



Alien Trace Metal Elements in the Body: Changes May Explain Recent Epidemics and Diseases

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Abstract

It is now well-known that many elements of the periodic table find a way into our bodies and have the potential for disturbing the delicate homeostasis (balance) of body chemistry. Nevertheless, in spite of the volume of research published in this area, only vague suppositions result concerning any involvements and little progress has been made concerning human health or addressing the preponderance of the innumerable epidemics that now are evident. This results from the inability for statistical analyses to be sufficiently precise to pinpoint specific causes. As a result, a simpler analysis is presented herein based on the premise that environmental chemical epidemics can only arise from an increased change. As a result, global diets and life-styles have been examined in detail to establish items of change. Such a needed criteria in the recent decades poses strict requirements eliminating most candidates. Two areas of rapid growth in life-style changes clearly are evident and involve the diet of fish (sushi) (high methyl mercury) and the increase in medical vaccines (aluminum hydroxide). It is apparent that people now live never knowing whether they are at risk from these due to genetic susceptibilities. This is especially important for women of child-bearing years, where a fetus is always at high toxic risk levels. As a result, the availability of general population testing now is desperately needed especially for the neurotoxins, Hg, Al, As, and Pb, all alien species to the body together with Se that appears to be the body's natural healthy chelator.

Keywords: Alien Elements; Epidemics; Observed Changes; Susceptibilities; Mercury, Aluminum; Blood Testing; Personal Health

Introduction

The human body is a remarkable example of excellence in design. It displays automatic self-sufficiency, survival maintenance and repair. Unfortunately, we humans casually accept this, generally think very little of it, until it malfunctions. Then we more fully appreciate these built-in capabilities, but soon continue our lives fully hoping that this finely tuned mechanism will continue unchecked for an extended longevity. Various epidemics of illnesses have always arisen over the centuries, occur naturally,

are often unexpected and in the past have been caused by some modified viral form. Historically, this has always been a factor of life and accepted as a hazard. However, times now appear to differ, and some current concerns that are at epidemic levels are no longer only viral but appear to center more on environmental causes, and for which the body has no response. This has initiated necessary new conjectures by the medical community that previously often had known treatments, either a vaccine or a medication to control or cure such an event. Now, with no understanding in many cases, the introduction of environmental aspects in

the modern age poses problems with impossible long lists of potential causes. It would appear to be a very difficult if not an impossible task to unravel any single item or group for explanations. This is partially true, but if the cause produces an epidemic this introduces innumerable required conditions that are necessary and begins to eliminate many potential suggestions. The medical literature is now ripe with such exercises and has considerably reduced the options. Additionally with neurological epidemics, the possibilities are even more restrictive, as the brain itself has to be affected. Such epidemics if not common in the past also need the basic factor of a needed change. As a result, although we now live in the realm of genetic explanations, our genes are not apt to suddenly change drastically. As a result, genetic explanations are necessarily not a primary but have to be a secondary component if involved, possibly due to epigenetic changes that are now being suggested as moderating genetic susceptibilities [1]. This paper concerns environmentally induced epidemics that have arisen, are global, and have become apparent in recent decades. A generally accepted consensus now is that these appear connected to changes in life-style that have occurred in modern-day living. As a result, partly based on such concerns, the field of medicine has turned more aggressively to a better understanding of body chemistry, its balances and the nature of possible changes. This has been facilitated by advances in analytical ability such that in recent years it has become possible to monitor numerous components of the human body through analysis of its measurable components. This has resulted in an overwhelming wealth of publications that for medicine introduces the further difficult task of analysis. If anything, it has illustrated more clearly how every human is different [2]. As a result, even with extensive statistical aid, analyses become limited in value due to the array of variable parameters and the necessary variations introduced in any collected data. The dilemma is that although it would seem obvious that if a large sample of a control group are compared to a group that has a certain illness, the differences should clearly imply a role from any apparent observed correlations. The problem is that the control sample may not be a truly rigid constant representative group in that its body chemistry can constantly vary depending on behavior and many other factors. This is true for the test case group also. It is hoped that large sampling will dilute and buffer such differences but this does not appear to be the case. The data needs to have a more significant degree of precision for a rigorous solution [3]. As a result, although hundreds of such analyses have been published relating to toxic substances and enumerable illnesses, although certain groups of correlations have appeared possible, analyses are always left with non-specific conclusions and suppositions. Even so, such analyses are continuing today further examining multiple illnesses to no avail [4-9]. Moreover, it is interesting that none of these studies appear to be repeated to gain any

level of validation. No scientific rigorous singular solutions are possible under such circumstances. I know this from personal experience in science when one of my apparently correct statistical fit to a large body of combustion data was finally shown to be in error due to such minor variations in the input data [10-12]. In other words, medical analysis if to be meaningful has to turn to a different approach. The continuing collection of data with little hope of meaningful analysis may be of some interest but is not worthwhile. A most recent analysis of blood plasma in Tunisian children with autism monitored 33 chemical elements and although an impressive effort only shows all to be present at some level [13]. An alternate common-sense aspect not yet in extensive practice is to simply look for changes that have occurred in the world. Are there geographic or life-style factors that fit into this required time slot and occur globally? This paper emphasizes such an approach concerning such an area that has been quite extensively studied but previously not been open to such a simple concept. A more scientific approach now is presented. What has emerged so far in previous research is a new interest concerning the inorganic chemistry of the body. Initial analyses of the generally used biomarkers were surprised to find a large array of elemental compounds in the body, especially many that had no biological roles. These now have become suspect due to their natures and ready presence in everyone. If nothing else, the many studies with humans and animals now have indicated a potentially important role for the inorganic elemental materials. Also, that the delicate homeostasis (balance) of the elements in the body can be easily disrupted by some illness. The question addressed in the present study is whether these elements can be aggravators capable of playing major roles as inflammatory sources. Out of the myriad of medical publications concerning humans or animals is their now sufficient evidence to highlight any single element or group that has changed significantly? Moreover, are such consequences in the body quite general and form a basis not only for being a cause in a single but for several disorders?.

The Significant Elements Found in the Blood and those Alien to the Human Body: The Basic Value of Large General Surveys

Partly as a result of the ICP-MS (Inductively Coupled Plasma Mass Spectrometer), most of the metal elements in the periodic table can be readily monitored to very minimal levels. Blood is one useful biomonitor for humans and analyses of all the metals present down to low levels are available in a vast array of published surveys from around the world. Some appearing in recent years that are studies solely sampling general populations to observe their distributions and averages have widened the number of elements measured now up to 45 or even 52 elements [14,15]. Since the 1960's, the US in its National NHANES program also has

monitored about 5000 people/year and included coverage of about 14 of the trace elements in their blood or urine samples [16]. Human biology now is well studied and the important elements required as essential nutrients are well defined having either major or minor roles [17]. As listed in Table 1, 8 elements are basic to the body's requirements and are present in blood at significant levels on a gm or mg/L level.

Required Elements		Alien Elements	
Major (mg/L)	Minor (µg/L)	(µg/L)	(µg/L)
Ca 55	Cr ^{III} < 2	Ag < 1	Hg ≤ 9
Cu 1.5	Co < 1	Al ≤ 6?	Pb ≤ 50
Fe 1	Mn ≤ 15	As ≤ 12	Rb ≤ 2.5 mg/L
K 170	Mo < 3	Ba < 7 *	Sb ≤ 3
Li 7	Ni < 1.5	Be < 1	Sc ≤ 1
Mg 50	Se 240	Bi < 1*	Sn ≤ 5
Na 3300		Cd ≤ 2	Sr < 35*
Zn 10		Ce ≤ 2	Ti ≤ 1*
		Cs ≤ 3	Tl ≤ 1
		Ga < 1	V ≤ 0.4
		Ge < 10*	

Table 1: Approximate suggested reference values (RV₉₅) for health of trace elements monitored in human adult blood samples.

^a Preliminary set of values drawn from several references [18-22] and numerous other surveys. They will vary country to country and are still being established.

*Values can be variable and larger at times depending on location/population, and other factors such as dialysis, vaccines, prosthetic devices (Al), therapeutics (Bi), industry (Ge), and prosthetics (Ti). Sr is generally significant due to its chemical similarity and association to Ca. Value uncertain at present due to the introduction of Al as the major adjuvant in vaccines.

Al, As, Hg, Mn, Pb, Se and Tl are the known major neurotoxins. From an evolutionary point of view this Table is quite remarkable. It appears as a necessary measured recipe for life.

The ASTDR US Agency for toxic substances and disease registry [23] now has accepted responsibility for releasing detailed toxicological and environmental reports that are freely available on the Web. They now include 26 metal elements and generally are the most current reviews. They generally supersede earlier reports available in the World Health Organization's EHC Monograph Reports (Environmental Health Criteria), or their similar IPCS, INCHEM, and CICAD reports on chemical safety [24], which

do still include valuable extensions to include Pt, Pd, and Ti elements and do actually have more recent dated reports for Hg, Ag, Sr and Tl. Six other elements are listed in Table 1 as being essential, playing various minor roles in the body. Although in several cases these can be toxic (Cr if in its hexavalent form), they are minor and are required only in µg/L amounts. Two neurotoxins, Mn and Se, important to the body do fall in this category. As will be seen, Se is now becoming established as a very essential element from this list. It is interesting that the body utilizes only elements from the initial part of the periodic table and the seven later elements of the first row of transition elements. Any possible minor roles for As and V still remains unclear. Mo at atomic number 42 is the heaviest element required. Ones lighter than this, that seem to have been overlooked in the body's design are namely Be, Al, Sc, Ti, V, Ga, Ge, Rb, Sr, Y, Zr, and Nb that play no roles. Some of these are toxins but only at more elevated levels. Together with Hg, Pb and Tl, these are listed in Table 1 as Alien elements, all found in the body but serving no purpose. Due to their neurotoxic access to the brain, and also having basic body toxicity Al, As, Hg, Mn, Pb, Se and Tl gain in importance. With the exception of thallium, their concentrations generally are a little larger than the other non-essential alien elements. Thallium, generally still rare in most environments is not widely encountered, existing mainly in specific geographical locations. Surprisingly, as noted in the surveys, most of these non-essential elements of the periodic table do creep into most diets. What is more surprising is that the chemicals in the body are in a delicate balance (homeostasis). The introduction of only traces of a toxin, a biological organism or even stress can disturb this balance and induce serious illnesses. Several elements, such as Ba, Rb, Sr, Sb, and Sn can be present at low levels and are tolerated by the body. The possible elevated levels for Rb, Sr and Ba generally arise from their chemical connection and similarity to the other alkali or alkaline earths. A recent inventory of global anthropogenic atmospheric emissions listed 12 typical hazardous trace elements, all listed in Table 1 and all found present in the human body [25].

Several countries have published blood survey data indicating their approximate general baseline values observed for their citizens. There are many other such studies but these often limit the measures to selected combinations of elements such as Pb, Cd and Hg, due to their ever presence and considered importance. Such survey results are generally presented in statistical form, the frequency distribution often being portrayed by listing values that encompass the 10, 25, 50, 75, 90 and 95% of the population tested. From this, an average value normally is acquired and occasionally a maximum value quoted. They are rarely shown pictorially. However, if so produced, as here in Figures 1-4, the nature of their distributions is more readily apparent and the variations and magnitudes more obvious. The cases illustrated, namely

for As, Cd, Cu, Hg, Mn, Pb, Se, and Zn, represent data from various countries. Magnitudes span a range of mg/L (zinc and copper), selenium ($< 300 \mu\text{g/L}$), whereas the other 5 for Cd to Pb and are on lower scales of 0-60 $\mu\text{g/L}$. These magnitudes are interesting in themselves and show several generalities immediately. Firstly, differences and similarities can exist between nations, distributions can have similar shapes and average values can vary globally. Levels of Cu, Zn

and Se can have similar distribution shapes with differing averages. Mn appears quite tightly controlled by the body. The other 4 minor species, As, Cd, Pb and Hg show differing averages, similar shapes but obviously are geographically affected. Consequently, although humans are all genetically different, there is an obvious underlying similarity of body chemistry even for the alien elements Figure 1.

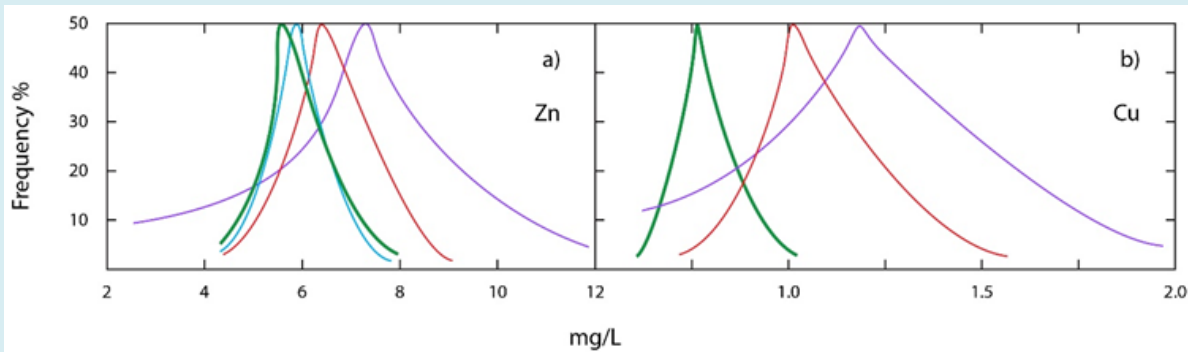


Figure 1a, b: Survey distributions of blood testing for Zn and Cu. [26] red, Italy; [27] blue, France; [28] green, China; [20] purple, Brazil.

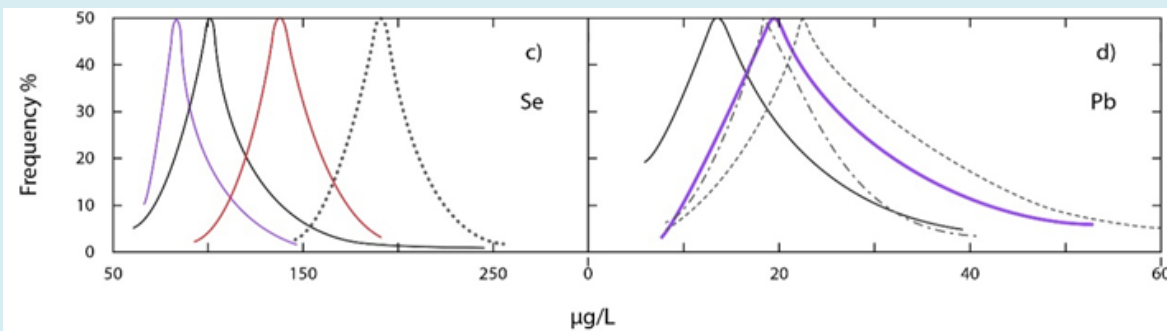


Figure 2c, d: Survey distributions of blood testing for Se and Pb. [26] red, Italy; [20] purple, Brazil, [29] black, Finland; [30] USA, [31], heavy dash-dot Norway; [32] light dash line, Korea.

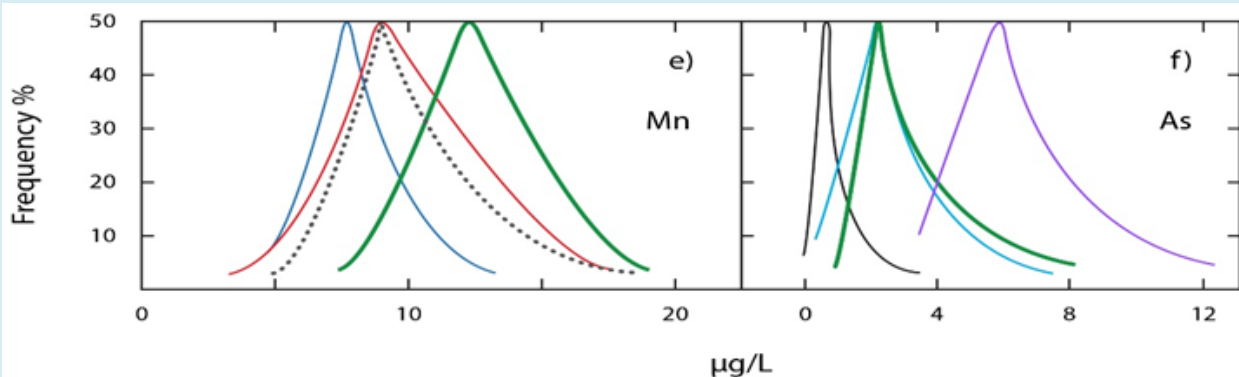


Figure 3e, f: Survey distributions of blood testing for Mn and As. [26] red, Italy; [27] blue, France; [28] green, China; [20] purple, Brazil, [29] black, Finland; [30] USA.

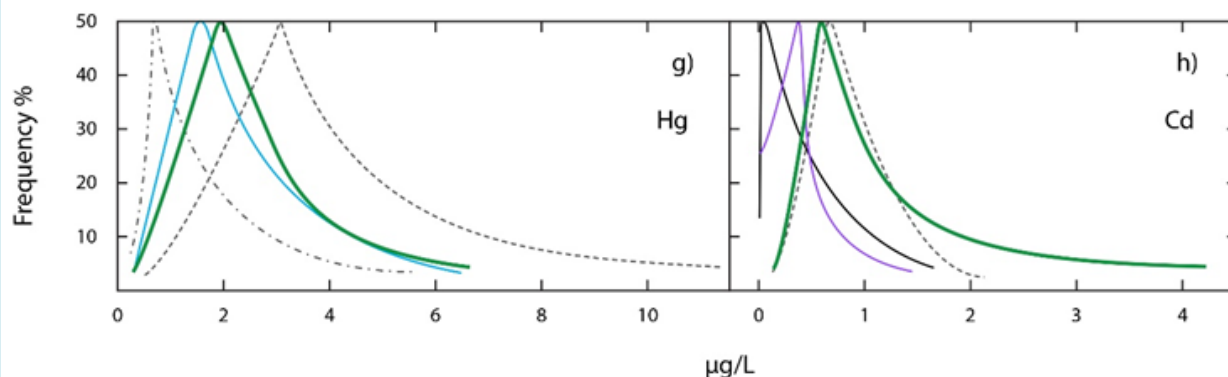


Figure 4g, h: Survey distributions of blood testing for Hg and Cd. [27] blue, France; [28] green, China; [20] purple, Brazil, [29] black, Finland; [32] ... Korea, [33] dash-dot, USA.

Elements that May be Introducing Risk: Survey Implications

As a result of many such global surveys it is possible to begin to assess which elements may possibly be posing risks to health. It is not unreasonable to assume that those elements essential for life are managed effectively and automatically by the body. Any fault or disruption with them will not be long in becoming evident and generally be effectively diagnosed and corrected. Over the years, toxicity limits have been established for most of the elements from human and animal studies and values obtained that correspond to levels where symptoms affecting the body become apparent, the so-called NOAEL and LOAEL, no or lowest observed adverse effects levels. These have formed the basis for establishing minimum risk levels (MRL), Biomonitoring values that can be suggested by taking a built-in safety buffer of possibly 10- to 100-fold lower margin than the NOAEL value if possible, and this has become a useful medical guide. However, on several distributions it has become noted that the fall-off region can vary to different extents and readily stretch even beyond a 95% cut off of the sample and that an MRL value did not adequately reflect risk in such slow fall-off distributions. This was becoming commonly noted particularly for mercury where a large part of current survey distributions can extend well beyond the US MRL suggestion [34].

As a result, the actual value encompassing 95% of the survey now is being accepted as a better risk assessment magnitude, the so-called Reference Value (RV_{95}) and is becoming accepted as a better diagnostic value [18-22,35]. Such values are listed already in Table 1. However, this is still based on the accepted premise that if levels are sufficiently low, they can be accepted. This of course results from the fact that we have been living with nature quite well for many centuries indicating that the human body appears to tolerate many elements at levels that occur naturally. None

the less, such a set of benchmark values remains invaluable and a basic guide for doctors. Surveys arise by sampling normally labeled healthy people. As a result, the field of toxicity is not an exact science and some of its assumptions now are being questioned, especially as humans are living longer and some elements found in the body may not have been in common use for long. However, in a basic manner this remains irrelevant in the present discussion. Changes are required and if a noted risk factor is relevant to an epidemic it has to satisfy various conditions such as having global availability. This and other requirements become very restrictive and extensively minimize considerations of periodic table options. Additionally, metals heavier than Mo do become suspect automatically as alien species in the body, but are also less encountered in most diets. Other than the aspect of slow accumulation, which may be relevant to diseases of the elderly, the question of higher exposures is obvious. However, without symptoms there is always an assumption of health. Levels falling within the RV_{95} values of these figures are automatically acceptable. This is apparent in the distributions illustrated in Figs.1 -4. For any of the toxic elements other than Mn and Se needed by the body, all distributions are characterized by a slow fall-off to outlier cases occurring well beyond even the 98% of the distribution, often in some cases to higher values. Until recently there has been little interest in such extended values that can be creeping towards levels of toxicity. For elements required by the body the risk assessment for health differs in needing to examine extremes, essentiality and toxicity [36]. There are now models relating dose-response aspects to assess risk [37]. The problem becomes different though for alien elements when only the upper limit is of interest. As a result, for most of these, the important data mainly come from survey levels, human observations and animal studies. Lead which appears to be the most toxic alien element has been very extensively studied. Human and animal studies note cognitive decline at even low levels, leading to the conclusion

that a zero tolerance is most appropriate implying no model is needed [38-40]. Tests on rats now confirm oxidative stress and neurodegeneration also with low doses of methyl mercury [41] and arsenic exposure also indicates neural impairment at low levels [42]. Surprisingly, even strontium thought to be benign in the body now has been reported to produce oxidative stress in pregnant women [43]. Low concentrations of these trace toxic alien species in mixtures (As, Cd, Hg, Pb) are reported to have deleterious effects on mice and rats and moderate their bodily distributions [44-46]. Pregnancies are of particular concern as safe levels still need establishing [47]. Consequently, even though supposedly safe blood levels are being suggested, these are only a useful rough guide for medical consultations and remain the best realistic supposition. It is the nature of variation between humans that remains complex and additionally the variation of genetic susceptibilities that is apparent in the data. Nevertheless, the simple conclusion that can be drawn from all toxicity studies is that less is recommended.

Assessment of Diets and Which Alien Elements are More Commonly Encountered?

The assessment of what foods humans need to eat for good health arose from the advance of analytical analysis only about 50 years ago. Before that our diet was fixed by habit, culture and experience. A large body of data has been analyzed since, assessing the needed components and recommendations derived for bodily daily intake levels [48]. With such a baseline set of values, countries have been able to better gauge the adequacy of diets, and manage and control their general food supplies now in a more meaningful way. The detailed analysis of the elements in food examines not only sufficiency in the diet but can highlight dangerous possible health aspects. As a result, basic diets are now analyzed in chemical detail in many countries of the world. One outcome of this, is also the monitoring of the alien elements that we unknowingly ingest. The major importance of course is to ensure adequacy in required elements and bring this into balance by managing their sources. Such dietary reports are important and available, ones are for the US [49], UK [50], France [51], Germany [52], China [53], Cambodia [54], Sub-Sahara Africa [55,56], Brazil [57], and Norway [58]. Their ranges of values are seen to vary to some degree on comparing different countries. However general magnitudes are consistent. The UK study had the important conclusion that, over the recent period of 30 years, dietary changes were minor in the UK. In fact, in solely examining most foods, there appears to be little significant global change in eating in these surveys consistent with explaining any epidemic. However, this assessment now is in error due to life-style changes that have occurred and have not yet been fully included. One significant addition to diet, overlooked in all these previous reports, is the eating of fish, Japanese

sushi style. Although around for several decades, sushi-style of eating fish began in the US as a rather limited exotic food. Then as people changed to consider a healthier lifestyle that included dieting, it rapidly became accepted due to its high nutrition, low-fat and calorie character. It began to flourish in the 90's and particularly in the US began to experience exponential growth now witnessed globally [59,60].

The Japanese government recently estimated that outside of Japan there are more than 20,000 Japanese restaurants globally. The US has at least 4000 and now almost every grocery food store carries a sushi display. Fish are now a major source of alien mercury in its most toxic organic form, methyl mercury. It has also re-introduced unexpected mercury poisoning cases for the medical profession to diagnose among the general public consuming high fish diets. The World Health Organization had long realized the potential risk factor of mercury in fish consumption having completed a risk analysis for this in 2006 [61]. They established a recommended daily intake, however noting then that this left 6% of women of child-bearing age above the then accepted EPA blood level recommendation of $\leq 5.8 \mu\text{g/L}$. This value has been accepted ever since but now is clearly regarded as too high a level extensively exceeded and a missing factor in people's diets. Normal diets generally are sufficient to satisfy the body needs for the major and minor elements in Table 1, and it is rare to ingest these to levels of excess, the body normally has automatic controls on its major elemental needs. This is true both for food and water supplies even though some may show toxicity especially from highly contaminated water supplies. Toxicity also can be complex in that it depends on the chemical form of an element, particularly its water solubility, and also its valence state. For example, the ore of mercury is cinnabar, HgS , totally insoluble in water and as a result non-toxic. Similarly, chromium has two major valences, trivalent (III, non-toxic and required by the body) and hexavalent (VI), for example chromate compounds that are soluble and highly toxic. Water sources become a consideration due to solubility and the nature of their source. Surface supplies appear to have less problems for potable water than from water wells, but major impurities of As, Mn, Pb or U tend to be a regional geographic problem now quite widespread. The World Health Organization (WHO) realizes this problem and currently is reevaluating guidelines for drinking water [62]. Domestic filtering of drinking water is helping to reduce this component of diet in more advanced cultures. However, certain countries, such as parts of India and Bangladesh, are geographically unfortunate in having water wells now very rich in arsenic to the point that drinking water alone causes many cancer deaths per year [63-66]. The US has less of such a problem, now being able to suggest lowering its arsenic National water standard to $<10 \mu\text{g/L}$ [67]. Even so, there do remain sections of the South Western United States where many wells remain in

excess [68]. Modern day industrialization and urbanization can also lead to groundwater contamination certainly of the heavy metals as witnessed in the Pearl River Delta region of China [69]. The Flint Michigan region of the US accidentally raised Pb levels in its drinking water to dangerous levels, but it also remains a problem in other areas of the US and certainly in Bangladesh where spice adulteration with lead also is a problem of concern [70,71]. As a result, water problems are ever present and non-negligible regarding illnesses. For example, currently Mo and Pb are raising concerns in various US counties [72,73] and MN in water is suspected as having effects on children [74-76]. Even strontium levels have been addressed recently in the water of some Indian villages [77]. Consequently, although water cannot be casually disregarded, its quality is very variable. Also, although the alien elements are ingested to varying levels, global sources will generally remain more from food than from water. An interesting observation is that food and water supplies in normal diets are fortunately not often both rich in the same element. Also, it has to be remembered that some elements can be important even in minor quantities such as the need for vitamin B12 with its molecule having simply a single necessary Co atom at the center of a very complex structure. This raises the additional question of whether quantity can also be an important aspect in some disease assessments. Most humans live most of their lives eating their conventional diet and survive quite adequately. Nevertheless, some documented increase would appear to be necessary. Consequently, if the trace metals are to be held responsible for any epidemic a change in behavior has to be evident as discussed above with the example of enhanced fish intake sushi-style. Looking at the list in Table 1 of alien elements generally found in the body, it is soon apparent that most of these will be of little concern, mainly due to their very minor concentrations if presence at all in the body. The list can be broken down into several groups.

- Elements that appear harmless or have low toxicity at low levels (Ag, Al, Ba, Ce, Cs, Ga, Ge, Rb, Sn, Sr)
- Non-carcinogenic (Bi, Cd)
- Toxic and carcinogenic (As, Be, Hg, Pb, Sb, Sc, Tl)
- Neurotoxins (Al, As, Hg, Pb, Tl)

The major basic consideration as outlined above is the requirement of life-style changes, either in human diets or other aspects. Smoking has been one custom, but now is in decline in many countries, but medical advances with vaccines is another that has significantly expanded. Such an examination of the low ingestion of numerous of these elements coupled with food, water, life-style and medical services now can further reduce the above list of potential hazardous alien elements to Al, As, Ba, Cd, methylHg and Pb as having possible deleterious effects on the body that are worthy of further consideration. The question of whether quantity is important remains uncertain, but as outlined

may be irrelevant. Nevertheless, many experiments are now emerging from animal studies that do indicate effects from even low levels, well below the reference or safe minimum reference levels or from co-exposures [46]. As already indicated, the safe level for lead now is recommended as zero that clearly illustrates this may be part of any problem. Nevertheless, in order to explain global epidemics, change is required. Before the epidemics, people lived with contaminated food and water irrespective of their safe reference levels and quantities. The question now is what is different. They were living adequately before but why not now.

What Ingestion of Alien Elements has Really Changed?

As suggested, the question of quantity may be irrelevant unless it has increased significantly. Nevertheless, one relevant aspect of such research is that it has illustrated not only effects of trace quantities but has highlighted possible synergistic toxic effects between elements in some cases, which could also be a contributing factor. Although considered in the literature now for almost a decade, very little research has involved such mixed trace metal feeding. Studies with rats and mice do indicate low level effects and a disturbance of the body homeostasis balances with relative differences in organ absorptions [78-81]. One study already has examined possible human brain mechanisms for metal mixtures [82]. Meanwhile, for some of these trace elements, environmental public pressure has in fact resulted in their actual demise in society. Cd ingested partly from smoking has decreased in some countries, and a very significant reduction of lead and elemental Hg has occurred in recent years as most of their previous commercial applications now have become widely banned. Surveys are beginning to note the decreases particularly for Cd and also Pb [16,83]. From the list above of potentially important alien elements in the body Ba has been used medically for many years with no apparent adverse effects even though it is actually a heavy-metal. It does not readily accumulate in the body, is non-carcinogenic and is not a neurotoxin, and was once used commonly, added as a soot suppressant in oil combustion but now appears to raise no health concerns in any regard. In normal situations its toxicity is of no concern and its level in the body is rarely even tested. As mentioned above, cadmium is highly toxic and carcinogenic. It retains its inorganic nature, not forming organometallic compounds in the body. It generally is a low trace level in blood samples as seen globally in Figure 4h. It can be ingested as deposition from leafy vegetables especially from Cd rich-soil areas in China [84-86], from rice [87,88], fish and seafood [89-91], free-living game [92], and also from tobacco smoking [93]. It has a high retention rate by the body and can affect the kidneys. A recent review of cadmium's toxicity suggests its induced

oxidative stress on the liver and kidneys can cause pathogenic risks for a variety of cancer forms [94]. It is slowly chelated naturally by the body's selenium via its many protective protein metallothionein forms [95-99]. However, due to its long body half-life, aspects of it managing to pass into the brain still remain uncertain as also its possible synergism with other toxins. However, a major point of interest here stems from the reduced levels of tobacco smoking in the world, which is reflected as decreases in surveys of cadmium blood levels. Aluminum enters this discussion by recently having become the major adjuvant in most US and other vaccines, generally in the form of its hydroxide. Generally regarded as being medically safe, this is based stressing mainly oral data. However, because the intestines have a very low absorption rate of only about 1 to 2% for such orally ingested aluminum, this assumption now is becoming questioned in that inoculations increase this retention value closer to 100% [100]. As a result of the great success and value of vaccines, this now reflects into a significant change and re-assessment for this element in its human-lifestyle consumption and also modifies many prior assessments from studies with both humans and animals. It is particularly important for children in the US, who receive about 35 inoculations by the age of five, a much-enhanced rate from earlier years. As a result, when considered with other neurotoxins, this has concerned many major groups [101-103]. Depending on body weight, it can readily introduce a high risk of toxicity, as suggested even from animal studies [104-106]. Significant levels also have been noted in brain autopsies [107,108], and in cases of death from autism with ages from 15-50 years old [109]. This latter study, finding one case at age 15 is particularly disturbing. Although selenium has been shown to counteract the aluminum in the brains of mice and rats, uncertainties remain and glutathione peroxidase may even become depleted possibly suggesting a slow rate of its replenishing formation capability [110-115]. Additionally, a study with human brain cells has noted a synergistic collaboration between Al and Hg as neurotoxins [116]. As a result, the addition of a new ingested source of Al to the already normal dietary intake is significant particularly for young people [117]. The case with arsenic is particularly interesting as it is already an epidemic of major proportions in several parts of the world. The extreme case is in Bangladesh and has resulted in recent decades through changing the water supply from surface sources to ground water wells. It is now affecting millions of people and as a result about 20,000 deaths occur per year in Bangladesh [118]. This has facilitated many studies in various countries concerning arsenic toxicity. It obviously leads to a myriad of medical illnesses affecting the skin, lungs, kidneys, a series of cancers, cardiovascular risk, and is thought to induce fetal loss, premature births and low birth weights [119-121]. There are indications of neural effects in some cases, but are evident as cases of dementia and memory loss effects. Studies

with rats do clearly show possible enhanced oxidative stresses and neural changes [122-123]. The Western countries such as the US and Canada have low arsenic and few if any cases of such arsenic poisoning [124]. Arsenic is unavoidable and often present in both food and water. Dietary intake also is complicated by arsenic's tendency to methylate and be in an organic form. However, some of these forms become less toxic, as is the case in fish entailing a full speciation analysis for an exact arsenic toxicity level [125-127]. Rice is another general food source, affected by soil and pollution conditions, sometimes becoming methylated [128-131]. Whether Se protects the brain from more serious illnesses such as Alzheimer's Disease remains uncertain but the eating of lentils rich in selenium has been proposed in Bangladesh [132], and selenium appears protective in arsenic induced impairments in mice and rat studies [133,134]. The geographic comparisons between countries tends to minimize a critical overall role for arsenic in the major epidemical illnesses in the West, but arsenic is ubiquitous in the world as a potential toxic collaborator and a source of some illnesses. Even though lead has been a health risk factor from at least Roman days, it has remained an important commercial element until recent decades. However, through extensive environmental public pressure it has gradually been banned from most commercial products. Nevertheless, even today I recently heard of a child being poisoned in the US from a newly purchased lead-glazed bathtub. It also remains as a glaze for clay pottery in Mexico [135], and is still a major concern due to its continuing presence. It is with us in all older homes, present as old paint, it is on copper water pipes joints in any Pb/Ag solder and may even result from old lead connecting water pipes, besides being possibly in a drink served from a cut crystal glass decanter. Lead is detected in all humans showing a significant level in blood. Physicians now are content if it is below 50 µg/L in adults or children [136], even though it is known that the safe healthy level for lead is zero [38, 39]. It remains a significant concern in pregnancies [47], especially as lead and most of the other metal elements have unrestricted flow in blood through the placenta [137]. It has a toxic potential regarding human reproduction even at low levels [138]. Effects on children are more significant than adults and Pb exposure at low levels continues to be a major public concern [139,140]. Young children are particularly prone to paint dust gathering on floors. One analysis of data from an earlier drinking water "lead crisis" in Washington DC (2000-2004) concluded that fetal death rates and reduced birth rates were also a consequence [141]. Consequently, even though lead-based paints remain in use in many countries [142-145], lead blood levels are noted to be in decline globally in all developing societies [146-148]. As a result, lead does not appear to be a primary element inducing recent epidemic growths in illnesses but may be an epigenetic modifier as noted in animal studies [149]. Its levels in water

and food though remain a medical concern and it may continue to play a major role triggering or contributing to certain illnesses. A role for selenium as a chelator remains uncertain but in areas of lead pollution, residents have been noted to have a selenium deficiency [150]. Numerous studies with mice and rats clearly document the potential oxidative stress that arises from lead exposure and the possible beneficial role of selenium [151-155].

Mercury now is regarded as the neurotoxin of most concern to health. Although it has played a major role in commerce for millennia, its health risk became more seriously apparent 70 years ago through the neurological birth defects originating from the environmental disaster in the Minamata village in Japan. Until then, neural illnesses were not really at a significant level to be of major concern. The phrase "Mad as a hatter" arose from the felt-hat industry where mercuric nitrate was used in the process. Mercury's main use centered on its elemental ability to amalgamate with other metals, most importantly gold and silver. From even Egyptian times this has been a major role and although now no longer commercially mined, artisanal mining for gold is still an important occupation in numerous parts of the world ultimately utilizing mercury amalgamation and separation. Its unusual chemical symbol, Hg, originates from the Greek "hydrargyrum" (liquid silver). It found use in innumerable processes in industry and medicine. These ranged from switches, thermometers to the chloralkaline process and it has been important in dentistry being used as a silver/tin-mercury amalgam in teeth. It is also common in certain medications and still as a skin lightener [156-158]. Although generally banned, this latter use remains common particularly in India and Saudi Arabia. Until recently, one of mercury's main medical uses for decades has been as the primary adjuvant and preserver in vaccines as the water-soluble organic form of thimerosal (sodium 2-ethylmercurithiosalicylate). In the US it has now been replaced in recent years by aluminum hydroxide in most vaccines, but remains present in many of those exported and can be reintroduced into US vaccines during pandemic times. Mercury now has been extensively banned globally and only remains in the illicit mining for gold, in the largely still uncontrolled gaseous emission from certain combustion processes (primarily coal and cement industries), in several US vaccines and still is used by some dentists, although banned and replaced now in numerous countries [159]. It is no longer mined from its ore cinnabar and not easily purchased having lost its intrinsic value. Human ingestion can be in the elemental form as its vapor, possibly from its leaching and vaporization from dental fillings before being absorbed and then oxidized to its inorganic divalent ion in the blood. It is also in most fish diets as the more toxic organic form, methyl mercury, having been extensively bio accumulated in nature and the fish as this methylated

structure. Pollution of most water expanses now has arisen and remains from historical colonial days when silver and gold mining were extensive [160].

Although now coupled to possibly decreasing anthropogenic additions to the environment, the still large evasive, recycling of these historical excesses in the earth's waters and land retains an uncertainty that will remain into the foreseeable future before it may one-day return to natural pre-industrial levels. Mercury is the most researched element in the periodic table with about 5000 publications/year in the areas of medical and environmental interests. Nevertheless, even with the reduction of mercury in vaccines, the growth of consuming sushi from the 1980's in the US diet to now significant levels, and also throughout the world has elevated methyl mercury to a major human toxin, especially due to its neurotoxic organic nature and ready bio accessibility. Studies of heavily fish-eating communities have been used to establish the NOAEL and LOAEL, no or lowest observed adverse effects levels. Through such studies of the Faroe Islands community (whale consumers), and that of the Seychelles (Ocean fish-eaters) differences have highlighted a missing factor. This appears to be the selenium fish component, now realized to be the body's natural chelator for mercury through its many seleno-enzymes and also for many of the other alien elements consumed in diets. From the current wealth of research several conclusions now can be concluded. One is that mercury's toxicity depends on its form, elemental, ionic or organic. From the gold miners, chloralkali and dental employees many of whom have been subject to prolonged mercury elemental vapor inhalation, they show mainly the symptoms of kidney function difficulties (prime target organ), with some lesser secondary neural effects [161-163].

Obviously, over time elemental mercury does appear to probably pass across the blood/brain barrier. Once in the blood the elemental form is oxidized to the divalent ion [164]. Peru still has artisanal gold miner's shops located in its towns. However, there are no reports of severe neural consequences in their neighborhoods from released inorganic mercury vapor [165]. However, miners are diagnosed with oxidative stress and DNA methylation that may have some effect on their health [166]. Elemental mercury's half-life in the body is measured in days or several weeks. It is excreted mainly in urine and feces. Any related neural effects in fact appear reversible with time [167] but in some cases of dental fillings, dementia appears to persist [168]. Radioactively labeled tooth fillings of sheep were reported to be leached and retained by the body [169], however low doses of inorganic mercury with rats did show signs of slight entry into the brain causing oxidative stress and cell death [170,171]. Organic forms of mercury, namely the thimerosal in vaccines and the methyl mercury in fish are very neurotoxic and have been

extensively examined in humans and numerous animals, from mice and rats to rabbits, hamsters and monkeys, some studies with labeled mercury. They are readily absorbed and have the brain as a major target, passing freely through the blood/brain barrier. One study with monkeys was very detailed [172]. Thimerosal, readily breaks down in the body to ethyl mercury and thiosalicylate. In monkeys, the ethylHg has a shortened blood half-life of about seven-fold compared to the 22 days for methylHg, and similarly a shorter brain half-life of 24 compared to 60 days. What was noteworthy in studies was a process of de-alkylation in the brain that was significantly more with ethylHg, about 70% becoming inorganic compared to 10%. Both *in vitro* and *in vivo* studies now have been extended and reviewed confirming these behaviors [173]. For human diets, from fish-eating studies the half-life in the blood is quite variable reflecting human susceptibilities, data varying from <30 to >120 days [174,175].

Brain half-lives for inorganic mercury also are uncertain but surmised to be years in magnitude [176]. It became evident that seafood exposure to methyl could be neurotoxic even at low levels [177-180]. Also, it has been noted in 25 countries around the world that women of child-bearing age have high dietary mercury levels [181]. The two large cohort studies on humans utilizing the peoples of the Faroe and Seychelles Islands now have spanned several decades. Both groups have predominantly seafood diets [182-184]. Through these, from their contradictory results it was finally accepted that the differing levels of selenium in the fish (whale meat or ocean fish) was a major missing factor that was modifying their data. It was providing a countermeasure of protection from the mercury [185-187]. This was clearly confirmed by selenium's neural protection from methylHg now reported in rats and mice [188,189]. The research has highlighted the health benefit value of selenium in the body and how it differs from the other elements [190-193]. The fact that the body is programmed to produce 25 selenoproteins appears purposeful [194], as well as its magnitude over all the alien elements found in the blood. It is clearly apparent that selenium is the body's natural chelator, not only for mercury, but for the alien elements. It has also been suggested as a protector against manganese, possibly not necessary in a healthy person [195]. However, this aspect of selenium now introduces a need for a reassessment of fish in diets [196-198]. As long as selenium is present in excess of the mercury on an atomic level, it has the potential to neutralize or sequester mercury's deleterious effects [199]. The fact that selenium has an atomic weight of 79 compared to mercury's 201 introduces an additional factor of 2.5 advantage for selenium on an atomic basis. This is important as many fish analyses are generally analyzed by weight and now require conversion to molar quantities to test for this ratio [200-204]. In addition, the nature of the specific

selenoprotein appears to be involved and complicates this further [205,206]. Also, it has also been suggested that high levels of organic mercury together with other alien elements may lead to a dangerous deficiency of required selenium enzymes [207]. Selenium is a unique element being necessary for life but is also a neurotoxin. It displays a narrow dosage range between being therapeutic or toxic. An acceptable dietary range is 40-250 µg/day, optimum being an intake of 100-200 µg/day [208], but a consistent dose of 300 µg/day for 5 years now has shown the possibility of increased mortality [209]. Many soils around the world are deficient in selenium and are of great concern for agriculture and diets [210-213]. Since 1984, Finland has been using Se-enriched fertilizers to enrich crops [214], while others tend to enrich feed stocks. Nevertheless, it has now been realized that selenium plays a very important role in the body in the form of its glutathione peroxidase enzymes, which regulate body inflammation [215], and have a role also in brain signaling [216]. Nevertheless, some doctors presently do not recommend selenium use during pregnancy [217] due to the observed overall uncertainties [206].

Are Epidemics Due to Increased Levels of Alien Elements that Deplete Selenium's Protection?

The medical profession has realized for some time that the heavy metals are a major health concern, their mechanism being one of oxidation [218]. As indicated above, their mitigation in the body can be by a large regimen of selenoenzymes that chelate and sequester them before elimination [219]. Canada has recognized this importance, monitored their total population for blood selenium levels, and finding it fully in the desirable 100-400 µg/L range with a mean close to 200 µg/L [220]. Nature has endowed most people with body selenium levels in excess over any alien metals present [221], an interesting feature in itself. Currently the literature is very rich with research on selenium surmising that its deficiency may be associated with a whole string of many illnesses that involve oxidative stress, namely organ failure in critically ill children [222], thyroid problems [223-225], strokes, atherosclerosis, oxidized LDL (low density lipids), osteoporosis, and all cardiovascular illnesses [226-228], cancers [229-232], Huntington's disease [233], Parkinson's [234-236], Alzheimer's [235,237-241], pregnancy and adverse outcomes [206,242-246], autism [247,248], amyotrophic lateral sclerosis (ALS) [249,250], schizophrenia [251], and others. Its importance in pregnancy currently is being emphasized, recommending maternal blood levels of at least 100 µg/L. Recent research is important in possibly explaining how a fetus survives the high toxicity of its environment [252]. In two noteworthy studies it was reported that the selenium blood level in the umbilical cord was much higher than that of methyl-mercury. Converting

these to molar or atomic quantities it was found that the Se to Hg ratios were 62-fold [253] in one study, and in a range of 5 to 626 [254] in another, indicating possibly the overlooked required protection needed for the low weight fetus during pregnancy. Missing data now needed are the potential rates of depletion and formation of these selenoenzymes and whether selenium can become depleted [255]. Such research remains primitive and selenium's biology of selenoprotein degradation and metabolism remains uncertain [256].

Conclusion

On analyzing the necessary components of human diet, it can safely be concluded that few pronounced changes have occurred in recent decades. However, it is quite extraordinary that diets do contain a significant number of elements that serve no purpose and are regarded as alien species, do nothing other than increase the body's burden for required elimination. Many of these are toxins and neurotoxins but fortunately generally at low levels in the blood. A detailed examination for the changes necessary to trigger modern epidemics concludes that the only elements of pronounced interest are Al, As, Hg, Pb, all in fact neurotoxins and hazardous. From these Al and Hg have gained more importance due to their global growth through life-style changes. Arsenic poses severe problems in drinking water around the world but is largely controlled in the Western developed countries. Pb is a major toxin that certainly still remains dangerous particularly for young children but is in a continuing state of decline in diets, particularly in adults, as it gets more heavily controlled and removed from commerce. This tends to leave Hg and Al as the prime suspects at present for most medical illnesses. Animal research also is noting that these can also be accentuated by association with other trace elements. They are necessarily in all peoples who are vaccinated and/or eat a fish diet. The latter is most common around the world and although Al now is being reported in many brain autopsies, Hg is most probably the more toxic, occurring also more frequently now in individuals as mercury poisoning from fish diets. The medical profession emphasizes the nutritional benefits of fish, which is true, and as a safeguard smaller class of fish now should be eaten for which Se > Hg rather than the larger fish categories that remain rich in methylHg. As a result, it can be quite positively surmised at present that adults are more likely to be suffering from a mercury body burden while for young infants' aluminum becomes the major concern. The toxicity of these metals during pregnancy remains an ignored subject. The fetus when small technically should not survive the toxic levels to which it is subjected. Whether the high levels of the selenoproteins, blood brain barrier and yet unknown other defenses exist has to be resolved. Nevertheless, younger women of child bearing ages require guidance.

What is becoming apparent is that health is becoming the accepted responsibility of each individual. This is now quite broadly accepted in patients with Cardio or diabetic conditions in Western societies where monitoring is more readily available. However, in the present case of knowing one's susceptibility to metal toxins there is a void. Although many studies are now reporting a need for this information, it still cannot be readily prescribed by a doctor [257-260]. The public needs to establish its location on blood survey curves to establish their individual genetic susceptibilities concerning possible high retention of dangerous chemicals or satisfactory rejection. If established, additional steps can be identified to reduce any levels of concern. As a result, testing from an early age till death has to become standardized in the near future concerning specifically the neurotoxins Al, As, Hg, Pb, Mn and Se to enable a personal management of health. By using a simple low-cost blood test available to the general public, it is possible in one analysis of a small blood sample to resolve this issue. Such a test now has been validated utilizing the ICP-MS instrument [261,262]. It remains ridiculous that everyone goes through life not knowing the state of their bodies and whether they are living at high risk or not, the necessary technology now is available. This is of major importance especially for pre-pregnancy testing in younger women.

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