Thinking about Clinical/Medical Nutrition Issues and Applications of RDAs, RDI, DRIs, ULS, AIs, etc.:

(from the series "How Am I Supposed to Remember All This Stuff?!")

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CB Notes:

As a rule, we tend to assume that people in the US have reasonable stores of nutrients unless they look really odd. That's because we learned about the roles of nutrients initially by observing the consequences of severe deficiency. We saw pellagra and scurvy and beri-beri. People LOOKED funny. We memorized that zinc deficiency can cause dwarfism and skin lesions … and **in the absence of dwarfism or serious skin lesions we just assume things are fine.**

Additionally, we often erroneously assume that people who appear to be overly nourished calorically are very unlikely to have a problem with nutrient inadequacy. **We still have not become attuned to the likelihood that some degree of inadequacy is present … sometimes a very significant degree of inadequacy … and that it compromises the patient's health and recovery from illness.**

Another big change in the world of Clinical Nutrition is that patients are not hospitalized as long as they used to be. The window of opportunity to help people with the nutrition issues affecting their health is much smaller. Additionally, the role of the clinical dietitian is much different now, **with greater emphasis placed on quickly recognizing key nutritional threats to rapid recovery and recommending and implementing appropriate interventions.**

Additionally, the shorter stay and the advent of ubiquitous computer access has resulted in much of the in-house patient food selection now being managed by computer at a call center manned by food service workers and not by dietitians. This is another very big change in focus because much of the hospital dietitian's job used to be taken up with this kind of felt-pen food selection from various special menus. [I am not making this up … some of us here in the Nutrition Therapy Department are old enough to have spent quite a lot of time doing that exact job. ☺]

The shorter stays make extensive teaching about special diets more likely to be assigned to a dietitian outside of the hospital. [However, whether that out-patient nutrition expertise is available all over the region served by a hospital is an emerging need that will need to be addressed … and such services are certainly NOT automatically available to patents.

Bottom line: We are living through a time of great change in the role of the hospital dietitian, and the skills we now need to do the job well are significantly different from what many of us studied in school or how we practiced in the past. Embracing this change can be fairly terrifying, but doing so has the potential to be very beneficial for staff and patient alike**.**

We Are Data-Rich but Theory-Poor

Lots of questions pop up in everyone's mind about providing any particular nutrient(s) to hospitalized patients.

Would it help the patient recover or would it just get in the way?

Is this the right time to look at this? Isn't nutritional status primarily an out-patient issue, since nobody eats really well when hospitalized with serious illness (for a million reasons.)

Aren't people already getting "too many pills" as it is?

Might giving a supplement actually be harmful? What if their nutrient stores are actually good and I give a supplement … would they have a bad reaction?

Should I ask for a blood test to see which patients are actually deficient? If so, who pays for that?

If I suggest a nutrient supplement, what level should I recommend?

What if I suggest in my chart note that the patient may benefit from sort of nutrition supplement but the doctor does not act on it?

What kind of nutrition supplement (if any) can a clinical dietitian simply order for a patient? What kind can't they automatically simply order? Why?

How can we figure out safe, inexpensive, not-in-the-way interventions that get the job done without having to bug the doctor for every little thing?

Should we have some things set up automatically for planned admissions? What nutrients, what amounts and which planned admissions ?

Should we have some things set up automatically for an identified subsection of patients on admission? What?

Sometimes all those questions keep us frozen and unable to comfortably make recommendations. The purpose of this paper is to help us sort things like this out, using the mineral zinc as an example.

Standard Intake Ranges:

Looking at and thinking about various recommended intakes and upper and lower ranges of safe intake, etc. in text books and on official websites.

Many of us actually have many of these numbers already in memory from going to school or doing internships; what we may NOT have, though, is a good understanding about <u>when a patient's nutrient needs depart significantly from this average number</u>.

<u>Clinical</u> Dietitians need to be aware just what those terms are based on and what these recommendations will <u>fail to account for</u>, especially in "non-healthy" populations.

The issue is best sorted out by identifying the key differences between recommendations in the world of "Clinical/Medical Nutrition" vs. the world of "Public Health Nutrition."

A Little History of RDAs, etc.

The Public Health figures and recommendations are all based on groups and averages … and they may have little in common with your patient:

1. **They are designed only for application to groups in programs like school food service, and not for application to individuals.**

2. **As a rule, the RDAs were set at levels assumed to meet the needs of "98% of the healthy population."** I guess that means that it would be OK if the needs of 2% of those healthy folks would not be met at this level.

3. **An additional key issue: The nutrient needs of people who are NOT members of the healthy population are not considered at all.** Patients in a hospital have a strong tendency, at least for the moment, to fall into the group of people who are not members of the "healthy population" group. **That means we need a better guide for specific nutrition recommendations for patients in a hospital or with any condition that compromises health.**

It is useful to remember that "RDA-like" recommendations were not handed down carved onto clay tablets by God. It is not blasphemy to suggest that the RDA level of a nutrient is unlikely to be best for a particular patient. This kind of general recommendation is always somebody's best guess at the moment based on the research available at the time.

An example: In 1968 when I started college, the RDA for vitamin C was 45 mg. Later it was changed to 70 mg, then back to 60 mg for some reason, and then to 90 mg. The next go-round it is more likely to be about 200 mg, based on newer research. That makes memorizing them particularly difficult and usually not very useful except if there are certain nutrients one works with a lot. But even then … they are just looking at the presumed requirements of groups of healthy people.

The RDA, for example, was the first national try. It was developed in 1943 because the "Great Depression" that lasted for over ten years (1929-1941) had resulted in a massive increase in the incidence of "malnutrition" … the real thing, **like overt pellagra, scurvy, rickets, and beriberi**. In fact, pellagra (niacin deficiency) was the number one cause of being put into a mental institution in the American South during the depression. When Pearl Harbor was attacked in 1941, America entered the war and the military tried to move quickly to draft men to fight. However, many guys were in seriously wretched health and totally unfit to be drafted, and the reason for much of it was related to nutritional deficiencies.

It is also useful to remember that **many micronutrients were not even discovered to exist until the 1920s**, including niacin. Vitamin B12 was not discovered until 1948. Nutrients like biotin, choline and others were not even on the radar. I always wonder about what else we don't have a clue about even now …

Anyway, the 1943 initiation of the first RDAs was an attempt to solve this particular problem: "How much of everything does a guy need to be draft-able?"

They did not ask "How much of everything does one need to achieve optimal health?"

Neither did they ask "If a guy has some big health problem like alcoholism or cancer or diabetes, then how much of everything does he need to take in to achieve optimal health for him?"

As noted earlier, they are all based on estimates of the presumed needs of "the healthy population" and not even those of "the healthy individual." They tell us even less about the needs of members of the NON-healthy population.

Since Clinical Dietitians often work with a large number of people who are NOT members of the "healthy population," we need to think through just how a patient's needs might vary when we add in all the other health and social issues involved. Failure to differentiate between these populations can be quite harmful to the patient.

One approach would be to design collections of standard interventions that would be safe and beneficial to everyone in general, but also particularly beneficial to patients with certain patterns of health issues. Ideally, a protocol could be put in

place that puts key recommendations into practice automatically, leaving the RD more time to look closer at the OTHER nutrition concerns that may be affecting a patient's health.

Example: Some Questions about Zinc for Hospital Clinical Dietitians (in no particular order)

How much should zinc be provided for everybody?

What foods are good zinc sources?

Are zinc supplements useful? If so, in what forms and what amounts?

Are there folks in the hospital who should be provided with more than the RDA of ~15 mg/day?

Are there folks in the hospital who should not be given zinc even at RDA levels?

How safe is giving zinc over that amount in general, and in the hospital specifically?

Do we need to get a zinc level to see if giving zinc is needed or safe?

Wouldn't the doctor have ordered a zinc level if there was any risk of zinc deficiency?

What if a patient's zinc stores were fine when admitted and we gave them a generous amount (e.g. well above the RDA) of absorbable zinc anyway?

Are most Americans likely to have good zinc stores?

What factors might be indicators of risk of having poor zinc stores on admission?

What factors might be indicators that more zinc is need than average by a patient?

If we identify a patient with a likely need for more zinc than average, can we do anything to send them home with that information in the hands of the patient or caretakers? Or is that the job of the out-patient dietitian?

The clinical dietitian's job is to know about more than just public health concepts about nutrition.

Ideally, one needs to:

1. **Have a general knowledge of the usual public-health concepts regarding nutrition. Most of us come to the job with much of that in place.**

2. **We all have to study up to acquire a more detailed knowledge of nutrition issues of particular relevance to our patients … you can't know everything, but you also don't need to.**

3. **Some issues affect pretty much everybody, but clinical/medical dietitians should set out to identify what are the big issues faced by their patients. Then they would come up with ways to provide them with a real health benefit.**

4. **We need skill at assessing the general nutritional status of patients especially as they relate to this hospitalization.**

5. **When able, providing insight into helping to keep people healthy after discharge.**

6. **Be a bit of a Nutrition Detective.**

Some Official Stuff:

Recommended Intakes, etc. and some Zinc Specific Information

http://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/

Recommended Intakes

Intake recommendations for zinc and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies (formerly National Academy of Sciences) [2]. **DRI is the general term for a set of reference values used for planning and assessing nutrient intakes of healthy people.** These values, which vary by age and gender [2], include the following:

- **Recommended Dietary Allowance (RDA):** average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals.
- **Adequate Intake (AI):** established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy [also looking only at healthy people.]
- **Tolerable Upper Intake Level (UL):** maximum daily intake unlikely to cause adverse health effects [2].

The current RDAs for zinc are listed in Table 1 [2]. For infants aged 0 to 6 months, the FNB established an AI for zinc that is equivalent to the mean intake of zinc in healthy, breastfed infants.*****

Table 1: Recommended Dietary Allowances (RDAs) for Zinc [2]

Age	Male	Female	Pregnancy	Lactation
0–6 months	2 mg*	2 mg*		
7–12 months	3 mg	3 mg		
1–3 years	3 mg	3 mg		
4–8 years	5 mg	5 mg		
9–13 years	8 mg	8 mg		

***** Adequate Intake (AI)

Table 1: Recommended Dietary Allowances (RDAs) for Zinc [2]

Age	Male	Female	Pregnancy	Lactation
14–18 years	11 mg	9 mg	12 mg	13 mg
19+ years	11 mg	8 mg	11 mg	12 mg

Sources of Zinc

Food

A wide variety of foods contain zinc (Table 2) [2]. Oysters contain more zinc per serving than any other food, but red meat and poultry provide the majority of zinc in the American diet. Other good food sources include beans, nuts, certain types of seafood (such as crab and lobster), whole grains, fortified breakfast cereals, and dairy products [2,11].

Phytates—which are present in whole-grain breads, cereals, legumes, and other foods—bind zinc and inhibit its absorption [2,12,13]. Thus, the **bioavailability of zinc from grains and plant foods is lower than that from animal foods**, although many grain- and plant-based foods are still good sources of zinc. [2]

CB Note: There are other things that have the same effect of lowering the bioavailability of zinc and iron from inorganic sources (i.e. plants or pills.) For example, oxalates in certain vegetables, tannins in tea, and milk can all significantly decrease absorption of inorganic zinc and iron.

Some Questions:

1. How might this influence the effectiveness of using milk-based nutritional beverages (like Ensure, etc.) as the zinc and/or iron supplement?
2. How about giving fortified cereal with milk?
3. How about taking the vitamin/mineral with milk or tea?

Answers:

If folks are generally healthy and eat a typical mixed American diet (whatever the heck THAT is) including at least some meat each week, the potential impairment of zinc and iron absorption in these situations is likely not an issue.

(The absorption from these sources is still untrustworthy, but the person is not showing up at the hospital with a likely really poor zinc or iron status, so it is not as pressing to get a bunch of zinc and iron into them.)

Another question: What if the person in the hospital is theoretically at risk of having poor zinc and/or iron status already? (E.g. for the usual reasons: due to unintentional weight loss, inability to eat normally for some time, presence of wounds or infection or serious disease, generous regular use of alcohol, gastrointestinal problems including bariatric surgery, or vegetarianism etc. etc. …

Answer: These "fixes" will be much less effective than we might think from just doing the math about "HOW MUCH IS IN THERE?" The form and the other foods can make a big difference.

Zinc Intakes and Status

Most infants (especially those who are formula fed), children, and adults in the United States consume recommended amounts of zinc according to two national surveys, the 1988–1991 National Health and Nutrition Examination Survey (NHANES III) [19] and the 1994 Continuing Survey of Food Intakes of Individuals (CSFII) [20].

However, some evidence suggests that zinc intakes among older adults might be marginal. An analysis of NHANES III data found that 35%–45% of adults aged 60 years or older had zinc intakes below the estimated average requirement of 6.8 mg/day for elderly females and 9.4 mg/day for elderly males. When the investigators considered intakes from both food and dietary supplements, they found that 20%–25% of older adults still had inadequate zinc intakes [21].

Zinc intakes might also be low in older adults from the 2%–4% of U.S. households that are food insufficient (sometimes or often not having enough food) [22]. Data from NHANES III indicate that adults aged 60 years or older from food-insufficient families had lower intakes of zinc and several other nutrients and were more likely to have zinc intakes below 50% of the RDA on a given day than those from food-sufficient families [23].

Table 2: Selected Food Sources of Zinc [11]

* DV = Daily Value. DVs were developed by the U.S. Food and Drug Administration to help consumers compare the nutrient contents of products within the context of a total diet. The DV for zinc is 15 mg for adults and children age 4 and older. Food labels, however, are not required to list zinc content unless a food has been fortified with this nutrient. Foods providing 20% or more of the DV are considered to be high sources of a nutrient.

The U.S. Department of Agriculture's (USDA's) Nutrient Database Web site [11] lists the nutrient content of many foods and provides a comprehensive list of foods containing zinc arranged by nutrient content and by food name.

Dietary supplements

Supplements contain several forms of zinc, including zinc gluconate, zinc sulfate, and zinc acetate. The percentage of elemental zinc varies by form. For example, approximately 23% of zinc sulfate consists of elemental zinc; thus, 220 mg of zinc sulfate contains 50 mg of elemental zinc. The elemental zinc content appears in the Supplement Facts panel on the supplement container. Research has not determined whether differences exist among forms of zinc in absorption, bioavailability, or tolerability.

In addition to standard tablets and capsules, some zinc-containing cold lozenges are labeled as dietary supplements

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Other sources

Zinc is present in several products, including some labeled as homeopathic medications, sold over the counter for the treatment and prevention of colds. Numerous case reports of anosmia (loss of the sense of smell), in some cases long-lasting or permanent, have been associated with the use of zinc-containing nasal gels or sprays [14,15]. In June 2009, the FDA warned consumers to stop using three zinc-containing intranasal products because they might cause anosmia [16]. The manufacturer recalled these products from the marketplace. Currently, these safety concerns have not been found to be associated with cold lozenges containing zinc.

Zinc is also present in some denture adhesive creams at levels ranging from 17–34 mg/g [17]. While use of these products as directed (0.5–1.5 g/day) is not of concern, chronic, excessive use can lead to zinc toxicity, resulting in copper deficiency and neurologic disease. Such toxicity has been reported in

individuals who used 2 or more standard 2.4 oz tubes of denture cream per week [17,18]. Many denture creams have now been reformulated to eliminate zinc.

Zinc Deficiency (still from http://ods.od.nih.gov/factsheets/Zinc-HealthProfessional but highlighted for this discussion/)

Zinc deficiency is characterized by growth retardation, loss of appetite, and impaired immune function. In more severe cases, zinc deficiency causes hair loss, diarrhea, delayed sexual maturation, impotence, hypogonadism in males, and eye and skin lesions [2,8,24,25]. Weight loss, delayed healing of wounds, taste abnormalities, and mental lethargy can also occur [5,8,26-30].

Many of these symptoms are non-specific and often associated with other health conditions; therefore, a medical examination is necessary to ascertain whether a zinc deficiency is present.

> **CB note:** Thought --- is there any reason why one should first identify the presence of overt deficiency before providing a generous amount of well absorbed zinc?

Zinc nutritional status is difficult to measure adequately using laboratory tests [2,31,32] due to its distribution throughout the body as a component of various proteins and nucleic acids [33]. Plasma or serum zinc levels are the most commonly used indices for evaluating zinc deficiency, but these levels do not necessarily reflect cellular zinc status due to tight homeostatic control mechanisms [8].

Clinical effects of zinc deficiency can be present in the absence of abnormal laboratory indices [8]. Clinicians consider risk factors (such as inadequate caloric intake, alcoholism, and digestive diseases) and symptoms of zinc deficiency (such as impaired growth in infants and children) when determining the need for zinc supplementation [2].

Groups at Risk of Zinc Inadequacy

In North America, **overt** zinc deficiency is uncommon [2]. When zinc deficiency does occur, it is usually due to inadequate zinc intake or absorption, increased losses of zinc from the body, or increased requirements for zinc [26,27,34]. People at risk of zinc deficiency or inadequacy need to include good sources of zinc in their daily diets. Supplemental zinc might also be appropriate in certain situations.

People with gastrointestinal and other diseases

Gastrointestinal surgery and digestive disorders (such as ulcerative colitis, Crohn's disease, and short bowel syndrome) can decrease zinc absorption and increase endogenous zinc losses primarily from the gastrointestinal tract and, to a lesser extent, from the kidney [2,26,35,36]. Other diseases associated with zinc deficiency include malabsorption syndrome, chronic liver disease, chronic renal disease, sickle cell disease, diabetes, malignancy, and other chronic illnesses [37]. Chronic diarrhea also leads to excessive loss of zinc [24].

Vegetarians

The bioavailability of zinc from vegetarian diets is lower than from non-vegetarian diets because vegetarians do not eat meat, which is high in bioavailable zinc and may enhance zinc absorption. In addition, vegetarians typically eat high levels of legumes and whole grains, which contain phytates that bind zinc and inhibit its absorption [31,38].

Vegetarians sometimes require as much as 50% more of the RDA for zinc than non-vegetarians [2]. In addition, they might benefit from using certain food preparation techniques that reduce the binding of zinc by phytates and increase its bioavailability. Techniques to increase zinc bioavailability include soaking beans, grains, and seeds in water for several hours before cooking them and allowing them to sit after soaking until sprouts form [38]. Vegetarians can also increase their zinc intake by consuming more leavened grain products (such as bread) than unleavened products (such as crackers) because leavening partially breaks down the phytate; thus, the body absorbs more zinc from leavened grains than unleavened grains.

Pregnant and lactating women

Pregnant women, particularly those starting their pregnancy with marginal zinc status, are at increased risk of becoming zinc insufficient due, in part, to high fetal requirements for zinc [39]. Lactation can also deplete maternal zinc stores [40]. For these reasons, the RDA for zinc is higher for pregnant and lactating women than for other women (see Table 1) [2].

Older infants who are exclusively breastfed

Breast milk provides sufficient zinc (2 mg/day) for the first 4–6 months of life but does not provide recommended amounts of zinc for infants aged 7–12 months, who need 3 mg/day [2,33]. In addition to breast milk, infants aged 7–12 months should consume age-appropriate foods or formula containing zinc [2]. Zinc supplementation has improved the growth rate in some children who demonstrate mild-to-moderate growth failure and who have a zinc deficiency [24,41].

People with sickle cell disease

Results from a large cross-sectional survey suggest that 44% of children with sickle cell disease have a low plasma zinc concentration [42], possibly due to increased nutrient requirements and/or poor nutritional status [43]. Zinc deficiency also affects approximately 60%–70% of adults with sickle cell disease [44]. Zinc supplementation has been shown to improve growth in children with sickle cell disease [43].

Alcoholics

Approximately **30%-50% of alcoholics have low zinc status** because ethanol consumption decreases intestinal absorption of zinc and increases urinary zinc excretion [44]. In addition, the variety and amount of food consumed by many alcoholics is limited, leading to inadequate zinc intake [2,46,47].

Zinc and Health

Immune function

Severe zinc deficiency depresses immune function [48], and even mild to moderate degrees of zinc deficiency can impair macrophage and neutrophil functions, natural killer cell activity, and complement activity [49]. The body requires zinc to develop and activate T-lymphocytes [2,50]. Individuals with low zinc levels have shown reduced lymphocyte proliferation response to mitogens and other adverse alterations in immunity that can be corrected by zinc supplementation [49,51]. These alterations in immune function might explain why low zinc status has been associated with increased susceptibility to pneumonia and other infections in children in developing countries and the elderly [52-55].

Wound healing

Zinc helps maintain the integrity of skin and mucosal membranes [49]. Patients with chronic leg ulcers have abnormal zinc metabolism and low serum zinc levels [56], and clinicians frequently treat skin ulcers with zinc supplements [57]. The authors of a systematic review concluded that zinc sulfate might be effective for treating leg ulcers in some patients who have low serum zinc levels [58,59]. However, research has not shown that the general use of zinc sulfate in patients with chronic leg ulcers or arterial or venous ulcers is effective [58,59].

Diarrhea

Acute diarrhea is associated with high rates of mortality among children in developing countries [60]. Zinc deficiency causes alterations in immune response that probably contribute to increased susceptibility to infections, such as those that cause diarrhea, especially in children [49]. Studies show that poor, malnourished children in India, Africa, South America, and Southeast Asia experience shorter

courses of infectious diarrhea after taking zinc supplements [61]. The children in these studies received 4–40 mg of zinc a day in the form of zinc acetate, zinc gluconate, or zinc sulfate [61].
In addition, results from a pooled analysis of randomized controlled trials of zinc supplementation in developing countries suggest that zinc helps reduce the duration and severity of diarrhea in zinc-deficient or otherwise malnourished children [62]. Similar findings were reported in a meta-analysis published in 2008 and a 2007 review of zinc supplementation for preventing and treating diarrhea [63,64]. The effects of zinc supplementation on diarrhea in children with adequate zinc status, such as most children in the United States, are not clear.

The World Health Organization and UNICEF now recommend short-term zinc supplementation (20 mg of zinc per day, or 10 mg for infants under 6 months, for 10–14 days) to treat acute childhood diarrhea [60].

The common cold
Researchers have hypothesized that zinc could reduce the severity and duration of cold symptoms by directly inhibiting rhinovirus binding and replication in the nasal mucosa and suppressing inflammation [65,66]. Although studies examining the effect of zinc treatment on cold symptoms have had somewhat conflicting results, overall zinc appears to be beneficial under certain circumstances. Several studies are described below in which zinc is administered as a lozenge or zinc-containing syrup that temporarily "sticks" in the mouth and throat. This allows zinc to make contact with the rhinovirus in those areas.

In a randomized, double-blind, placebo-controlled clinical trial, 50 subjects (within 24 hours of developing the common cold) took a zinc acetate lozenge (13.3 mg zinc) or placebo every 2–3 wakeful hours. Compared with placebo, the zinc lozenges significantly reduced the duration of cold symptoms (cough, nasal discharge, and muscle aches) [67].

In another clinical trial involving 273 participants with experimentally induced colds, zinc gluconate lozenges (providing 13.3 mg zinc) significantly reduced the duration of illness compared with placebo but had no effect on symptom severity [68]. However, treatment with zinc acetate lozenges (providing 5 or 11.5 mg zinc) had no effect on either cold duration or severity. Neither zinc gluconate nor zinc acetate lozenges affected the duration or severity of cold symptoms in 281 subjects with natural (not experimentally induced) colds in another trial [68].

In 77 participants with natural colds, a combination of zinc gluconate nasal spray and zinc orotate lozenges (37 mg zinc every 2–3 wakeful hours) was also found to have no effect on the number of asymptomatic patients after 7 days of treatment [69]

In September of 2007, Caruso and colleagues published a structured review of the effects of zinc lozenges, nasal sprays, and nasal gels on the common cold [66]. Of the 14 randomized, placebo-controlled studies included, 7 (5 using zinc lozenges, 2 using a nasal gel) showed that the zinc treatment had a beneficial effect and 7 (5 using zinc lozenges, 1 using a nasal spray, and 1 using lozenges and a nasal spray) showed no effect.

More recently, a Cochrane review concluded that "zinc (lozenges or syrup) is beneficial in reducing the duration and severity of the common cold in healthy people, when taken within 24 hours of onset of symptoms" [70]. The author of another review completed in 2004 also concluded that zinc can reduce the duration and severity of cold symptoms [65]. However, more research is needed to determine the optimal dosage, zinc formulation and duration of treatment before a general recommendation for zinc in the treatment of the common cold can be made [70].

As previously noted, the safety of intranasal zinc has been called into question because of numerous reports of anosmia (loss of smell), in some cases long-lasting or permanent, from the use of zinc-containing nasal gels or sprays [14-16].

Age-related macular degeneration

Researchers have suggested that both zinc and antioxidants delay the progression of age-related macular degeneration (AMD) and vision loss, possibly by preventing cellular damage in the retina [71,72]. In a population-based cohort study in the Netherlands, high dietary intake of zinc as well as beta carotene, vitamin C, and vitamin E was associated with reduced risk of AMD in elderly subjects [73]. However, the authors of a systematic review and meta-analysis published in 2007 concluded that zinc is not effective for the primary prevention of early AMD [74], although zinc might reduce the risk of progression to advanced AMD.

The Age-Related Eye Disease Study (AREDS), a large, randomized, placebo-controlled, clinical trial (n = 3,597), evaluated the effect of high doses of selected antioxidants (500 mg vitamin C, 400 IU vitamin E, and 15 mg beta-carotene) with or without zinc (80 mg as zinc oxide) on the development of advanced AMD in older individuals with varying degrees of AMD [72]. Participants also received 2 mg copper to prevent the copper deficiency associated with high zinc intakes. After an average follow-up period of 6.3 years, supplementation with antioxidants plus zinc (but not antioxidants alone) significantly reduced the risk of developing advanced AMD and reduced visual acuity loss. Zinc supplementation alone significantly reduced the risk of developing advanced AMD in subjects at higher risk but not in the total study population. Visual acuity loss was not significantly affected by zinc supplementation alone. A follow-up AREDS2 study confirmed the value of this supplement in reducing the progression of AMD

over a median follow-up period of 5 years [75]. Importantly, AREDS2 revealed that a formulation providing 25 mg zinc (about one-third the amount in the original AREDS formulation) provided the same protective effect against developing advanced AMD.

Two other small clinical trials evaluated the effects of supplementation with 200 mg zinc sulfate (providing 45 mg zinc) for 2 years in subjects with drusen or macular degeneration. Zinc supplementation significantly reduced visual acuity loss in one of the studies [76] but had no effect in the other [77].

A Cochrane review concluded that the evidence supporting the use of antioxidant vitamins and zinc for AMD comes primarily from the AREDS study [71]. Individuals who have or are developing AMD should talk to their health care provider about taking a zinc-containing AREDS supplement.

Interactions with iron and copper

Iron-deficiency anemia is a serious world-wide public health problem. Iron fortification programs have been credited with improving the iron status of millions of women, infants, and children. Fortification of foods with iron does not significantly affect zinc absorption. However, large amounts of supplemental iron (greater than 25 mg) might decrease zinc absorption [2,78]. Taking iron supplements between meals helps decrease its effect on zinc absorption [78].High zinc intakes can inhibit copper absorption, sometimes producing copper deficiency and associated anemia [79,80]. For this reason, dietary supplement formulations containing high levels of zinc, such as the one used in the AREDS study [72], sometimes contain copper.

Health Risks from Excessive Zinc

[CB Interpretation Note: This section is called "High Risks **FROM** Excessive Zinc," and it is not saying that there is a high risk **OF** excessive zinc. In other words, way too much is very bad, -- as "way too much" of anything is very bad by definition. But "excessive zinc" is invariably due to some weird supplementation of big never-recommended doses … not intakes like an RDA amount or an amount commonly used to correct inadequacy. I just want to keep this in perspective.]

Zinc toxicity can occur in both acute and chronic forms. Acute adverse effects of high zinc intake include nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headaches [2]. One case

report cited severe nausea and vomiting within 30 minutes of ingesting 4 g of zinc gluconate (570 mg elemental zinc) [81]. Intakes of 150–450 mg of zinc per day have been associated with such chronic effects as low copper status, altered iron function, reduced immune function, and reduced levels of high-density lipoproteins [82]. Reductions in a copper-containing enzyme, a marker of copper status, have been reported with even moderately high zinc intakes of approximately 60 mg/day for up to 10 weeks [2]. The doses of zinc used in the AREDS study (80 mg per day of zinc in the form of zinc oxide for 6.3 years, on average) have been associated with a significant increase in hospitalizations for genitourinary causes, raising the possibility that chronically high intakes of zinc adversely affect some aspects of urinary physiology [83].

The FNB has established ULs for zinc (Table 3). Long-term intakes above the UL increase the risk of adverse health effects [2]. The ULs do not apply to individuals receiving zinc for medical treatment, but such individuals should be under the care of a physician who monitors them for adverse health effects.

Table 3: Tolerable Upper Intake Levels (ULs) for Zinc [2]

Age	Male	Female	Pregnant	Lactating
0–6 months	4 mg	4 mg		
7–12 months	5 mg	5 mg		
1–3 years	7 mg	7 mg		
4–8 years	12 mg	12 mg		
9–13 years	23 mg	23 mg		
14–18 years	34 mg	34 mg	34 mg	34 mg
19+ years	40 mg	40 mg	40 mg	40 mg

Interactions with Medications

Zinc supplements have the potential to interact with several types of medications. A few examples are provided below. Individuals taking these medications on a regular basis should discuss their zinc intakes with their healthcare providers.

Antibiotics

Both quinolone antibiotics (such as Cipro®) and tetracycline antibiotics (such as Achromycin® and Sumycin®) interact with zinc in the gastrointestinal tract, inhibiting the absorption of both zinc and

the antibiotic [84,85]. Taking the antibiotic at least 2 hours before or 4–6 hours after taking a zinc supplement minimizes this interaction [86].

Penicillamine

Zinc can reduce the absorption and action of penicillamine, a drug used to treat rheumatoid arthritis [87]. To minimize this interaction, individuals should take zinc supplements at least 2 hours before or after taking penicillamine [85].

Diuretics

Thiazide diuretics such as chlorthalidone (Hygroton®) and hydrochlorothiazide (Esidrix® and HydroDIURIL®) increase urinary zinc excretion by as much as 60% [88]. Prolonged use of thiazide diuretics could deplete zinc tissue levels, so clinicians should monitor zinc status in patients taking these medications.

Zinc and Healthful Diets

[CB Note: Remember that this is, by definition, a Public Health view of life … guessing about what healthy people might need. It is not necessarily directly applicable to guessing about what people with health problems might need… and notice that in all cases we are all just guessing based on the data currently available.]

The federal government's 2010 *Dietary Guidelines for Americans* notes that "nutrients should come primarily from foods. Foods in nutrient-dense, mostly intact forms contain not only the essential vitamins and minerals that are often contained in nutrient supplements, but also dietary fiber and other naturally occurring substances that may have positive health effects. …Dietary supplements…may be advantageous in specific situations to increase intake of a specific vitamin or mineral."

For more information about building a healthful diet, refer to the *Dietary Guidelines for Americans* and the U.S. Department of Agriculture's food guidance system, MyPlate.

[CB Note: The Dietary Guidelines for Americans are discussed further in this context on the next page.

"The *Dietary Guidelines for Americans* describes a healthy diet as one that:

- Emphasizes a variety of fruits, vegetables, whole grains, and fat-free or low-fat milk and milk products. **[CB: For zinc??? Holy cow! There is a lot of great nutrition there in those foods, but zinc? Not so much.]**
  Whole grains and milk products are good sources of zinc. Many ready-to-eat breakfast cereals are fortified with zinc. **[CB: What about <u>ABSORPTION</u> of zinc from these foods? [Please see the "Zinc and Iron in Food" paper for more on this issue.]**

- Includes lean meats, poultry, fish, beans, eggs, and nuts.
  Oysters, red meat, and poultry are excellent sources of zinc. Baked beans, chickpeas, and nuts (such as cashews and almonds) also contain zinc.

- Is low in saturated fats, *trans* fats, cholesterol, salt (sodium), and added sugars. *****

- Stays within your daily calorie needs.*"

[CB Note: These last two are certainly reasonably healthful suggestions in general, but mostly **<u>these recommendations are a very good example of how completely unrelated Public Health recommendations are to solving the zinc problems being raised in this paper</u>.** Usually we tell folks broadly that to be healthy one should avoid meat … especially red meat, etc. **<u>These recommendations are not conducive to correcting serious zinc inadequacy in an individual and the Clinical Dietitians need to be able to sort this out for folks.]</u>**