Adverse Effects of Zinc Deficiency: A Review from the Literature

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Zinc (Zn) has been known to be an essential element for more than a hundred years, ever since it was discovered by Raulin in 1869 to be required for the growth of Aspergillus niger.[1] However, it has not been until relatively modern times that the universal importance of this metal for both human and animal health became fully appreciated.[2-12] To date more than 200 zinc dependent enzymes have actually been identified in all the main biochemical pathways. It acts uniquely as a Lewis acid catalyst (an electron acceptor) in all life processes. The metal is known to be essential for the function and/or structure of several dehydrogenases, aldolases, peptidases, phosphatases, an isomerase, a transphosphorylase, aspartate transcarbamylase,[4,13,14] pancreatic carboxpeptidase, and tryptophan desmolase.[4,15] Zinc-dependent metalloenzymes are also found among oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases.[4,16] Zinc is also required for the action of both carbonic anhydrase and superoxide dismutase.[4,17] The metal has also been found to be an essential component of both DNA[4,14,18-20] and RNA polymerases.[4,14,21-22] It is also vital for a variety of hormonal activities, including the thymic hormone,[4,23] glucagon, insulin, growth hormone, as well as the sex hormones.[4,24-27] Furthermore, zinc has been found to be essential for normal brain development, particularly concerning the hippocampal function.[4,28-31] In addition, zinc is also known for its antiviral, antibacterial, antifungal, and anticancer properties, and has been found to protect animals against otherwise lethal irradiation by neutrons.[4]

Zinc and Growth

Retardation of growth has been found to be an early and prominent feature in young animals experimentally deprived of zinc.[3] However, it was not until in the early 1960s, when first reports on the adverse effects of zinc deficiency in man were described. These included dwarfism, hypogonadism, hepatosplenomegaly, rough and dry skin, mental lethargy and geophagy.[32-34] A decade later, these observations were confirmed by others.[35]

Zinc and Immunocompetence

The discovery that zinc deficiency is known to decrease immunity and to produce thymic involution and loss of T-cell function in animal studies,[36-38] provided basis for further interest of the action of zinc on immunity.[4,16,39,40] It is now known, that zinc acts as a mitogen for human lymphocytes in both animals and humans.[41-46] It has been also established that zinc stimulation of lymphocytes in vitro can be used to assess patients' proliferative capacity in various clinical settings.[47] This process of lymphocyte transformation initated by zinc, appears to require binding of a Zn-transferring complex, acting both pharmacologically and physiologically on the lymphoid system.[16] Research has also found, when peripheral blood mononuclear cells were studied in vitro, that zinc deficiency leads to decreased percentages of T-lymphocytes, increased percentages of T-suppressor cells, and to deficient responses to mitogens.[48,49] Other experimental studies on human volunteers have found zinc deficiency leading to a depressed NK-cells activity, with a similar decline in cytoxic function.[50,51] Conversely, zinc has been found to activate NK cells in vitro.[52] Although virtually all the data on zinc interaction with immune system have focused on T-cells, findings indicate that B-cells can also be affected, as zinc has been shown to act synergistically with B-cell mitogens, thus producing a greatly enhanced response.[46,53] Since the immune system develops during gestation, maternal zinc deprivation has been studied in mice. The results showed that the offspring born to zinc deficient dams had a greatly reduced immu-

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nocompetence, the lymphoid organs being particularly affected.[54] The following study by the same authors found that this diminished immunocompetence can persist as long as for three generations of normally fed offspring.[55] Further studies showed that if the offspring were only moderately deprived of zinc, during the latter two-thirds of pergnancy, even this can lead to long-lasting, aberrant patterns of serum IgG and IgA levels, despite a complete nutritional rehabilitation beginning at birth.[56] The authors concluded that an optimal dietary zinc is essential during both pregnancy and lactation to ensure the development of an intact immune system in the offspring. Furthermore, that lack of adequate dietary zinc during these critical periods in the fetal development, can lead to a marked long-term immunodeficiency, that may persist for generations to come.[56]

Zinc and Brain

Numerous studies have shown that zinc is one of the most prevalent trace elements found in the brain, where it is primarily retained in the hippocampus .[28-31,57] In fact, levels of zinc in the hippocampal area are greater than those of any other element, including calcium or iron.[58,59] Much of the zinc in the hippocampal area is associated with the axons of the mossy fibres projecting from the granule cells in the fascia dentata to the apical dendrites of the pyramidal cells.[28-31,57,60-62] By virtue of its limbic connections, the hippocampus is able to influence many brain activities, thus zinc depletion in mossy fibres may to contribute to a wide variety of cerebral physiopathologies.[29] The hippocampus is not the only region in the brain with a high zinc content: the neocortex,[58] amyglada,[63] gray matter, substania nigra, lentiform nucleus, caudate and thalamus all contain zinc.[64]

Zinc and Neural Function

Zinc has an essential role in axonal transport and neuronal microtubule and tubulin synthesis and assembly.[65-68] Using animal experiments, axonal transport has been found to occur for opiate receptors in the vagus nerve, and for muscarinic cholinergic receptors in vagus sciatic and splenic nerves.[30] However, similar axonal flow is probably common to all other receptors.[69] Zinc ions are essential in the brain tubulin phosphorylation and in the induction of tubulin to form transport sheets, as well in increasing the number of neurofilaments.[70] Furthermore, as zinc is the most important trace metal in subcellular DNA and RNA fractions, this will also explain its vital role in the neuronal maturition and profileration.[30]

Zinc and Brain Development

Research on rodents has allowed in depth examination on the above subject. It has been found that if pregnant rats are deprived of zinc early in pregnancy, it leads either to fetal reabsorption, abortion, or surviving fetuses displaying a variety of severe malformations, with the brain being one of the tissues affected.[31] On the other hand, if the maternal zinc deficiency is limited to the latter one-third of pregnancy, abortion or teratology may not occur, instead zinc deficiency at that stage of the gestation is able to impair seriously the fetal growth, brain size and total brain cell count, as well as to increase cytoplasmic nuclear ratio, implying an impaired cell devision during the critical period of macroneuronal proliferation.[30,31,57,71] Postnatal zinc deficiency has also been found to retard brain growth and maturiation. For example, when zinc deficiency was induced from birth to weaning, by zinc deprivation of nursing dams, pups were found to suffer impaired incorporation of thymidine into brain DNA, depressed incorporation of sulphur into the TCA precipitate, and a decreased rate of brain protein synthesis.[72] A deficiency of dietary zinc during the suckling period also resulted in the pups having smaller forebrains, reduced cell numbers, decreased total amount of brain DNA, a smaller hippocampus as well as a marked retention of the external granula layer of the cerebellum, compared to pups receiving adequate zinc.[30,57,72-73] Zinc is also necessary for many homeostatic processes in the brain, some of which indicate neurotransmitter function. For example, the activities of 2'-3' cyclic nucleotide - 3 - phosphohydrolase and L-glutamic acid dehydrogenase are decreased in the hippocampus and cerebellum of zinc deficient suckling rats.[31] The former enzyme is involved with myelination, while the latter

dehydrogenates glutamic acid.[31] Furthermore, when animals were severely deprived of zinc, levels of brain catecholamines increased i.e. elevation of noradrenaline occurred consistently, dopamine irregularly and serotonin relatively, when compared to controls.[30,74]

Zinc in Reproduction

Pregnancy

Consequently, as the participation of zinc is centrally involved in most events relating to cell division and nucleic acid synthesis and probably repair, including many other enzymatic pathways, its presence is most important during periods of rapid cellular development i.e. during organogenesis and fetal growth. Indeed, the time of conception, and the following pregnancy, represents the most vital period for assuring an optimum zinc status. In fact, it has been already established, using both animal experiments and human studies, that inadequate parental zinc status can result in a variety of deleterious effects on the offspring. The most obvious connection between clinical and/or sub-clinical zinc deficiency and fetal teratology seems to relate directly to its central role in all processes concerning cell differentiation and replication.[4,30,31,57,71-73,75-80] Studies with pregnant rats has found, that zinc deficiency will lead the offspring to be born with gross congenital malformations encompassing every organ system of the body. In addition, zinc deficiency in both male and female weanling rats resulted in extreme retardation of growth, abnormal hair and dermal lesions, depression of plasma protein level, anencephalus, abnormal estrous cycles, as well as with histological lesions in both testes and oesophagus.[81] In humans, inadequate zinc nutriture has been associated with an increased risk of pregnancy complications, including intrauterine growth retardation, prolonged labour, abnormal deliveries, vaginal bleeding and a variety of intrauterine malformations.[82] Inadequate zinc during prenatal period had been particularly linked with low birth weight.[4,78-80] This became apparent, yet again, when Drs Neil Ward and Robert Watson with Professor Bryce-Smith studied 37 placental element levels of known potential relevance to the fetal development of 100 obstetrically normal births .[78] The results showed a clear correlation between low placental zinc status and intra uterine growth retardation. The lower the zinc, the lighter the birth weight and the smaller the head circumference. In some studies small head circumference at birth has been related to the future growth of the whole central nervous system and to the total brain DNA, which may subsequently lead to inadequate central nervous system function and to slow mental development.[78] Other investigators have linked human prenatal zinc deficiency to pre-eclampsia,[83,84] pregnancy complications,[85-88] intrauterine growth retardation,[89-99], and a variety of congenital malformations.[85,90,94,100-103] Furthermore, since the immune system develops during gestation, maternal zinc depreviation has been found to lead to a greatly diminished immunocompetence, that can persist for generations to come.[54-56]

Lactation

Deficiency of dietary zinc during the suckling period of the rat resulted in the pups having smaller forebrains, a smaller hippocampus, reduced cell numbers, fewer brain neurons and decreased RNA and DNA, as well as an impairment in the body growth.[72,73] In addition, zinc deficiency during this critical period of brain growth and development seems to have a permanent effect on the brain and the hippocampal function. After growth to young adulthood and thereafter following nutritional rehabilitation, the previously zinc deprived offspring still displayed inferior learning and working memory, poor active avoidance shock and an increased aggression to a shock stimulus.[31] The adverse effects of zinc deprivation on the brain structure on human infants are obviously impossible to specify. However, differences in growth rates of breast-fed and formula-fed infants have been associated with the difference of zinc absorption from these two dietary sources ,[11] as it has now become apparent that zinc availability from human milk is far greater than from cow's milk, soya milk and combined formulas.[104] The greater bioavailability of zinc from human milk has been ascribed to the presence of low molecular weight zinc-binding ligand,[105,106] as opposed to cow's milk where

zinc binds avidly to cow's milk proteins, rendering it far less available for absorption.[107]

Male Reproduction

Zinc is vital for spermatogenesis and for the development of primary and secondary sexual characteristics.[11] Low zinc intake by young males of several species, including humans, interferes with normal sexual development.[3,4,33,34,85] In the young rat severe zinc deficiency has a marked effect on testicular weight [108-110]. Testicular lesions in young zinc deficient rats were similar to those experimental rats with cryptoridchism; severe atrophy of seminiferous tubules, sperm with malformed tails, and lesions of the axoneme.[111] In mildly zinc deficient rats, in which testicular weight was not reduced, epididymal sperm numbered only 35% of that from zinc adequate rats, motility was reduced, and sperm had various defects.[112] Sixty-day-old mice were sterile after three weeks of low zinc intake.[113] Experimental zinc deficiency in humans leads reversibly to reduced sperm count combined with reduced serum testosterone.[114] Zinc deficiency in humans has also been linked with oligospermia.[115]

Zinc Responsive Syndromes

Zinc and Mental Health

A variety of mental and behavioural changes have also been associated with zinc deficiency in humans, including apathy, lethargy, amnesia, irritability, depression and paranoia, as well as mental retardation.[116] In addition, a research study found a low plasma magnesium and zinc in 112 acute psychiatric patients when compared to controls.[117] Zinc supplementation has also found to be helpful in treating and curing postnatal depression.[12] In children, zinc deficiency has been associated with hyperactivity[118] and sleeping disorders[119] as well as with mental retardation.[120]

Schizophrenia

Several different biochemical imbalances can produce clinical manifestations termed as "schizophrenias". They include: heavy metal toxicity, drug intoxication, hypothyroidism, cerebral allergy, wheat-gluten sensitivity, hypoglycemia, folic acid/vitamin B_{12} deficiency, etc.[57] Other researchers have observed a greatly diminished zinc content in the hippocampus in both early onset schizophrenics as well as in chronic alcoholics.[121,122] In recent years, the biochemical defects in schizophrenia have been thought primarily to result from an excess of brain dopamine activity.[123,124] Therefore, it has been speculated, that as zinc deficiency can lead to a significant elevation in brain catecholamines, including dopamine,[125,126] some schizophrenias may be directly caused by zinc deficiency.[30,57] An excess of copper and a reduction of zinc metabolism has also been linked in some schizophrenias.[30,57,127,128] It is now known that zinc and copper are antagonists in the human body, both competing for the sites of the same protein carrier,[57] therefore the subsequent zinc depletion was considered to be due to an excess of copper intake and/or accumulation.[30,57] The most effective treatment for the reduction of the copper burden was found to be a dietary zinc supplement, combined with manganese,[30,57,128,129] as a prolonged zinc therapy can result to manganese deficiency.[30,57,128] Furthermore, a definite percentage of schizophrenics have also been found to excrete a chemical kryptopyrrole in their urine.[30,57,130,131] Kryptopyrrole is an avid aldehyde-reacting agent which has been shown to combine irreversibly with pyridoxal phosphate. The resulting kryptopyrrole-pyridoxal complex binds voraciously with zinc, the combined product being leached out with the urine. This condition, termed as pyroluria (or malvaria), has been found to responds readily to zinc and vitamin B_6 therapy.[30,57,129,131]

Anorexia

That zinc status might be directly related to anorexia and bulimarexia is not new.[132] Already in 1934 research described the clinical manifestations of zinc-deficient animals besides growth retardation, testicular atrophy, skin changes etc., also a poor appetite.[133] Other studies have shown that food consumption of zinc deprived rats decreased 30% compared to controls, and that force feeding of these zinc deprived animals rapidly induced signs of ill-health. Furthermore, that the animals responded to zinc supple-

mentation within 1-2 hours with increased food intake.[134,135] It has been also known that symptoms of zinc deficiency in humans leads to mental depression, neurosis, sleep disturbances as well as to a reduction in appetite.[5,136] The idea that zinc might be directly related to anorexia nervosa was first hypothesized Bakan[137] and Horrobin.[138] However, Bryce-Smith and Simpson were the first to demonstrate a case in which anorexia nervosa was simply and effectively treated by oral zinc supplementation,[139] hence the interest by other researchers.[140-142] Zinc deficiency may indeed play the major role in the development of anorexia nervosa in adolescents because it leads invariably to a suppression of appetite, primarily due to an impairment of taste and smell sensitivity.[4,143-147] Zinc is essential for the taste perception because taste is mediated through a salivary zinc dependent polypeptide termed gustin, therefore low salivary zinc levels invariably leads to a reduction of taste, hence to a greatly reduced appetite.[4,106,132] Zinc depletion is particularly detrimental during adolescents due to an increased demand for most nutrients, including zinc. Investigators have also noted, that oral contraceptive use in female adolescents was liable to impair zinc status.[148,149] In addition, psychological and physical stresses tend paradoxically to increase the urinary loss of zinc.[3,4,148-150] As a consequence, when zinc levels decline, the impairment of zinc-dependent taste can be expected further to reduce the desire for food.[132] A recent study by Ward compared the presence of zinc in five tissue and fluid samples collected from fifteen anorexic patients to that from fifteen controls (Fig. 1)[142] The results showed a statistically significant reduction in zinc content in whole blood, blood serum, plasma, urine and washed scalp hair in anorexic patients compared to controls. Following zinc supplementation, zinc levels increased in all anorexic patients, with the subjective improvement in appetite.[142]

Currently anorexia nervosa is a poorly understood disorder of unclear etiology, associated with high morbidity and mortality, for which most conventional therapies have been found to be highly unsatisfactory.[151] It is stressed therefore, that on the basis of currently available research information, zinc supplementation should always be tried first for any patient with anorexia nervosa, particularly as such therapy cannot cause the patient any harm. In this context it is also interesting to note that in some hospitalized patients that were exhibiting poor appetite, appropriate weight gain was not achieved, in some instances, until zinc supplementation was begun.[152] Furthermore, it is also documented that both anorexia and poor growth rate in some children have been corrected with zinc supplementation.[144,153-155]

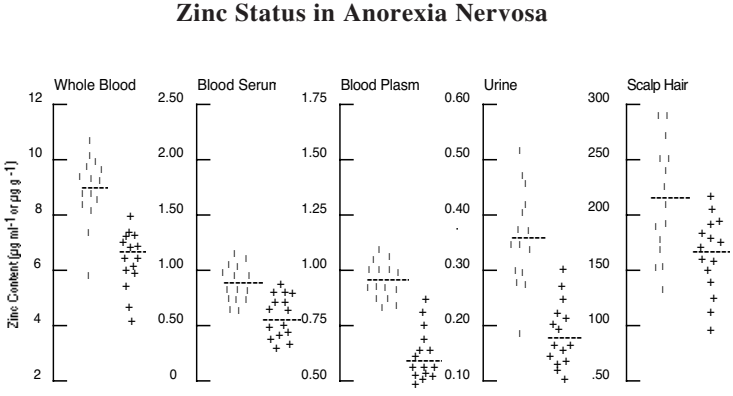

Figure 1. Zinc content of body fluids and tissues for control (•) and anorexic (+) individuals: (---) mean.

Alzheimer's Disease/Dementia Memory Loss

Recent research has associated an excessive aluminium concentration in the brain structure in some people suffering from Alzheimer's disease,[156-158] despite this toxic element having a low permeability of the blood-brain barrier,[156] suggesting that some form of membrane defect may permit the excessive influx of aluminium to enter the brain.[159] It is already known that adequate zinc is necessary to maintain the integrity of all biological membranes.[160] For example, it was found when experimenting with rats fed with sub-optimal zinc, that aluminium concentrations increased three-fold in the frontolateral cortex and eight-fold in the hippocampus.[161] Therefore, it has been suggested, that a reason for Alzheimer's disease could be suboptimal zinc nutriture, leading to 'leaky' blood-brain barrier and thereby to increased transfer of aluminium and other toxins to the brain.[162] The onset of senile dementia has also been associated with zinc deficiency, due to a possible genetically based processive inability of neurons to incorporate zinc ions into the DNA-handling system.[163] In addition, patients with an increased serum aluminium, due to a marked deficiency of zinc and/or manganese, have been found to experience a variety of memory disturbances.[164] In addition, some children displaying hyperactive behaviours and/or learning disabilities were found to have similarly an increased serum aluminium and a deficiency of zinc and/or manganese.[164]

Other Zinc-Responsive Syndromes

Acrodermatitis enterophatica is presently the most well recognised human zinc responsive syndrome attributable to an inherited defect of zinc absorption.[165] However, there are also a variety of other conditions that have been found to respond to zinc therapy, such as idiopathic hypogeusia,[4,144,145,166] improvement in wound healing,[4,167-169]gastric ulcers ,[4,170] acne,[4,171] rheumatoid arthritis,[4,172] as well as dyslexia.[173] In addition, an inadequate zinc nutriture has also been linked with a variety of immune deficiency disorders,[4,16,46-53] including cancers in both animals and in humans.[174-176] Furthermore, zinc deficiency have been suggested to participate in the development of AIDS.[4,12,177] In fact, as zinc is absolutely vital for an efficient immune system function, inadequate zinc status should always be corrected in all patients found either to be HIV-postive, or have AIDS, in order to stimulate their immunocompetence.[4,12]

Current Knowledge of Zinc in Nutrition

Recommended Dietary Allowances

According to the recommended dietary allowances in the U.S.A, the optimum daily intake of zinc for most adults should be 15mg, for the pregnant woman 20mg and for the lactating woman 25mg.[178] However, a 1981 survey by the Ministry of Agriculture Fisheries and Food revealed that the typical daily diet provided only about 10.5mg, with less for vegetarians.[179] The figure has been subsequently revised to 9.7mg.[79] Research has also shown that an average daily intake of zinc in pregnant women was found to be well below the recommended 20mg.[180,181] One study on pregnant women showed that the mean dietary zinc intake was only 61% of the US recommended daily allowance.[182]

Zinc Absorption

Zinc is present in most foods, but meat and fish provide the best sources, as bioavailability of zinc from animal products is considered to be far greater than from plant foods.[75,183-185] Even though plant foods do contain zinc, the the bioavailability from them is relatively poor due to their high phytic acid[186-191] and fibre content .[192,193] In fact, zinc availability from vegeterian diets has been reported to be exceptionally low.[194] Wheat germ is very rich in zinc, but unfortunately it is invariably disregarded during food processing, which further depletes the vegetarian diet of zinc. Furthermore, both calcium[195] and iron[182,196] have been found to interfere with zinc absorption. Interestingly, it is only the inorganic, nonheme form of dietary iron which competes with the absorption of dietary zinc, as opposed to iron in the form of haemoglobin, as from red muscle meats, which has no effect.[106] Also, such everyday dietary stables as coffee, and milk products have been shown to reduce the bioavailability of zinc in human subjects.[106,197,198] In addition, patients with gastrointestinal disorders such as malabsorp-

tion syndrome, diverticulitis and active Crohn's disease, as well as liver cirrhosis are obviously predisposed to a reduction of zinc absoption.[199-202]

Toxic Elements and Zinc

Cadmium

Zinc has a profound influence on the biochemistry and toxicology of cadmium, of which the largest single source for humans is tobacco smoking.[203-206] One reason for this is that cadmium can act as a antagonist to zinc in zinc-requiring metalloenzymes, such as carbonic anhydrase,[203,207] alkaline phosphates,[203,208] as well as with others.[203,2] Thus inadequate zinc nutritional status can influence the absorption and uptake of tissue cadmium thereby increasing its toxic effect.[203,209] This was also found when Ward and his team studied 37 placental elements of known potential relevance to fetal development of 100 obstetrically normal births, that both cadmium and lead had a highly negative relationship to infant birth weight, head circumference and placental weight. Furthermore, that zinc had a significant positive relationship.[205] It should also be noted here that lead is able to displace zinc from the hippocampal mossy fibre system,[210,211] as well as that zinc has an antagonistic effect to the toxic effects of lead.[212-214] Unlike lead, cadmium cannot be safely removed by chelating agents such as calcium EDTA or penicillamine.[213]

Alcohol

It is well known that alcohol consumption greatly increases urinary excretion of both vitamins and minerals. Alcohol-induced zinc depletion is particularly well documented.[215-220] One study compared zinc status of 25 alcoholic to 25 non-alcoholic pregnant women, finding a significantly lower plasma zinc in the women who abused alcohol, even though plasma zinc is not generally a reliable index of general zinc status. However, a reduced birth weight and a higher indicence of birth defects were recorded in infants born to these women with the lower zinc status.[219] It was also observed that although the patterns of birth defects were not consistent with that of zinc deficiency alone, the related abuse of alcohol by the pregnant women in the study could cause a specific targeting of the zinc-deficient teratogenic manifestations that are directly associated with alcohol-related fetal dysmorphogenesis.[219,220]

Assessment of Zinc Status

It has been establised that outward signs of zinc deficiency are primarily cutaneous striae and/or white-speckled fingernails, often also including poor skin and hair tone.[12,57] In clinical settings zinc deficiency is usually assessed using any of the following; plasma, serum, leucocyte, muscle, urine, hair, sweat or taste.[148] However, it has now been established that both plasma and serum zinc concentrations are subject to acute variations, being highest in the morning and falling after a meal. Stress alone can cause a rapid fall in plasma zinc values, as can certain steroid drugs, such as oral contraceptives.[148,221] Furthermore, all manner of infections tend to reduce both plasma and serum zinc levels in a way that is not necessarily related to primary nutritional zinc status. Only repeated low plasma zinc tests can provide grounds for suspecting zinc deficiency.[148] Muscle and leucocyte zinc are probably the most reliable analytical methods for the assessment of primary nutritional zinc status.[148] Hair zinc analysis represents a permanent deposition of zinc status, as the metal is firmly bound in the hair protein structure. However, caution is urged in the interpretation, as animal studies show that reduced dietary zinc leads at first to low hair zinc levels, but when zinc depletion continues, values seem to return to the normal range, presumably because the reduced hair growth resulting from impaired protein synthesis leads to a compensating increased concentrations of zinc and other elements in such hair when it grows.[148] Sweat zinc is presently regarded one of the most sensitive indexes of zinc status.[11] The "Taste-Test" for zinc deficiency is based on the evidence that the sense of taste is indeed among the first senses to be adversely affected in zinc deficiency.[4,12,143-147] The test is based on four clearly distinguished categories of taste response on test solution of 0.1% zinc sulphate heptahydrate diluted in distilled water.[4,12,148,149,221] Recently the taste-test scores have been found to correlate closely with

sweat zinc levels.[132]

Discussion and Results

As seen from the above, the recommended dietary allowance for zinc is 15mg daily. However, according to recent statistics, the typical daily diet provides only about 9.7mg of zinc. The reasons why modern diets are so deficient in zinc are manifold. One reason lies in modern agricultural practices as farmers can grow large crops and lush greenery by using masses of NPK fertilizers containing only nitrogen, potassium and phosphorus, thus progressively inhibiting the availability and the uptake of other essential micronutrients, such as zinc and maganese etc. from the soil.[12,222-226] In a survey by the UK Agriculture Research Council, zinc concentrations for cattle were found to be more than 50% deficient from all the herbage sampled.[227] Similar results were recorded from the US.[228] Such findings could hardly fail to reflect the diminished zinc concentration in human diets. In addition, food processing is designed to remove anything from the food that encourages the growth of bacteria, fungi etc.[229] Therefore, for example, 80% of zinc is removed from wheat flour during the milling process to ensure longer shelf life.[230] Furthermore, besides phytic acid, which is found naturally in foodstuffs, many other polyphosphates, such as hexametaphosphate, acid pyrophosphate and tripolyphosphate are added to foods during processing, causing an additional defect in zinc absorption.[231] The food additive tartrazine is now also found to act directly as a zinc-chelating agent.[118,232] Therefore, looking at the above, under present nutritional policy, it is not at all suprising that zinc deficiency is more a norm than a rarity. This is particularly worrying because zinc requirements for infants, children and teenagers are relatively high in relation to body size because of their increased requirements for physical growth and development. The fact which is even more disturbing, is the obvious zinc deficiencies frequently encountered in pregnant women. Because of the mildness, or a comparative lack of symptomatology, maternal zinc deficiency is unlikely even to be suspected, until it is too late, and the infant is already born with irreversible damage, including a low birth weight, brain dysfunction, malformations and/or with a sub-optimal immuno-competence. It is also noteworthy to remember that these adverse effects of maternal zinc deprivation seem to remain, despite a complete nutritional rehabilitation. There also has been recently a considerable debate whether a routine iron supplementation given during pregnancy is at all wise in the absence of iron deficiency anaemia, as iron supplementation tends to exacerbate zinc deficiency by competing for its binding sites that facilitate its intestinal absorption.[79,85,182,233-234] Considering that maternal zinc deficiency is already relatively common, an additional iron supplementation will further reduce the already diminishing zinc stores. In addition, it has also been demonstrated, that experimentally induced zinc deficiency in man results in impaired absorption of folic acid.[79,235] Folic acid deficiency in turn is now recognised as the major cause of spina bifida.[236] Besides optimal zinc being absolutely vital for female reproduction, it is likewise vital for male reproduction, as a sub-optimal zinc intake has been directly linked with malformed sperm, reduced sperm count and oligospermia. In addition, zinc deficiency also leads to an impairment of vitamin A metabolism,[4,237] as well as to an inhibition of prostaglandin synthesis from essential fatty acids, either by blocking linoleic acid desaturation to gamma linolenic acid, or by inhibiting the mobilization of dihomo-gamma-linolenic acid from the tissue membrane stores.[238] Though a trace metal like zinc is, in weight terms, only a miniscule part of the human metabolism, its presence is absolutely vital in all the major metabolic pathways. This being the case, on the basis of current evidence, the treatment with zinc supplementation should become a norm in all cases of anorexia, bulimia, immunodeficiency, alcoholism and mental depression, as well as in cases of both male and female infertility. Furthermore, all would-be mothers should be made aware of the vital importance of an optimal zinc status before and during pregnancy to prevent their offspring to be born with congenital malformations, prematurely and/or with a low birthweight and a small head circumference, the latter leading to a greater risk of brain damage and to a subsequent mental

backwardess. Because of this, all would-be mothers must be made immediately aware of the vital importance of dietary zinc in preventing birth defects, just as they have been made recently aware about importance of dietary folic acid in preventing spina bifida. This is of particular importance, as according the latest UK statistics, one child of every ten is now born with low birth weight. Furthermore, six babies of every 100 live births are now born either with 'minor' or 'major' physical malformations. In addition, it has been also estimated that one in every four babies is now born with some degree of learning disability and/or mental deficiency.[239] These statistics are absolutely appalling! After all, our children are supposed to be our future, so what is happening to our future? If we can help our future just by adding few milligrams of zinc supplementation to our diet, it certainly should be worth it.

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