Environmental hypothesis: is poor dietary selenium intake an underlying factor for arsenicism and cancer in Bangladesh and West Bengal, India?

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Abstract

To reduce the incidence of dysentery, cholera and other water-borne diseases and mortality of people drinking from surface contaminated sources of water, the World Bank and United Nations Children’s Fund began to sink tube wells into the underlying aquifers of Bangladesh and West Bengal, India, in the 1970s. Many of the tube wells were drilled into underground aquifers that provided microbiologically clean water that was later determined to contain arsenic (As). As contamination of drinking water is a problem of natural occurrence throughout the world and domestic water often exceeds the World Health Organization limit of 50 μg As/l in the countries of Bangladesh, West Bengal, India and Nepal as well as other areas occupying much of the Ganges–Brahmaputra delta. It is estimated that as many as one-half of these tube wells discharge water with sufficient amounts of As to produce arsenicism, i.e. As toxicity in the human population. Access to clean As free water is the priority of most organized relief efforts. Where As free domestic water cannot be provided, an improved diet and/or dietary supplements may ameliorate As toxicity or prevent its toxicity all together. The dietary status of the essential human trace element, selenium (Se) may be adversely affected by a chronic excessive ingestion of As. As added to animal diets has been known to counteract Se toxicity in animals since the 1930s. It is reasoned therefore, that high levels of chronic As ingestion from well water by people within the delta will accelerate the excretion of Se lowering the body’s content of this essential trace element. Excessive Se excretion owing to Se/As complexation may add to the likelihood of As being more toxic and carcinogenic over time, due to the oxidative stress imposed by the excessive As and low Se ingestion. Because of the unique environment of the Ganges–Brahmaputra delta in which millions of people are presently exposed to As, we ask the question: are low dietary Se ingestion and accelerated Se depletion by As possible contributing factors to arsenicism? © 2003 Published by Elsevier B.V.

Keywords: Selenium; Arsenic; Arsenite; Arsenicism; Keratosis; Cancer; Bangladesh; West Bengal; Tube wells; Water quality

Abbreviations: Se, selenium; As, arsenic; UNICEF, United Nations Children’s Fund; WHO, World Health Organization; US EPA, United States Environmental Protection Agency; μg, microgram; mg, milligram; g, gram; ml, milliliter; l, liter; ppm, parts per million (μg/g, mg/l); ppb, parts per billion (ng/g, μg/l); GSH, reduced glutathione; RDA, Recommended Dietary Allowance for the United States; As/Se/GSH, the seleno-bis(S-glutathionyl) arsenium ion

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1. Introduction

Arsenic (As) toxicity and human carcinogenesis due to the consumption of naturally contaminated ground waters and foods containing As in Bangladesh and West Bengal, India is a common occurrence. Securing As free ground water has been technically problematic and is presently economically unrealistic in many parts of these countries (Chowdhury et al., 2000; Frisbe et al., 2002). The problem of As contamination in ground water within the regional area of the Ganges–Brahmaputra delta also extends into heretofore previously undetected remote areas as in Bihar, India (Chakraborti et al., 2003) and into Nepal (Shrestha et al., 2003; Kumar, 2003). In the absence of As free domestic water, improvement of the diet of people where As toxicity is marginal may afford complete or partial protection from arsenicosis. In areas of highly contaminated As ground waters, selenium (Se) supplements might prevent, delay or ameliorate arsenicosis. It has been recently demonstrated in China (Wang et al., 2001, 2002) that Se supplements caused remission of many of the measurable signs and symptoms of human arsenicosis.

We proposed in 1998 to United Nations Children’s Fund (UNICEF) that the essential dietary nutrient, Se, if supplemented to children’s as well as adult diets given as a tablet might have an ameliorating effect on the wide spread pandemic of As toxicity in Bangladesh and West Bengal. The rationale for the original proposal made by us in 1998 was and remains multifactorial. The difference between our proposal in 1998 to UNICEF and now is the additional evidence from the literature and our own research that continues to reinforce the probability that the hypothesis may be true. To understand the role of dietary Se in ameliorating As toxicity, we set forth below an outline of six rationales with selected but important supporting references and some previously unreported data relevant to arsenicosis. Because this remains a working hypothesis without definitive proof, specially directed research needs to be done in the delta area measuring Se and As in soils, in foods and in people with and without arsenicosis.

2. Primal on As

As is a naturally occurring non-metal, atomic no. 33 located beneath the element phosphorus within the periodic table. As is toxic to animals and humans in most chemical forms depending upon the amount of exposure. As naturally occurs in the earth’s crust at approximately 2 ppm but can be found in more concentrated forms in mineral complexes such as in association with iron as arsenopyrite (FeAsS) or with sulfur as in Orpiment (As4S6). These and other minerals in association with As are often found in geological strata and as As containing strata are exposed to groundwater there is degradation and dissolution of the minerals within strata releasing inorganic As. A consequence of the dissolution of these strata bearing As is the As released contaminates domestic sources of subsurface ground water. The chemical forms of As in domestic ground water are usually arsenites and arsenates, which are odorless and nearly tasteless. These inorganic forms of As are the major sources and only forms of As presently believed to be contaminates of the ground waters of Bangladesh, West Bengal, Nepal and the greater Ganges–Brahmaputra delta. Contamination of ground waters by organic forms of As is much less common. Toxicity of As, as with other toxic metals or non-metals, is solely dependent upon the concentration of the toxin in the contaminated source and the amount of contaminant ingested. For As the upper level of safety in groundwater, (World Health Organization (WHO) standard) it is set at 50 μg/l or 50 ppb (0.05 mg/l). Foods will often contain 0.020–0.014 μg As/gm usually in the less toxic organic forms. Elimination of ingested As is primarily from urinary excretion but some may also be eliminated via the bile and fecal excretion. The relative toxicity of As compounds is arsenite >> arsenate >> organic arsenicals. The exact mechanism of As toxicity is unknown although toxic trace minerals and heavy metal toxicity in general is thought to be due to (1) the generation of free radicals, or (2) the interaction and interference with sulfur containing compounds that are biologically important, i.e. glutathione (GSH) generating free radicals and (3) the resulting oxidative stress. It is likely that As,
particularly arsenite toxicity, functions as a pro-
oxidant in addition to its biological interference
with phosphate metabolism. Detoxification of
arsenate/arsenite in vivo has been thought to be
primarily by methylation reactions and urinary
excretion. It has been recently shown that As also
complexes Se and glutathione and is excreted as
an As/Se/GSH complex in bile. The suggestion
has also been made that As may be dietarily
essential for animals and possibly humans at very
low levels of ingestion but there is no definitive
scientific evidence for the implication. As is clas-
sified as a human carcinogen of the skin, liver,
bladder, kidney and lungs by the US Environmen-
tal Protection Agency (US EPA).

3. Primal on Se

Se has been known to be an essential human
dietary trace element since 1973 and received a
Recommended Dietary Allowance (RDA) in the
United States in 1989. The RDA for Se in 1989
was set at 70 μg/day for men, 55 μg/day for
women and 10–15 μg/day for infants and 20 μg/
day through age six. The presently set 2000 RDI
for Se is 55 μg Se/day for both men and women
and is for the synthesis of the Se-containing
proteins including a family of glutathione pero-
idases, 5'-deiodinase, thioredoxin reductase and
selenoprotein-P. The minimum adult dietary
requirement for Se of 16–20 μg/day is met
primarily by the consumption of animal protein,
cereal grains and seafoods. Fruits, vegetables and
domestic water supplies contain very low and
usually dietarily insignificant amounts of Se. Se
deficiency is well known for many animal species
but in humans Se deficiency, <10 μg Se/day, is
limited to China. Marginal dietary intakes of Se
that are not sufficient to cause reportable human
disease very likely exist in other parts of the world
including England, Europe, Scandinavian countries
and New Zealand. In addition to a nutritional
requirement, Se can be toxic to animals and
humans if consumed in excess. Se compounds are
generally more toxic than As compounds. Like As,
inorganic forms of Se are more toxic than organic
Se compounds. Toxic effects from the various
chemical forms of Se in vitro and in vivo are
similar but not identical to the corresponding As
compounds i.e. selenite and arsenite. Toxicity
depends upon the amount and chemical form of
Se ingested, as it does for As, and under some
circumstances toxicity of Se and As compounds
together are synergistically toxic. Toxicity of Se
arises from its ability to redox cycle producing
oxidative stress. Detoxification of Se is also similar
to As in that Se is methylated three times to the
trimethylselenonium ion and excreted in urine.
Methylation of Se, like As, is viewed as a detoxi-
fication mechanism. As noted above for As, Se
will complex with As and glutathione and be
excreted in bile. A unique property of Se not held
by other elements is the ability to detoxify a
number of essential and toxic heavy metals. Se, if
dietarily present, can detoxify the heavy metals,
lead, cadmium, mercury, as well as the precious
metal silver and the essential trace minerals, copper
and iron. Most important to the hypothesis below
is Se's ability to detoxify As's toxicity and vice-
versa. The route to detoxification is the ability of
Se to form insoluble selenides with all of these
metals and As. In seems almost fictional that two
toxic elements can combine rendering both non-
toxic but this is scientific fact and is indeed what
happens in vivo between Se and other elements.
Se is not classified as a known human carcinogen.

4. The hypothesis: is dietary Se supplementation
in Bangladesh and West Bengal relevant to the
prevention of arsenicism and human cancer?

4.1. Rational 1. Se is an essential trace element
for humans and significant amounts of Se are
almost always associated with dietary animal
protein

Se is a dietary essential nutrient with a minimum
adult requirement of approximately 20 μg/day
(Raymond, 2000). This is easily fulfilled by diets
of people in the US whose dietary intake of Se
likely ranges between 80 and 120 μg/day who
can ingest 40–60 g or more of animal protein a
day. Se is primarily associated with animal and
plant protein consisting mostly of selenomethion-
ine and lesser amounts of selenocysteine (Combs,
2001). In the US, Se is routinely supplemented to
animal feeds as approved by the Food and Drug Administration. Such supplementation of Se improves animal performance and raises the dietary Se intake for most Americans consuming meat products. Se is not usually abundant in fruits and vegetables and is highly variable in cereal grains (see below) depending on the soil Se content.

We learned when in Bangladesh (May, 2000) that the diet of many people within the delta is likely low in total protein, especially animal protein. Fish, poultry and meat are infrequent dietary additions, once or twice a week for fish, once or twice a month for poultry or meat. Dietary Se is only contained in significant amounts in association with animal protein and only to the extent that animals themselves get Se in their diets. Fruits and vegetables are, again, often-poor sources of dietary Se reflective of the Se content of soils in which they are harvested and their inherent low content of protein. Fish and other seafoods when consumed in the coastal areas likely provide more Se to people. The diet of many of the people of the rural delta we expect therefore, although not yet proven, to be low in Se because of the low consumption of animal protein.

4.2. Rational 2. Se is essential for humans and widespread Se deficiencies likely exist in soils within the Ganges–Brahmaputra delta

While Se is essential for humans and animals, plants are not known to require Se and therefore if soil Se is low, plants are not adversely affected. Consequently, if the soils do not contain absorbable Se the plant crops will have very low to no nutritionally significant Se content for people. Animal protein from those animals that feed on the low Se forage will also contain low amounts of Se. The Ganges–Brahmaputra delta area encompassing Bangladesh, West Bengal and Nepal is a flood plain with an annual monsoon rain and flood season. These are not environmental conditions in which one would expect to find available sources of soluble Se in soil for the uptake by plants. Data on Se from the Yangtze delta in China indicate that the soil Se is low and not readily available for plant absorption (Cao et al., 2001). We anticipate that the soil levels of Se throughout the area of the Ganges–Brahmaputra delta will be found to be generally very low in Se and like the Yangtze delta not in a readily absorbable form for plants. Iron oxides, iron-hydroxides and iron-sulfides in soils bind and hold Se in a manner similar to the use of iron oxides and sulfides to remove As from contaminated water.

Many areas of the world’s soils have been mapped for their Se content (Oldfield, 1999, 2002) the most recent being Japan (Mizutani et al., 2001). To our knowledge, there are no soil Se maps of Bangladesh, West Bengal or the regional delta area. We have had the opportunity to measure approximately 25 samples of Bangladeshi soils from five locations in the As contaminated area of Jessore for Se by the fluorometric method (Spalholz et al., 1978). The soil samples look like sand and the levels of Se we have measured in them are listed below in Table 1. All but one sample indicated that Se levels in soil we measured from Jessore are less than that of the Keshan-disease areas reported in China (Oldfield, 2002, p. 45). The Chinese have produced the finest soil-crop Se maps in the world, county by county, precisely because of Keshan-disease, the well-known Se deficient cardiomyopathy. Soils low in Se automatically produces low Se containing crops, which in turn produces low Se containing animal foods. The present literature also provides almost no data on the Se content of foods within the Ganges–Brahmaputra delta. Older data available on the Se content of rice (Table 1) show it to be lower in Bangladesh (BIERI AND AMAND, 1976) and from China (CHEN et al., 2002, Venkatesh et al., 2002) than from the US. More disconcerting, Se in rice from Bangladesh was much less bioavailable in an animal assay than Se from US rice. A new concern should be the reported As content of foods in West Bengal (ROYCHOWDHURY et al., 2002) and recent increases of As in rice in Bangladesh (MEHARG and RAMAN, 2003) both due to irrigation with As contaminated groundwater.

4.3. Rational 3. In vivo As and Se interact and complex with each other

The literature is replete with research articles demonstrating that As will counteract the toxicity
Table 1
Facts about As and Se

<table>
<thead>
<tr>
<th>Arsenic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>As-5, arsenate, Na$_2$AsO$_4$, not acutely toxic, chronically toxic</td>
<td></td>
</tr>
<tr>
<td>As-3, arsenite, NaAsO$_2$, acutely toxic, chronically toxic</td>
<td></td>
</tr>
<tr>
<td>MMA, monomethylarsenide, may be very toxic as is methylselenide</td>
<td></td>
</tr>
<tr>
<td>DMA, dimethylarsenide, not very toxic as it is dimethylselenide</td>
<td></td>
</tr>
<tr>
<td>(GS2AsSe) - seleno-bis(S-glutathionylarsenium ion), major</td>
<td></td>
</tr>
<tr>
<td>As excretory product from excess arsenite</td>
<td></td>
</tr>
<tr>
<td>Human toxicity from chronic arsenite/arsenate ingestion from water &gt; 300 µg As/l</td>
<td></td>
</tr>
<tr>
<td>Human toxicity from chronic As ingestion, 200–250 µg As/day</td>
<td></td>
</tr>
<tr>
<td>No USRDA for As, essentially not for humans not proven</td>
<td></td>
</tr>
</tbody>
</table>

Arsenic in the environment

| Arsenic standard for drinking water                                   | 50 µg As/l                                                                                     |
| US EPA standard for domestic water                                    | 50 µg As/l                                                                                     |
| US EPA standard for domestic water (in 2006)                          | 50 µg As/l                                                                                     |
| WHO standard 50 µg As/l                                               |                                                                                               |
| WHO recommendation 10 µg As/l                                        |                                                                                               |
| Bangladesh/Indian standard 50 µg As/l                                 |                                                                                               |
| Maximum upper limit for inorganic As consumption, adult,              |                                                                                               |
| not known but estimated to be >200 µg/day                             |                                                                                               |
| Human liver degeneration at 814 µg As/l of water (Santra et al., 1999)|                                                                                               |

Arsenic in domestic water from tube wells lower in middle Ganges/ BP delta (very approximate estimates)

| Percentage of population consumes water with 10–50 µg As/l             | 25%                                                                                           |
| Percentage of population consumes water with >50 µg As/l               | 57%                                                                                           |
| Percentage of population consumes water with >300 µg As/l              | 20%                                                                                           |
| Population at risk for arsenicosis estimated at 30–100 million          |                                                                                               |
| but likely unknown because of differences in gender, age and dietary variables |                                                                                               |

Se

<table>
<thead>
<tr>
<th>Se</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human toxicity from Se ingestion from domestic waters is not known</td>
<td></td>
</tr>
<tr>
<td>Maximum safe limit (NOAEL) for Se ingestion from foods,</td>
<td>481 µg/day, depending on speculation</td>
</tr>
<tr>
<td>Very minimal essential human ingestion of Se, 16–20 µg Se/day,</td>
<td></td>
</tr>
<tr>
<td>almost all selenomethionine</td>
<td></td>
</tr>
<tr>
<td>Recommended dietary allowances for Se (1989-USRDA) 72 µg/day men,</td>
<td></td>
</tr>
<tr>
<td>55 µg/day women, 20 µg/day children, age 1–6, 30–55 µg/day adolescents,</td>
<td></td>
</tr>
<tr>
<td>age 7–18. The present US RDI for Se for adults is 55 µg Se/day.</td>
<td></td>
</tr>
<tr>
<td>Se content of domestic water in Bangladesh not known and likely insignificant.</td>
<td></td>
</tr>
<tr>
<td>Se ingestion µg Se/day from foods in Bangladesh not known or not known to be reported.</td>
<td></td>
</tr>
</tbody>
</table>

Asian and other rice Se content

<table>
<thead>
<tr>
<th>Asian rice Se content</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice in UK 0.13 µg Se/g long grain</td>
<td></td>
</tr>
<tr>
<td>Rice in UK 0.10 µg Se/g brown</td>
<td></td>
</tr>
<tr>
<td>Rice in Bangladesh, Barisal white 0.060 µg/g²</td>
<td></td>
</tr>
<tr>
<td>Rice in Bangladesh, Barisal brown 0.070 µg/g²</td>
<td></td>
</tr>
</tbody>
</table>
of Se. These articles begin to appear in the literature beginning in the 1930s and 1940s (Moxon, 1941; Morris and Moxon, 1943) when researchers began looking for ways to counteract Se toxicity in livestock in the western United States. It was found in experimental animal studies that As added to drinking water could counteract dietary Se toxicity in rats, pigs and dogs. We reasoned that if As could counteract Se toxicity would it not follow that Se could counteract As toxicity? In a review of the literature in 1997 few articles were found showing any such direct effects of Se counteracting As toxicity and yet it would, we reasoned, have to be true (Hilmy et al., 1991).

Beginning in 1999, the first references showing a specific interaction of Se in animals with As toxicity and prevention of As toxicity by Se began to appear in the literature (Biswas et al., 1999). This report gave credence to the idea that Se supplements could possibly be helpful in dealing with As toxicity. In 2000, an important paper was published which we believed may have far reaching consequences for the people of the delta. Gailer et al. published on the synthesis and identification of the seleno-bis (S-glutathionyl) arsinite ion (As/Se/GSH) (Gailer et al., 2000). Here is perhaps the most important direct metabolic link between arsenite (As toxicity) and dietary Se. This As/Se/GSH complex appears to be an excretory route for excess ingested As, not Se, via the hepato-biliary route and fecal elimination. This As/Se/GSH complex has just now been directly identified in the bile of the rabbit (Gailer et al., 2002). Se, like As, is detoxified via methylation reactions with the urinary trimethylenonion ion ((CH₃)₃Se +) being an excretory metabolite for Se (Sun et al., 1987). Thus, the absence of or a low non-bioavailable dietary Se intake from staple foods like rice and other foods would appear to adversely affect As excretion as has been shown in the mouse (Kenyon et al., 1997). The earlier literature as reviewed by Levander (Levander, 1977) indicated in animals that As in counteracting Se toxicity greatly accelerated As excretion in bile and vice-versa (Levander and Baumann, 1966). A second way in which Se interacts with As is to complex directly in tissues with arsenite without an imposition of GSH (Glattre et al., 1995; Zeng, 2001; Gregus et al., 2000; Csany and Gregus, 2002). It is little appreciated and even less well
known that Se will counteract the toxicity of mercury, lead, cadmium, silver, copper and iron (Howell and Hill, 1978; Raie, 1996). It does so by forming and depositing insoluble selenides directly in tissues. Formation of insoluble selenides likely accounts for the reports of higher As accumulation in tissues when Se is fed to animals or As is used to counteract Se toxicity (el-Begearmi et al., 1982; Beckman and Nordenson, 1986; Lowry and Baker, 1989). The complex formed in tissues between As and Se is likely As hemiselenide (As$_2$Se) (Ben and Galf, 1994; Kenyon et al., 1997; Berry and Gale, 2001). The As hemiselenide complex is insoluble and black in color possibly contributing to the darkening of the skin in arsenicosis. Since Se and sulfur have similar chemical properties As, hemiselenide in tissues closely corresponds to similar sulfur analogs, i.e. As$_2$S$_3$, as found in nature (Frost, 1967). Thus Se can and will directly counteract As in two different ways by eliminating and/or annihilating its toxicity by increasing biliary excretion or by forming deposits of As hemiselenides in tissues.

4.4. Rational 4. Se is an antioxidant and anticarcinogen as a component of the glutathione peroxidase family of enzymes

Se is a component of the non-essential dietary amino acid, selenocysteine synthesized by modification of serine (Stadtman, 1996). Selenocysteine is made from the dietary intake of inorganic Se (normally very little Se in the diet) and from the metabolism of the organic selenoamino acids of the diet which are > 99% of the dietary intake of Se in the absence of Se supplementation. Glutathione peroxidases (Rotruck et al., 1973) and the other selenoproteins, like thioredoxin reductase, (Stadtman, 2002) synthesized from dietary Se have an antioxidant role in cells protecting the cytoplasm, the mitochondria, the plasma membrane and the DNA from oxidative damage. Many animal dietary deficiency diseases of Se are known, i.e. white muscle disease in sheep, and human deficiency diseases of Se are known to the Chinese (Keshan disease and Kaschin–Beck’s disease). There is a strong epidemiological association between Se ingestion and cancer prevention in humans. Dietary Se supplements are remarkably carcinostatic in animal cancer experiments (Wangner, 2002) and have been shown to reduce colon, lung and prostate cancer in one human supplementation trial (Clark et al., 1996). Se deficiency in animals causes or permits viral mutations to occur transforming non-virulent viruses into virulent ones (Nelson et al., 2001). Thus adequate dietary Se, even in the absence of As toxicity, is very important in the prevention of oxidative stress, mutations of DNA and cancer prevention via glutathione peroxidase and other antioxidant activity. As in contrast, when added to diets, increases carcinogenesis of spontaneous viral cancers (Schrauzer et al., 1978; Schrauzer, 1987) and in association with UV light increases skin cancers and their severity (Rossman et al., 2001).

4.5. Rationale 5. As is a pro-oxidative stressor and human carcinogen

As, mainly arsenite, is a pro-oxidant and reacts with thiols to induce oxidative stress, the product of free radical reactions and subsequently apoptosis of cells (Chattopadhyay et al., 2002; Pi et al., 2002). Arsenate does not cause oxidative stress per se, but becomes a pro-oxidant upon its rapid reduction to arsenite (Nemeti and Gregus, 2002a,b). Chronic ingestion of high levels of arsenate is therefore likely nearly equivalent to similar levels of arsenite ingestion over time. Pro-oxidant minerals can deplete GSH, produce free radicals and free radical stress, and therefore can be mutagenic, teratogenic or carcinogenic (Stoeh and Bagchi, 1995). As noted above, As has been experimentally shown in mice to be a co-carcinogen with UV light (Rossman et al., 2001). Alone, UV radiation is a pro-oxidant as it causes the formation of singlet oxygen in skin which can damage DNA causing squamous cell carcinoma or melanoma (Pence et al., 1994). Where arsenicosis occurs in human cancers of the skin, liver, lung, kidney and bladder are prevalent.

4.6. Rationale 6. Se counteracts As toxicity and Se deficiency in rats increases As toxicity

There are now several reports in the literature showing that Se can directly counteract As toxicity
in tissue culture (Sweins, 1983; Babich et al., 1989; Hu et al., 1996; Davis et al., 2000) and it has been known for some time that Se accelerates As excretion via the bile and consequently urinary Se excretion declines. The identification of As/Se/GSH in bile now explains past experimental observations of As’s prevention of selenosis and requires reassessment of the speciation and effect of Se on urinary As excretion in humans (Vähter, 1999).

Our own unpublished investigations of As toxicity in Fischer 344 rats showed that (1) at certain ratios of a combination of arsenite/arsenate in water, 50%/50%, Se added to diets can reduce growth depression effects of As toxicity even under rather acute conditions (8 weeks of feeding animals Se and As in water) at levels up to 200 mg As/l and; (2) Se deficiency (rats fed torula yeast diets) appears to significantly increase the arsenite/arsenate toxicity effects on growth in rats (Spallholz et al., 2001). Furthermore, at dietary levels of Se considered adequate for the rat, 0.15 μg Se/gm, Se protected against As induced growth depression even at fairly high levels of As ingestion to 50 mg As/l (50%/50%—arsenite/arsenate). Toxicity in rats from As was observed at higher levels of concentration intake from water.

We have concluded on the basis of the limited animal data now at hand that only adequate dietary levels of Se may be required to protect against elevated levels of As/arsenite from water in the rat. For as outlined above, the relationship between a low, perhaps non-bioavailable source of dietary Se and an unwanted increase in the level of As intake from water in the face of the environmental circumstances with which the people of the Ganges–Brahmaputra delta find themselves, may have profound implications for resolution of the As crisis.

5. Conclusions

Many people of Bangladesh and West Bengal, India are exposed to elevated levels of As in domestic ground waters once originating from As laden geologic strata in Nepal now underlying the Ganges–Brahmaputra delta (Witze, 2003). The As deposited in these delta sediments over the millennial is now being discharged by tube wells initially financed and installed by UNICEF and the World Bank. Many of these tube wells discharge inorganic As in excess of the WHO standard of 50 μg As/l with some wells reported to discharge water in excess of 3 mg As/l.

Ingestion of inorganic As, >300 μg As/day, from water together with a low or even just sufficient level of Se consumption from foods (20–60 μg Se/day) appears to be a recipe for the human tragedy now unfolding in the Ganges–Brahmaputra delta area. High or even moderate As ingestion from water relative to a low Se intake from foods over time, we suggest likely leads to lowered reserves of body Se from As/Se/GSH complexation in liver and excretion in bile. Thus, it is hypothesized that the end result is excessive biliary Se excretion due to chronic high As intake from contaminated ground water. Secondarily, As and Se complex in tissues as insoluble selenides further limiting the availability of Se for protein synthesis. Thus, over the years of As exposure, time and a high As concentration in water leads to chronic lower levels of glutathione peroxidases and other anti-oxidant proteins containing Se. Arsenite being the likely predominate oxidative stressor in the absence of sufficient antioxidant protection from the Se containing proteins, glutathione peroxidase, thioredoxin reductase, etc. (and likely other dietary antioxidants, i.e. vitamin E, in poor diets) leads to liver disease comparable to dietary liver necrosis in experimental rats and mice (Schwarz, 1951; Schwarz and Foltz, 1957). Thus we suggest that liver depletion of Se by high As ingestion via biliary excretion may increase the risk of liver cancer. Arsenite being a reported cocarcinogen with UV light leads to hyper pigmentation and over time, skin cancer. Extra urinary excretion of As in the absence of Se for biliary excretion leads to kidney and bladder cancer. And finally, extra As in the absence of or low levels of antioxidants may increase the lung cancer incidence.

Analysis of soil samples by us from Jessore, Bangladesh revealed low to very low amounts of the essential human dietary trace element, Se. Annual monsoon rainfall and flooding are not conducive or indicative of soils that would be
expected to contain adequate Se for assimilation by plants into foods from local cultivation (Iyengar et al., 2002) for human or animal consumption. If this latter proves to be correct, low soil Se, the unique geology and regional environment of the Himalayan alluvial fan that forms the Ganges–Brahmaputra delta region may be a major contributor to human arsenicosis with all its medical, social and economic consequences.

This is a relatively easy hypothesis to test within the As affected and non-affected areas of the Ganges–Brahmaputra delta, Nepal (Adamsen and Pokhrel, 2002), Bangladesh, India and other places in the world as in Chile (Smith et al., 2000) or Vietnam (Berg et al., 2001) when arsenicosis is a risk to the population. The above scenario of an As–Se relationship in arsenicosis as it was in selenosis makes historical, theoretical and experimental sense in view of the available past and most recent Se/As research data. The hypothesis is easily testable with regional soil, food, hair, nail and blood data quantifiable for As and Se. In part, and as referenced, this hypothesis has already been tested by the Chinese (Wang et al., 2001; Hu, 1989) a country with more experience with Se than any other in the world because of their unique geological conditions and Keshan disease (Diplock, 1981). Wang et al. have shown that (1) As concentration (0–1.0 mg As/ml) in drinking water is correlated with arsenicosis and the As content of hair; (2) that after 14 months of Se supplementation the severity of symptoms of people with arsenicosis was reduced by 75%; (3) that people with arsenicosis taking Se supplements showed no deterioration of symptoms whereas 16% of controls showed symptomatic deterioration and; (4) that As in blood, urine and hair declined with Se treatment over time in comparison to control subjects. Such human experimental results should encourage further research into the relationship between high As intake and low Se intake in the causation of arsenicosis and human cancer. Researchers can look to the Chinese Se experience with Keshan disease and arsenicosis for additional insight and inspiration with reasonable expectations for successfully treating and perhaps preventing arsenicosis.

6. Unedited references

Csanaky et al. (2003) and Srikumar et al. (1992).

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