by nor limited by the mantra of aluminium's perceived inertia in biological milieu.

4. WHERE ARE WE NOW?

Let us suppose that there exists an hypothetical balance which will define putative roles for aluminium in human disease and hence medicine.

EXPOSURE ↔ BURDEN ↔ EXCRETION

4.1. How Are We Exposed?

It is probably naïve to continue to assume that in humans the diet, our food and drink, is the main route of exposure to biologically available aluminium. This widely held assumption places the gut as the focal point of understanding of human exposure to aluminium and, thereby, immediately negates the surfaces of the skin, the lung and the nose as significant routes of exposure to aluminium. The focus upon the diet also tends to lead to an under-estimation of the significance of aluminium gaining entry to the body as the result of therapeutic and medicinal applications including the administration of parenteral solutions and vaccination.

There are clearly a number of ways in which humans are exposed to aluminium and while each of these will result in aluminium entering the systemic circulation the different pathways are not necessarily equivalent in the terms of the amount of aluminium that each might deliver per unit of time or indeed, the biological availability of the aluminium that has been delivered. In understanding how the body will respond to an aluminium challenge we have to think beyond such gross concepts as 'no effect levels' and similarly vague criteria. An argument which is regularly put forward is; 'how can such an insignificant amount of aluminium which impacts the body via route 'A' be of any consequence in comparison to the

much larger amount of aluminium which impacts the body via route 'B'? There are many reasons why such thinking should be considered as overly simplistic. For example, aluminium which is absorbed across the gut would be expected to have to pass through the liver before it had any opportunity to, for example, enter the brain. However, aluminium absorbed across lung or olfactory epithelia would not be subject to 'first pass' removal by the liver before encountering the blood-brain barrier. Additionally, aluminium absorbed via the olfactory system would bypass the defences of the blood-brain barrier and gain direct access to the hippocampal region of the brain.

Similar possibilities apply to aluminium entering the systemic circulation via its absorption across the skin. If these types of information are combined with additional data concerning the form of aluminium, for example, aluminium entering the lung or nose in an aerosol may be completely different to aluminium in food or drink, then it is clear that the exposure route may be just as important as the amount of aluminium in determining its eventual biological availability and potential toxicity. There has also been a tendency to assume that aluminium must gain access to the systemic circulation, and the blood in particular, in order to elicit a biological response.

The biological availability of aluminium which is retained at or within surfaces such as skin or lung and olfactory epithelia has largely been ignored and this is in spite of a wealth of scientific data which, for example, has reported adverse reactions to aerosols and topically and intramuscularly administered aluminium salts. It is abundantly clear that aluminium at the surface of the skin or within lung or olfactory mucosa or when injected as an adjuvant into the muscle can be biologically available and will participate in biochemical reactions in these regions, for example, promoting oxidative reactions such as those implicated in asthma or cancer.

Sound scientific data which relates specifically to the individual significance for medicine of each of these routes of exposure to aluminium are scarce though the lack of data should not be used to suggest that any particular route will pose less risk to human health than another. What can be taken from the information which is available to date is that the general attribution of primacy of aluminium effect to any particular route of exposure cannot be justified. The focus needs to be widened from aluminium exposure via the diet and gastrointestinal absorption to include the myriad ways that the body is challenged by aluminium on a daily basis.

So, by way of a brief summary, what we can be sure of is that in addition to the diet we are exposed to aluminium through; (i) smoking and chewing of tobacco; (ii) smoking and ingestion of cannabis; (iii) inhalation of heroin and cocaine; (iv) injection of heroin/heroin substitutes; (v) aerosol and topical application of anti-perspirants; (vi) aerosol and topical application of sunscreens and sun blocks and other skin-care products; (vii) ingestion of prophylactics such as anti-acids and buffered aspirin; (viii) allergenic and antigenic vaccinations which include aluminium-based adjuvants; (ix) intravenous parenteral solutions; (x) occupational exposure both within and not within the aluminium industry.

This cannot be an exhaustive list of potential routes of exposure to aluminium but should, at least, serve as a precautionary note as to how and where the human body may come into contact with aluminium.

Table 1. The routes of exposure to aluminium in humans. The ranking is not based upon the amount of aluminium but on the potential for that route to consistently and regularly deliver biologically available aluminium. Thus, the nose ranks highest as it provides direct access for aluminium to the brain, an organ with a high propensity to accumulate aluminium

ROUTE OF EXPOSURE	RANKING 1(LOW) – 10(HIGH)
Gastrointestinal Tract	5-7
The Skin	6-8
The Lung	7-9
The Nose	9-10
Intravenous eg. Parenteral Solutions	5-7
Intramuscular eg. Vaccination	6-8

4.2. What Is the Body Burden of Aluminium?

What do we mean when we refer to the body burden of aluminium? Can we develop a strict definition of this term, a definition which will be useful in linking aluminium exposure to medicine? While there are figures for the total body content of aluminium and there are data concerning its accumulation in almost every organ and tissue of the body there are actually very few modern data which have attempted to define the exact nature of the body burden of aluminium. Indeed it is not altogether clear what is inferred by the term body burden in that it is often used exclusively to describe systemic accumulation and, therefore, would exclude extracellular aluminium which was associated with body surfaces such as the mucus-lined epithelia of the gastrointestinal, respiratory and reproductive systems. These external surfaces of the body, along with the skin, are initially barriers to exposure to aluminium though they are also likely transitory sinks for biologically available aluminium and potential sources of the systemic body burden.

I have already argued herein that a burgeoning human exposure to aluminium has resulted in its ubiquitous distribution throughout the body. With this in mind the potential importance not just of the burden but its distribution throughout the body is probably a combination of the propensity for aluminium to accumulate over time in individual compartments and the physiologically-defined susceptibilities of such compartments to biologically reactive aluminium. Thus, where aluminium accumulates in the body will depend upon a compartment's accessibility by aluminium and its susceptibility to an aluminium burden. The latter will not become a factor if, for example, rapid rates of mitosis continually repackage and dilute the cellular aluminium burden and thereby prevent its accumulation towards a cytotoxic threshold. Alternatively significant cytosolic pools of ligands which are capable of binding and 'hiding' aluminium, such as citrate or ATP, will act so as to buffer an intracellular aluminium challenge. The cell types which combine a rapid cell-cycle with significant cytosolic pools of ligands for aluminium should be least affected by an aluminium challenge whereas longer-lived cell types, such as neurones and macrophages, will be prone to accumulate aluminium over their extended lifetimes with potential consequences for cell function and cell viability in the longer term. Cell susceptibility to an aluminium challenge is not only influenced by its burden of biologically reactive aluminium but also by how much

target ligand is present. For example, actively respiring cells which are replete with mitochondria would be expected to be more prone to the pro-oxidative effects of aluminium than other cell types. In addition the fact that, as a pro-oxidant, aluminium may be acting via a catalytic mechanism involving the superoxide radical anion may compound any such effects as the aluminium may be recycled and used over and over again in promoting oxidative damage [15]. There may be situations where the opposite might be the case such that comparatively large amounts of aluminium are inadvertently stored in slowly exchanged chemical compartments associated with such tissues as bone, hair and skin. While these may represent significant burdens of aluminium they may only be insignificant in the terms of the biological availability of that aluminium. It is clear that as a consequence of a burgeoning exposure to aluminium we should expect aluminium to be everywhere in the body and that wherever it is found it will be biologically reactive and it will be subject to normal cellular metabolism. I am using 'normal' in reference to general mechanisms of cellular metabolism since there is no evidence to date of any aluminium-specific metabolism. All of the evidence points towards aluminium being a 'silent' visitor to the human body and to it 'adopting' metabolic pathways which have been selected for and developed during the course of human evolution in its absence. In many ways the lack of specific pathways for dealing with the systemic burden of aluminium explains why we understand so little about its fate in and excretion from the body. Aluminium is not 'used' by the body and so its eventual fate should be its excretion though as to how this fate is approached and effected in normal physiology has remained for the most part unknown.

Table 2. The major sinks which together constitute the body burden of aluminium. The ranking indicates the potential for aluminium to accumulate in the sink and not the relative importance of each sink to the overall body burden. Thus, the high ranking of the brain reflects the longevity of neurons

SINKS FOR ALUMINIUM	RANKING 1(LOW) – 10(HIGH)
Skin	5-7
Kidney	3-5
Liver	5-7
Heart	6-8
Brain	8-10
Bone/Skeleton	8-10
Gastrointestinal Tract	5-7
Lungs	7-9
Reproductive System	6-8
Foetus	6-8
Blood Cells	7-9
Blood Vessels	5-7
Serum/Biological Fluids	3-5
Hair	7-9
Nails	6-8
Teeth	5-7

4.3. How Does the Body Excrete Aluminium?

How does the body excrete aluminium? What are the mechanisms by which aluminium is removed from the body? There are surprisingly few data on the excretion of aluminium in humans and there has not, to my knowledge, been any attempt to undertake a mass balance study of the ingestion and excretion of aluminium in humans. It is probably valid to assume that the majority of ingested aluminium will be excreted in faeces though this assumption has not actually been tested. There has not been an experiment in which the amount of aluminium excreted in faeces has been measured. It is worth bearing in mind that those studies which purportedly measured the proportion of ingested aluminium which was absorbed across the gastrointestinal tract all failed to support their analyses with measurements of aluminium excreted in faeces. A further assumption which could be made is that the main route for the removal of systemic aluminium is via its filtration in the kidney and subsequent excretion in urine. We all excrete about 10-15 μg of aluminium in urine each day though there are few reliable data to indicate if this is the main route of excretion of systemic aluminium. For example, the few data which exist for the aluminium content of human bile would suggest a role for biliary excretion in the removal of systemic aluminium.

Whether, of course, aluminium excreted in bile would then be re-absorbed in the gut is unknown. Similarly, how aluminium in bile influences its role in the emulsification of fats is also largely unknown. The liver is a likely sink for systemic aluminium and as such biliary excretion must be considered a potentially significant pathway for the excretion of systemic aluminium. Other mechanisms of excretion of systemic aluminium will include the shedding of hair, skin and nails. Each of these tissues is a sink for systemic aluminium and, as such, will also be involved in its removal. Similarly, one might expect some systemic aluminium to be excreted in secretions such as semen, sweat and tears.

Of course, in addition to the systemic burden of aluminium there is still a substantial additional burden associated with lung, primarily, and olfactory, probably less significant, epithelia and activities such as mucociliary clearance will continuously slough aluminium from these surfaces and direct it towards the gut.

Table 3. Primary routes of excretion of aluminium in humans. Secondary routes which involve primary routes would include biliary secretion and mucociliary clearance. The ranking is an indication of the relative importance of each of these routes in terms of the total amount of aluminium which is excreted. Thus, the ranking suggests that urine is the major route of excretion of aluminium

ROUTES OF EXCRETION	RANKING 1(Low) – 10(HIGH)
Faeces	5-7
Urine	7-9
Skin	4-6
Hair/Nails	3-5
Sweat/Tears/Semen	3-5

There are no data on how much aluminium will be trapped and passed through to the gut by these processes though the few data which do exist for the aluminium content of lung

tissue do suggest that they will contribute significantly to the overall body burden and, hence, excretion of aluminium.

While it may come as a surprise to many, contrary to current dogma, definitive data which specifically address the excretion of aluminium from the body are scarce and until whole body metabolic studies under tightly controlled conditions are carried out we can only guess as to the relative importance of each of the aforementioned routes of excretion of aluminium. Importantly, without such studies we shall remain uninformed also about the body's retention of aluminium and the burgeoning body burden.

5. BIOLOGICAL AVAILABILITY AND THE BODY BURDEN OF ALUMINIUM

How does medicine inform us about the burgeoning human body burden of aluminium? Where is the evidence that this burden of aluminium is biologically available? We know that the burden is biologically reactive we now need to identify those conditions under which biologically reactive aluminium has produced a biological response in the affected system. Much has already been written about human diseases which have been attributed to exposure to aluminium. Aluminium exposure is controversially linked to neurological conditions such as Alzheimer's disease [16] and recently, multiple sclerosis [17], and less controversially to conditions variously described as dialysis encephalopathy [18], osteomalacia [19] and iron-hyporesponsive microcytic anaemia [20]. With respect to the latter three conditions a consensus of opinion has accepted aluminium as a causative factor in their aetiologies though it has done so with the proviso that these are essentially one-off situations which are exceptions to the more likely benign presence of aluminium in the body. Even though aluminium is non-essential for all forms of life and serves no known role, essential or otherwise, in human physiology this does not preclude its participation in a wide and varied biochemistry. It remains one of the great paradoxes of life on Earth that the most abundant metal in the lithosphere, a metal which is unparalleled in the diversity of its chemical properties (cf. *The Aluminium Age*), has no biological function. There are few satisfactory theories to explain this paradox and the least satisfactory of these has attempted to define aluminium and its compounds as inert from a biochemical standpoint. Nothing could be further from the truth. It is worth recalling that all of the problems which come under the umbrella of 'Acid Rain' are related to an increase in the biological availability of aluminium and that the concentration of aluminium which under EU legislation is allowed in drinking water, 0.200 mg/L, will kill salmon fry within 48h! We need to take our collective heads out of the sand and accept that at all times the body burden of aluminium will be participating in some form of biochemistry and that at some point the level at which this biological activity is taking place may be manifested as a change in physiology which in turn may take the form of disease. The latter being the body's signature to a coping mechanism which may become slowly overwhelmed by a burgeoning body burden of aluminium. This must be one possible outcome of the continuous presence of a biologically reactive element which is inimical to all known forms of life.

If we can accept the potential for aluminium to contribute towards human disease then, in considering this likelihood, it is important to appreciate that aluminium is actually a foreign

substance in the body. It is a foreign substance in that it is not recognised as something either to be used by the body or to be excreted from the body. Aluminium as a foreign substance has major implications both in respect of its role as a potential antigen and in its propensity to 'piggy-back' upon systems (biochemistry) which almost certainly evolved functionality in its absence. We will consider these general implications of aluminium in the biological environment in their turn beginning with aluminium's propensity to substitute for other metals.

5.1. Aluminium Substitutes for Other Metals in Biochemistry

An important and well known example of the capacity for aluminium to 'piggy-back' upon a biological system is its binding in the blood by the iron transport protein, transferrin. While this interaction may play a role in the distribution of aluminium in the body it is not generally considered to have any immediate impact upon the transport and distribution of iron. Because the occupancy of transferrin by iron is low in normal physiology, perhaps only 30%, and there is little evidence of the competitive binding of iron and aluminium by transferrin it is assumed that this pathway is sufficiently robust to protect the body against the biological availability of aluminium. However, the presence of aluminium in blood must influence the equilibria which define the transport of iron by transferrin, if only through its changing of the proportion of unoccupied transferrin. Is the low occupancy of transferrin by iron simply a physiological anomaly or has it been the result of an extended process of evolution by natural selection. The latter would make the most sense as this transport route for iron is an integral part of an highly specialised mechanism controlling iron homeostasis and it is plausible that it will and indeed does respond in some way to its interference by aluminium in occupying previously unoccupied binding sites on transferrin. Under which conditions the response results in some form of toxicity are probably unknown though evidence for effects relating to, for example, erythropoiesis, are found in individuals with aluminium overload. Similarities in the bioinorganic chemistry of iron and aluminium do highlight iron homeostasis as an obvious target for intervention by aluminium while, as another example of aluminium's tendency to 'piggy-back' upon biochemical pathways, its putative *in vivo* associations with amyloid-forming peptides and proteins are not so immediately apparent.

There are a significant number of proteins and peptides which are known to precipitate *in vivo* as β -conformers of amyloid fibrils. While this protein conformation, which is often manifested *in vivo* as β -sheets arranged in plaque-like deposits, was generally believed to be aberrant there is strong evidence in lower organisms such as yeasts and increasing evidence in humans that amyloids may also be functional [21]. There is both *in vitro* and *in vivo* evidence that aluminium co-deposits with amyloid (perhaps all forms, it is yet to be ascertained) a number of which have been heavily implicated in the cytotoxicity which underlies particular chronic conditions. These amyloids include $A\beta_{40}$ and $A\beta_{42}$ in Alzheimer's disease [22,23], the ABri peptide in British familial dementia [24], NAC in Alzheimer's and Parkinson's disease [25], α -synuclein in Parkinson's disease [26], prion protein in Creutzfeldt-Jakob disease [27] and amylin in type 2 diabetes mellitus [28]. When each of these amyloidogenic peptides binds aluminium its precipitation as the β -sheet conformer is promoted, a process which can lead to

increased cytotoxicity. The secretion of amyloidogenic peptides is physiologically normal while their precipitation *in vivo* as amyloid is not favoured by their known concentrations in body fluids. Indeed their precipitation would seem to go against any putative function that they might have in, for example, cell signalling. However, super-saturated solutions of these peptides do form amyloid *in vitro* and something does act as a nidus for their precipitation as amyloid from under-saturated concentrations *in vivo*. Whether aluminium, an infamous cross-linker, (it was probably used to cure the leather in your shoes!) acts as such a nidus *in vivo* is unknown though there is evidence that amyloid which is co-deposited with aluminium is stabilised against both proteolytic and macrophagic degradation. The other metal which is co-deposited with amyloids in significant amounts is iron and recent research has shown that the combination of amyloid, iron and aluminium is extremely redox active with aluminium acting in the essential role of a pro-oxidant in promoting amyloid deposits as significant sources of reactive oxygen species (ROS) [29]. The latter have been heavily implicated in the cytotoxicity which is attributed to these amyloid deposits *in vivo* in conditions such as Alzheimer's disease. The 'piggy-back' element of the interaction of aluminium with amyloid-forming peptides may arise from the observation that the majority of amyloidogenic peptides which have been thus far investigated are known to bind copper with great avidity. Contrary to the effect from binding aluminium when, amylin or A β_{42} or ABri bind copper it prevents them from forming β -sheets of amyloid. Copper binding does result in their precipitation but as amorphous, diffuse deposits which as far as it is known, are not resistant to proteolytic or macrophagic degradation. Copper binding by amyloidogenic peptides may be an integral part of their normal metabolism and may even play a role in copper homeostasis and, importantly, should protect against amyloid involvement in diseases such as Alzheimer's disease and type 2 diabetes mellitus. However, the additional, perhaps 'evolutionarily unexpected', presence of biologically available aluminium can antagonise the protection afforded by copper binding. The mechanism underlying such an effect is not likely to be as straightforward as a one-for-one, metal for metal substitution as the bioinorganic chemistry's of copper and aluminium are probably sufficiently different to discount any direct competition between these metals for being bound by the same functional groups on peptides and proteins. The antagonism is more likely to be similar to aluminium's role in inhibiting the activity of the calcium binding protein calmodulin, a mechanism in which aluminium is bound to an alternative site to the calcium-binding group. The observation of a burgeoning number of studies highlighting aluminium as a putative antagonist of copper biochemistry might suggest that we should be looking beyond 'like for like bioinorganic chemistry' as the only prerequisite for aluminium 'piggy-backing' on a biochemical system.

The co-precipitation of aluminium with amyloids is an example of how the additional presence of aluminium in a biochemical system could make the difference between normal and aberrant physiology. An excellent example of aluminium 'piggy-backing' upon a biochemical system which is of fundamental significance is the substitution of magnesium for aluminium in adenosine triphosphate, ATP, and, indeed, other related nucleotides.

The role of ATP as both an energy currency and as an extracellular signalling molecule is heavily dependent upon the binding of its natural metal co-factor, magnesium and yet, given the opportunity, ATP will always prefer to bind aluminium in competition with up to a one thousand fold excess of magnesium. The natural selection of magnesium over aluminium as the metal co-factor for nucleotides would suggest some biochemical advantage and yet the

consequences of a change in metal co-factor are not always altogether predictable. For example, while aluminium-ATP does appear to be an unsuitable substrate for some biochemical reactions, such as the phosphorylation of glucose in the presence of hexokinase [30], it would seem to be entirely suitable for others, such as the hydrolysis of extracellular ATP by certain ectonucleotidases [31]. Where the substitution of aluminium for magnesium is disruptive the dysfunction would appear to be due to the enhanced stability of the aluminium-ATP complex compared to the magnesium-ATP complex with the result that the reaction pathway may be slowed down to the extent that it is no longer physiologically viable. However, there are other functions of ATP where an enhanced stability of the metal co-factor-ATP complex could potentiate a reaction pathway. For example, while we are all aware of the role played by ATP in the supply of energy it is less well known that ATP is of fundamental importance as an extracellular signalling molecule [32]. In fact, ATP should be considered as the pre-eminent extracellular signalling molecule since it is involved in myriad signalling systems acting all over the body. There are many known receptors for extracellular ATP which communicate both ionotropically (known as P_{2X} receptors) and metabotropically (known as P_{2Y} receptors) with the intracellular environment and each of these has specific affinities for binding ATP. While it is not completely understood whether or not the form of ATP which acts at its receptor is the free (protonated) anion or its magnesium complex the former, upon its secretion into extracellular milieu, will exist only briefly before binding magnesium and as such it is likely that it is magnesium-ATP which is the signalling moiety. In support of this view we have shown that the role of extracellular ATP in cell signalling in the coronary epithelium was influenced by the presence of aluminium [33] to the extent that we have speculated that the substitution of aluminium-ATP for magnesium-ATP at an ATP receptor will potentiate the signalling mechanism because aluminium-ATP will remain bound to the receptor for a longer period of time. Thus, aluminium does not actually disrupt the functioning of the ATP receptor but it keeps the receptor switched on for longer than usual which we suggested would contribute to a higher energetic load on affected cells and, thereby, would reduce their effective longevity. We have proposed such a mechanism to explain the putative role of aluminium in the age-dependent accelerated loss of neurones which is typical of Alzheimer's disease [34]. Clearly if signalling via extracellular ATP is a target for the body burden of aluminium then this could have implications for a very wide range of chronic conditions from asthma to Alzheimer's disease.

5.2. Aluminium as an Antigen

One of the most interesting areas of future research in relation to aluminium's impact upon medicine is the concept that was outlined earlier of the potential for aluminium to act as an antigen. Is aluminium really an antigen? Does the body actually raise an immune response against aluminium? The enhanced antigenicity which is associated with the use of aluminium-based adjuvants in a wide range of common vaccinations as well as in allergen immunotherapies would suggest very strongly that the answer to both of these questions must be yes though there is little consensus as to current understanding of the exact mechanism of action of aluminium adjuvants [35]. While historically aluminium-based adjuvants were thought of as simply long-lived depots of antigen we now know that aluminium adjuvants activate innate immune signals even in the absence of an adsorbed antigen. Monoclonal

antibodies have been raised against an immunogen which was prepared from aluminium chloride and bovine serum albumin and these antibodies have been labelled with a fluorescent tag and used to identify aluminium in human tissues [36]. Thus, if we are to accept that aluminium is antigenic then this must raise the question as to the exact nature of aluminium-based immunogens. Is the immunogen; (i) the free aluminium cation, $\text{Al}^{3+}_{(\text{aq})}$, or, (ii) is it a cluster of aluminium atoms which have been arranged in a specific orientation through their binding by a biomolecule(s) or, (iii) is the immunogen an aluminium hydroxide (hydroxyphosphate/sulphate) surface which can be presented to biological milieu either directly as the injected adjuvant itself or indirectly as a product of the injected adjuvant's dissolution and re-precipitation within a particular circumneutral environment? There are clearly a number of ways in which aluminium adjuvant acts as an immunogen and understanding which if any of these mechanisms is the closest to what is happening *in vivo* will significantly expedite our understanding of this 'unusual' example of the biological reactivity and availability of aluminium. For example, it would help to understand whether aluminium acts as an antigen in the classic sense such that following the initial exposure to an antigen (aluminium) the immune system retains a memory thereafter of that exposure and responds more rapidly to subsequent exposures to the same antigen (aluminium)? Such questions as to the mechanism of action of aluminium's antigenicity must raise important issues concerning whether or not, for example, mass vaccination programmes involving aluminium-based adjuvants, as is happening today, have the potential to influence the vaccinated individual's susceptibility to a future exposure to aluminium? Is the use of aluminium-based adjuvants predisposing individuals within the general population to an increase in their sensitivity to aluminium in later life? These questions may be particularly pertinent for childhood vaccination programmes involving aluminium-based adjuvants. While there have been only a few studies in this field recent research from Sweden showed that in 60,000 children vaccinated with the pertussis vaccine, which included an aluminium-based adjuvant, as many as 1% of these children showed delayed hypersensitivity to a future exposure to aluminium [37]. We should be concerned about something which could be predisposing as many as 1% of the population to living in *The Aluminium Age!* The ubiquitous and indeed burgeoning use of aluminium-based adjuvants in vaccinations which both cover the full spectrum of human diseases and are administered from new born babies through to the elderly may already have created cohorts of individuals which are hypersensitive to an aluminium exposure. In addition the use of aluminium-based adjuvants in allergen immunotherapy may already be acting so as to reinforce any such hypersensitivity and particularly since these treatments are often repeatedly administered over extended periods of time. Many of the symptoms of an hypersensitivity to aluminium may not be recognised as such and will not be recognised until it is recognised by medical practitioners as a real condition. At this point in time hypersensitivity to aluminium will probably only be diagnosed following patch tests on skin. However, evidence of such a condition might also take the form of; (i) an irritable skin condition, for example, in relation to the application of aluminium-based anti-perspirants; (ii) an asthmatic condition induced by, for example, particulate aluminium which had been trapped in lung mucosa following the inhalation of cigarette smoke; or (iii) an auto-immune response to the accumulation of aluminium as might be the case in diseases such as arthritis and even multiple sclerosis. There are many chronic conditions within the general population which are unlikely in the first instance to be linked to vaccination or allergen immunotherapy. However, the number of vaccine and allergen

immunotherapy-related illnesses which have been attributed to aluminium-based adjuvants is burgeoning and includes macrophagic myofasciitis (MMF) and cutaneous lymphoid hyperplasia (CLH) both of which have been linked to the persistence of aluminium adjuvants close to the point of vaccination. What is most worrying about aluminium adjuvant-related disorders is not necessarily the pathology which is directly associated with the muscle at or close to the injection site but the myriad non-specific symptoms and conditions which have been associated with these diseases. These include chronic fatigue syndrome (CFS), autoimmune disease, type one diabetes and multiple sclerosis. Environmental factors are implicated in the aetiology of each of these conditions and there are direct links to exposure to aluminium in all but type one diabetes. (Note that there is a link between aluminium and type two diabetes [38].) We have recently suggested aluminium as an environmental factor in multiple sclerosis and research from our laboratory has identified elevated urinary excretion of aluminium in individuals suffering from the disease [17]. Significantly, there is also evidence for an increased body burden of aluminium in CFS [39] and MMF [40]. These findings have raised the possibility that aluminium adjuvant-induced hypersensitivity to aluminium might take the form of an increased tendency to accumulate aluminium in the body. The identifiable diseases may then be the manifestation of immune-mediated responses to the burgeoning body burden of aluminium.

The twenty-first century human body is, through an improved and improving understanding of medicine, offering clear indications of not only a burgeoning body burden of aluminium but also the physiological response to an increase in the biological availability of this body burden. Since aluminium has no known function in life then the first manifestations of the evolution of human physiology in its presence will almost certainly be negative and most likely in the form of chronic disease. The finest of the most recent writings on aluminium and health which was published more than twenty years ago included in its summary a statement of surprise that aluminium could be linked to so many different human diseases [41]. Indeed the disbelief that biologically available aluminium could have such a profound influence upon human physiology has been aluminium's best defence against its inimical nature in all biota. There are few who would doubt the overt toxicity of an acute exposure to aluminium. When aluminium was dialysed into the brain in huge amounts, as it was in cases of dialysis encephalopathy, no one questioned aluminium's role in the acute toxicity which ensued. However, living in *The Aluminium Age* is not about acute exposure, though this does still occur, it is about how the body's physiology responds to an increasing burden of biologically available aluminium. The biological 'reactivity' of aluminium should not be in doubt as there are literally thousands of publications over the last several decades which have demonstrated the incredible diversity of aluminium's biochemistry. Some aspects of the major themes of this biochemistry have been covered in this Chapter and include; (i) aluminium's antagonism of magnesium biochemistry and not least that of ATP and DNA; (ii) aluminium's disruption of iron homeostasis; (iii) aluminium's role as a pro-oxidant, a function which requires only catalytic amounts of the free cation and (iv) aluminium's antigenicity, which has serious implications for a whole raft of auto-immune-like conditions. When in 1986 Ganrot wrote of his surprise that aluminium could be so widely implicated in human disease he was not as aware of the potential biochemistry of aluminium as we are today. The surprise today is not that aluminium should be a cause for concern but that we are so complacent about its potential role in the diseases of modern life. There has never been any question in my mind that we should in some way turn back the clock to a pre-Bayer process

era and cease to use aluminium. We live in the *Aluminium Age* and our aim should be to ensure that where we continue to use aluminium that we do so effectively and safely.

Table 4. Human diseases which have been linked to exposure to aluminium. The ranking is an indication of the probability that in the future aluminium will be shown to play some role in the aetiology of the disease. Thus, a ranking of 10 for dialysis encephalopathy shows that aluminium is already known to be involved in this disease

DISEASE	RANKING 1 (LOW) – 10(HIGH)
Alzheimer's Disease	7-8
Parkinson's Disease	4-6
Motor Neurone Disease (MND/ALS)	3-5
Dialysis Encephalopathy	10
Multiple Sclerosis	4-6
Epilepsy	7-8
Osteomalacia	10
Osteoporosis	4-6
Arthritis	5-7
Anaemia	10
Calciphylaxis	2-4
Asthma	7-9
Chronic Obstructive Pulmonary Disease	5-7
Vaccine-related Macrophagic Myofasciitis	8-10
Vaccine-related Cutaneous Lymphoid Hyperplasia	8-10
Vaccine-related Hypersensitivity to Aluminium	8-10
Immunotherapy-related Hypersensitivity to Aluminium	8-10
Cancer	4-8
Diabetes	5-7
Sarcoidosis	7-9
Down's Syndrome	5-7
Muscular Dystrophy	4-6
Cholestasis	6-8
Obesity	5-7
Hyperactivity	4-6
Autism	4-6
Chronic Fatigue Syndrome	5-7
Gulf War Illness	4-6
Aluminosis	10
Crohn's Disease	7-9
Vascular Disease / Stroke	6-8

6. HOW TO CONTINUE TO LIVE SAFELY IN THE ALUMINIUM AGE?

So, other than the unrealistic aim of totally avoiding exposure to aluminium in everyday life how do we live safely in *The Aluminium Age*? The lack of an aluminium-specific mechanism to enable its excretion from the body allows for the accumulation of aluminium and the persistence of any symptoms which might be the consequence of a body burden. Remission from the symptoms of an aluminium body burden may be obtained through either physiological changes which enable the enhanced excretion of aluminium in the urine, as, for example, may be occurring as demyelination in relapsing-remitting multiple sclerosis, or through specific intervention such as the intramuscular injection of the iron chelating drug desferrioxamine (DFO). The latter has been used extensively to treat individuals with suspected aluminium overload and, in spite of the significant side effects associated with its use, DFO remains, as yet, the only accepted course of treatment for the removal of systemic aluminium. While there is evidence that the symptoms of aluminium overload can be reduced or even reversed following DFO-facilitated excretion of aluminium, perhaps a more straightforward solution would be a preventative mechanism which helped to preclude the accumulation of a body burden of aluminium. We are currently investigating a non-invasive therapy which would concurrently reduce the gastrointestinal absorption of aluminium and facilitate the excretion of systemic aluminium in the urine. The latter objective is of particular importance as simply reducing human exposure to aluminium via its absorption across the gut, cannot be guaranteed to significantly influence the body burden of aluminium. We have shown over many years of research that the reaction of aluminium with the biologically available form of silicon, silicic acid, is fundamental to the biogeochemical cycle of aluminium [42]. Nature has acted so as to keep aluminium out of biota throughout the evolution of life on Earth by cycling potentially biologically reactive aluminium between sparingly soluble secondary mineral phases made predominantly of aluminium, silicon and oxygen [2]. We showed that such processes could be used in reverse to protect against aluminium toxicity in fish [43]. We speculated at the time that silicic acid would also protect against aluminium toxicity in humans and we have recently shown that silicic acid-rich mineral waters can be used to titrate aluminium from the bodies of healthy individuals and individuals with diseases such as Alzheimer's disease [44]. We are currently in the process of planning clinical trials in which silicic acid-rich mineral waters will be used to follow the urinary excretion of aluminium in healthy individuals and persons diagnosed with dementia. We are confident that by using this non-invasive method the human body burden of aluminium can be maintained at a sufficiently low level to prevent many if not all of the symptoms of living in *The Aluminium Age*!

7. AND SO TO CONCLUDE

Medicine, the study of human disease, is providing valuable information pertaining to the biological availability of a burgeoning body burden of aluminium. There is no evidence that human physiology is prepared for the challenge of biologically-reactive aluminium and it is naïve to assume that aluminium is a benign presence in the body. Aluminium is contributing

to human disease and will continue to do so if its accumulation in the body is not checked or reversed. If such a conclusion does not 'sit well' with the current inhabitants of *The Aluminium Age* then I am reliably informed of an aluminium-based sclerotherapy for such an uncomfortable condition [45].

REFERENCES

- [1] C. Exley, J.D. Birchall, The cellular toxicity of aluminium, *J. Theoret. Biol.* 159 (1992) 83-98.
- [2] C. Exley, A biogeochemical cycle for aluminium?, *J. Inorg. Biochem.* 97 (2003) 1-7.
- [3] J.P. Day, J. Barker, L.J.A. Evans, J. Perks, P.J. Seabright, P. Ackrill, J.S. Lilley, P.V. Drumm, G.W.A. Newton, Aluminium absorption studied by 26-Al tracer, *Lancet* 337 (1991) 1345.
- [4] J.A. Edwardson, P.B. Moore, I.N. Ferrier, J.S. Lilley, G.W.A. Newton, J. Barker, J. Templar, J.P. Day, Effect of silicon on gastrointestinal absorption of aluminium, *Lancet* 342 (1993) 211-212.
- [5] R. Flarend, T. Bin, D. Elmore, S.L. Hem, A preliminary study of the dermal absorption of aluminium from antiperspirants using aluminium-26, *Food Chem. Toxicol.* 39 (2001) 19-24.
- [6] O. Guillard, B. Fauconneau, D. Olichon, G.V. Dedieu, R. Deloncle, Hyperaluminemia in a woman using an aluminium-containing antiperspirant for 4 years, *Am. J. Med.* 117 (2004) 956-959.
- [7] C. Exley, Aluminium in antiperspirants: More than just skin deep, *Am. J. Med.* 117 (2004) 969-970.
- [8] R.E. Flarend, S.L. Hem, J.L. White, D. Elmore, M.A. Suckow, A.C. Rudy, E.A. Dandashli, In vivo absorption of aluminium-containing vaccine adjuvants using ²⁶Al, *Vaccine* 15 (1997) 1314-1318.
- [9] C. Exley, A. Begum, M.P. Woolley, R.N. Bloor, Aluminium in tobacco and cannabis and smoking-related disease, *Am. J. Med.* 119 (2006) 276e.9-276e.11.
- [10] C. Exley, U. Ahmed, A. Polwart, R.N. Bloor, Elevated urinary aluminium in current and past users of illicit heroin, *Addiction Biol.* 12 (2007) 197-199.
- [11] M. Durand, C. Florkowski, P. George, T. Walmsley, P. Weinstein, J. Cole, Elevated trace element output in urine following acute volcanic gas exposure, *J. Volcanol. Geotherm. Res.* 134 (2004) 139-148.
- [12] P. Ackrill, J.P. Day, Desferrioxamine in the treatment of aluminium overload, *Clin. Nephrol.* 24 (1985) S94-S97.
- [13] C. Exley, J. Beardmore, G. Rugg, A computational approach to the blood-aluminium problem, *Int. J. Quant. Chem.* 107 (2006) 275-278.
- [14] J. Beardmore, G. Rugg, C. Exley, A systems biology approach to the blood-aluminium problem: The application and testing of a computational model. *J. Inorg. Biochem.* 101 (2007) 1187-1191.
- [15] C. Exley, The pro-oxidant activity of aluminium, *Free Rad. Biol. Med.* 36 (2004) 380-387.

-
- [16] C. Exley, (Ed.) Aluminium and Alzheimer's Disease: the Science that Describes the Link, Elsevier Science, Amsterdam, 2001.
- [17] C. Exley, G. Mamutse, O. Korchazhkina, E. Pye, S. Strekopytov, A. Polwart, C. Hawkins, Elevated urinary excretion of aluminium and iron in multiple sclerosis, *Multiple Sclerosis* 12 (2006) 533-540.
- [18] A.C. Alfrey, G.R. LeGendre, W.D. Kaehny, The dialysis encephalopathy syndrome: Possible aluminium intoxication, *New Eng. J. Med.* 294 (1976) 184-188.
- [19] C.E. Dent, C.S. Winter, Osteomalacia due to phosphate depletion from excessive aluminium hydroxide ingestion, *British Med. J.* 1 (1974) 551-552.
- [20] J. Toulon, J.C. Sabatier, R. Gonthier, F.C. Berthoux, Microcytic anaemia and osteomalacia as early signs of aluminium intoxication in chronic haemodialysed patients, *Lyon Medical* 243 (1980) 729-736.
- [21] D.M. Fowler, A.V. Koulov, W.E. Balch, J.W. Kelly, Functional amyloid – from bacteria to humans, *Trends Biochem. Sci.* 32 (2007) 217-223.
- [22] C. Exley, N.C. Price, S.M. Kelly, J.D. Birchall, An interaction of β -amyloid with aluminium in vitro, *FEBS Lett.* 324 (1993) 293-295.
- [23] E. House, J. Collingwood, A. Khan, O. Korchazhkina, G. Berthon, C. Exley, Aluminium, iron, zinc and copper influence the in vitro formation of amyloid fibrils of $A\beta_{42}$ in a manner which may have consequences for metal chelation therapy in Alzheimer's disease, *J. Alzh. Dis.* 6 (2004) 291-304.
- [24] A. Khan, A.E. Ashcroft, O.V. Korchazhkina, C. Exley, Metal-mediated formation of fibrillar ABri amyloid, *J. Inorg. Biochem.* 98 (2004) 2006-2010.
- [25] A. Khan, A.E. Ashcroft, V. Higenell, O.V. Korchazhkina, C. Exley, Metals accelerate the formation and direct the structure of amyloid fibrils of NAC, *J. Inorg. Biochem.* 99 (2005) 19120-1927.
- [26] V.N. Uversky, J. Li, A.L. Fink, Metal-triggered structural transformations, aggregation and fibrillation of human alpha synuclein – A possible molecular link between Parkinson's disease and heavy metal exposure, *J. Biol. Chem.* 276 (2001) 44284-44296.
- [27] F. Ricchelli, R. Buggio, D. Drago, M. Salmona, G. Forloni, A. Negro, G. Tognon, P. Zatta, Aggregation/fibrillogenesis of recombinant human prion protein and Gerstmann-Straussler-Scheinker disease peptides in the presence of metal ions, *Biochemistry* 45 (2006) 6724-6732.
- [28] B. Ward, K. Walker, C. Exley, Copper(II) inhibits the formation of amylin amyloid in vitro, *J. Inorg. Biochem.* (In the press).
- [29] A. Khan, J. Dobson, C. Exley, The redox cycling of iron by $A\beta_{42}$, *Free Rad. Biol. Med.* 40 (2006) 557-569.
- [30] F.C. Womack, S.P. Colowick, Proton-dependent inhibition of yeast and brain hexokinase by aluminium in ATP preparations, *Proc. Natl. Acad. Sci. USA* 76 (1979) 5080-5084.
- [31] O.V. Korchazhkina, G. Wright, C. Exley, No effect of aluminium upon the hydrolysis of ATP in the coronary circulation of the isolated working rat heart, *J. Inorg. Biochem.* 76 (1999) 121-126.
- [32] B.M. Paddle, G. Burnstock, Release of ATP from perfused heart during coronary vasodilation, *Blood Vessels* 11 (1974) 110-119.

-
- [33] O.V. Korchazhkina, G. Wright, C. Exley, Action of Al-ATP on the isolated working rat heart, *J. Inorg. Biochem.* 69 (1998) 153-158.
- [34] C. Exley, A molecular mechanism of aluminium-induced Alzheimer's disease?, *J. Inorg. Biochem.* 76 (1999) 133-140.
- [35] J. Brewer, How do aluminium adjuvants work?, *Immunol. Lett.* 102 (2006) 10-15.
- [36] R. Levy, L. Shohat, B. Solomon, Specificity of an anti-aluminium monoclonal antibody toward free and protein-bound aluminium, *J. Inorg. Biochem.* 69 (1998) 159-164.
- [37] E. Bergfors, B. Trollfors, A. Inerot, Unexpectedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccines from a single manufacturer, *Vaccine* 22 (2003) 64-69.
- [38] T. Baydar, G. Sahin, A. Aydin, A. Isimer, S. Akalin, S. Duru, Al/Cr ratio in plasma and urine of diabetics, *Trace Elem. Electrolytes* 13 (1996) 50-53.
- [39] S.J. van Rensburg, F.C.V. Potocnik, T. Kiss, F. Hugo, P. van Zijl, E. Mansvelt, M.E. Carstens, P. Theodorou, P.R. Hurly, R.A. Emsley, J.J.F. Taljaard, Serum concentrations of some metals and steroids in patients with chronic fatigue syndrome with reference to neurological and cognitive abnormalities, *Brain Res. Bull.* 55 (2001) 319-325.
- [40] C. Exley, L. Swarbrick, R. Gherardi, J-F Authier, A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome?, *Med. Hyp.* (In the press.)
- [41] P.O. Ganrot, Metabolism and possible health effects of aluminium, *Environ. Health Perspect.* 65 (1986) 363-441.
- [42] C. Exley, C. Schneider, F.J. Doucet, The reaction of aluminium with silicic acid in acidic solution: An important mechanism in controlling the biological availability of aluminium?, *Coord. Chem. Rev.* 228 (2002) 127-135.
- [43] J.D. Birchall, C. Exley, J.S. Chappell, M.J. Phillips, Acute toxicity of aluminium to fish eliminated in silicon-rich acids waters, *Nature* 338 (1989) 146-148.
- [44] C. Exley, O. Korchazhkina, D. Job, S. Strekopytov, A. Polwart, P. Crome, Non-invasive therapy to reduce the body burden of aluminium in Alzheimer's disease, *J. Alzh. Dis.* 10 (2006) 17-24.
- [45] T. Ono, K. Goto, S. Takagi, S. Iwasaki, H. Komatsu, Sclerosing effect of OC-108, a novel agent for hemorrhoids, is associated with granulomatous inflammation induced by aluminium, *J. Pharmacol. Sci.* 99 (2005) 353-363.