Zinc and Health: Current Status and Future Directions

The Dynamic Link between the Integrity of the Immune System and Zinc Status\(^1,2\)

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ABSTRACT The results of more than three decades of work indicate that zinc deficiency rapidly diminishes antibody- and cell-mediated responses in both humans and animals. The moderate deficiencies in zinc noted in sickle cell anemia, renal disease, chronic gastrointestinal disorders and acrodynatitis enteropathica; subjects with human immunodeficiency virus; children with diarrhea; and elderly persons can greatly alter host defense systems, leading to increases in opportunistic infections and mortality rates. Conversely, short periods of zinc supplementation substantially improve immune defense in individuals with these diseases. Mouse models demonstrate that 30 d of suboptimal intake of zinc can lead to 30–80% losses in defense capacity. Collectively, the data clearly demonstrate that immune integrity is tightly linked to zinc status. Lymphopenia and thymic atrophy, which were the early hallmarks of zinc deficiency, are now known to be due to high losses of precursor T and B cells in the bone marrow. This ultimately leads to lymphopenia or a failure to replenish the lymphocytic system. Glucocorticoid-mediated apoptosis induced by zinc deficiency causes down-regulation of lymphopoiesis. Indeed, zinc itself can modulate death processes in precursor lymphocytes. Finally, there is substantial evidence that zinc supplementation may well reduce the impact of many of the aforementioned diseases by preventing the dismantling of the immune system. The latter represents an important area for research.


KEY WORDS: • apoptosis • immune response • lymphopoiesis • zinc deficiency

Link between immune integrity and nutritional status

Nutritional deficiencies may be the most common cause of secondary immunodeficiency states in humans (Chandra and Newberne 1977, Endre et al. 1990). Early studies made it clear that suboptimal nutriture associated with an inadequate diet or with the many diseases in which nutritional status is altered could significantly impair host defense systems (Keen and Gershwin 1990). As cancer, acquired immune deficiency syndrome (AIDS),\(^4\) renal and gastrointestinal diseases and other diseases advance, wasting and impaired host defense go hand in hand (Endre et al. 1990). These diseases, as well as suboptimal diets, create heightened incidences of opportunistic infections, sepsis, pneumonia and so on, which also increase morbidity rates in affected subjects (Chandra and Newberne 1977, Endre et al. 1990). Early human studies provided the first evidence that nutritional status and immune status were tightly linked, and recent data collected in mouse models affirm this relationship (Endre et al. 1990, Fraker et al. 1993). Perhaps the best developed nutritional-immunological paradigm is the zinc-deficient mice, in which the impact of a single nutritional element on the immune system could be probed in depth. The collective data, which are reviewed here, indicate that as zinc becomes suboptimal, its impact on the immune system is rapid and extensive, being far greater than its impact on other tissues and organs (Fraker et al. 1993). Indeed, the impact of zinc deficiency on the immune system of the young adult mouse was of such intensity that for some time it was difficult to understand. Also addressed is a better understanding of why the ties between zinc status and immune status are so interrelated.

For three decades, the hallmarks of malnutrition, especially of protein-calorie deficiencies (PCM) and zinc deficiency, were thymic atrophy and lymphopenia. The underlying mechanisms that create these two major changes in immune integrity are now documented and provide new insights into how nutritional deficiencies change the composition of the peripheral immune system and the regulation of hematopoiesis. The ability of zinc supplementation to offset the changes in immune function created by malnutrition and disease is also addressed.

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\(^4\) Abbreviations used: AIDS, acquired immune deficiency syndrome; Dex, dexamethasone; DTH, delayed type hypersensitivity; Gc, glucocorticoid; IL-2, interleukin-2; NK, natural killer; PCM, protein-calorie deficiency

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Deficiencies in zinc represent a fairly prevalent human health problem (Endre et al. 1990, Fraker et al. 1993, Keen and Gershwin 1990). In the United States, suboptimal intake of dietary zinc has been observed in children from low income families, low birth weight infants, frail elderly persons, children with chronic diarrhea and some pregnant teenagers (Endre et al. 1990, Sazawal et al. 1998). Acrodermatitis enteropathica, a genetic disorder affecting the assimilation of zinc, occurs in the human population although at an infrequent rate (Endre et al. 1990). Although data were collected in the late 1970s, it is evident from Table 1 that host defense was indeed altered in patients with acrodermatitis enteropathica (Anonymous 1981). This genetic disease was one of the first to provide the hallmarks of zinc deficiency, i.e., thymic atrophy and lymphopenia. Decreased cell-mediated responses and an increased incidence of infections were also noted in these patients.

However, deficiencies in zinc also accompany many Western diseases and conditions such as gastrointestinal disorders, renal disease, sickle cell anemia, alcoholism, some types of cancers, AIDS, burns and others (Baum et al. 1995, Chandra and Newberne 1977, Endre et al. 1990, Fraker et al. 1993, Keen and Gershwin 1990). Examples of the impact of several of these conditions on zinc and immune status are shown in Table 2. Prasad and coworkers (Kaplan et al. 1988) found defective natural killer (NK) function and anergic delayed type hypersensitivity (DTH) responses in patients with sickle cell anemia who had only modest depletion of serum zinc. Prolonged tube feeding created a zinc-deficient subject with lymphopenia and reduced NK responses (Allen et al. 1983). Elderly persons present a mixed picture with regard to zinc status; however, decreased interleukin-2 (IL-2) production and lymphopenia were noted in individuals with marginal zinc status (Kaplan et al. 1988). A subset of human immunodeficiency virus–positive patients exhibit deficiencies in zinc and selenium that correlate with reduced host defense and higher rates of morbidity (Baum et al. 1995). Although these studies provide useful information, they are typical of human studies in which immune assessments are limited in scope. Nevertheless, there are a variety of conditions in which suboptimal intake of zinc affects human health and immune status. They deserve more extensive research, especially because zinc supplementation might reduce the impact of these diseases and conditions.


Although animal and mouse models have provided invaluable information on the impact of zinc deficiency on various facets of the immune system, they must be reinforced by human studies. There have been surprisingly few human nutritional studies in the 1990s that have had a strong immunological component. Recently, only a few nutritionists have included measurements of immune parameters in their studies. Given the growing evidence that the immune system can be a rapid and sensitive indicator of nutritional status, this appears to be an unfortunate change. In general, the field as a whole would be greatly strengthened by additional human nutritional studies that include international studies that would assess the impact of nutritional deficiencies on host defense systems through the use of modern immunological tools and approaches.
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Role of glucocorticoids in the alteration of immune defense for zinc and protein-calorie deficiencies

That suboptimal zinc might induce the chronic production of glucocorticoids (Gc), which would alter immune defense, was initially received with some skepticism. However, there are now >50 reports that show that both zinc deficiency and PCM activate the hypothalamus-pituitary-adrenocortical axis, causing the chronic production of Gc in both animals and humans (Alleyne and Young 1967, Becker 1983, DePasquale-Jardieu and Fraker 1979, 1980, Smith et al. 1981). Moreover, these early experiments that indicate a decline in zinc status caused significant changes in endocrine function were important in our current understanding of the secondary physiological changes created by zinc deficiency and of their impact on the immune system, especially lymphopoiesis (DePasquale-Jardieu and Fraker 1979, 1980). These endocrine changes also provide part of the basis for assigning a major role to apoptosis in the loss of precursor lymphocytes during zinc deficiency, as discussed.

Impact of zinc deficiency on the immune system: Mouse models

Studies of the effects of zinc deficiency on immunity have practical as well as theoretical values. To better understand the impact of a single nutritional deficiency on the immune system and to identify additional roles for zinc in immune function, neuroendocrine function, apoptosis and so on, several groups of researchers have investigated the impact of moderate and severe dietary deficiencies in zinc, using the young adult mouse as the paradigm. For three decades, the mouse has proved to be a highly reliable immunological model for humans (Janeway 1998). Our laboratory and others found that as little as 30 d of zinc deficiency reduced cell-mediated, DTH, tumor defense and antibody-mediated responses by ∼30–80% depending on the degree of deficiency (Fernandes et al. 1979, Fraker et al. 1993, Keen and Gershwin 1990). Challenging zinc-deficient mice with subacute levels of infectious agents such as Trypanosoma cruzi or nematodes resulted in death due to impaired defense (Fraker et al. 1982, Shi et al. 1998). Thus, the essentialness of zinc to the integrity of the immune system was made very clear by these studies!

Nevertheless, the rapid impact of zinc deficiency on the murine immune system was surprising. When body weight losses were 24 and 32%, researchers observed 50 to 80% losses in thymus weight and 40 to 80% losses in antibody-mediated responses and so on (Cook-Mills and Fraker 1993, Fraker et al. 1993). The losses in defense capacity closely correlated with losses in absolute numbers of peripheral lymphocytes and splenocytes. Thus, zinc-deficient mice with half the number of splenocytes produced about half the number of antibody-producing cells as normal mice (Cook-Mills and Fraker 1993, Fraker et al. 1993). Earlier studies indicated that on a per-cell basis, the residual splenocytes of zinc-deficient mice produced normal amounts of antibody and IL-2 and responded well to a battery of mitogens (Cook-Mills and Fraker 1993, Dowd et al. 1986). More recent work using zinc-deficient weanling mice, however, showed deficient production of IL-4, IL-5 and so on (Shi et al. 1998), although we noted no changes in the phenotypic distribution (composition) of the various subsets of T and B cells in the spleen (King and Fraker 1991, Shi et al. 1998). Collectively, these studies suggested that changes in the production of lymphocytes (lymphopoiesis) might be a seminal cause of lymphopenia that would in turn reduce cell- and antibody-mediated responses. However, there has never been an extensive study of the effects of a nutritional deficiency on lymphopoiesis or myelopoiesis.

Changes in lymphopoiesis created by zinc deficiency: emerging role for apoptosis

The removal of Gc from the system via adrenalectomy greatly reduced the lymphopenia and thymic atrophy and the loss of cells from the B-cell compartment of the marrow (DePasquale-Jardieu and Fraker 1980, Fraker et al. 1995). Adrenalectomies also protected the thymus from atrophy in PCM mice (Wing et al. 1988). This increased our suspicions that zinc deficiency was altering the production of lymphocytes. However, the fact that endogenously induced Gc might play a significant role in the demise of a segment of the immune system was not a popular concept with some colleagues, who preferred that everything be more directly linked to zinc-related functions. These results remained in the background until it became evident in the 1980s that Gc were a classic inducer of apoptosis in thymocytes or precursor T cells (Cohen and Duke 1984, 1992). Subsequently, it was also shown that in vitro deprivation of serum could induce apoptosis in thymocytes, which seemed to us to be a facsimile for zinc deficiency and PCM (Cohen and Duke 1992). Thus, it also seemed probable that the combination of suboptimal zinc and chronic elevation of Gc might be causing the apoptotic elimination of precursor B and T cells in the marrow and thymus that would lead to lymphopenia (Fraker et al. 1993).

However, no one had shown that the precursor B cells and other progenitor cells in the marrow were susceptible to Gc-mediated apoptosis because of the lack of available methodology. One could not hope to purify sufficient precursor B cells (8–14%) (Hardy et al. 1991) to evaluate for apoptosis using DNA gels (seminquantitative) or morphology (laborious). Fortunately, the flow cytometer can be used to readily quantify apoptotic cells in a population (Telford et al. 1994). By using multicolor flow cytometry with fluorescently labeled antibodies specific for progenitor and precursor B-cell markers along with a DNA dye, it was shown that precursor B cells were as prone to Gc-induced apoptosis as were thymocytes. Moreover, they responded intensely both in vitro and in vivo to levels of steroid analogous to those found in zinc deficiency and PCM (Garvy et al. 1993a and 1993b). It was subsequently shown that B cells from the bone marrow of human subjects were equally sensitive to these steroids, making the phenomenon

<table>
<thead>
<tr>
<th>Zinc deficiency</th>
<th>Protein-calorie malnutrition</th>
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<tr>
<td>Lymphopenia</td>
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<td>Thymic atrophy</td>
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<td>Antibody-mediated responses</td>
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<td>Cell-mediated responses</td>
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<td>Reduced defense against infections</td>
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<td>Chronic elevation of glucocorticoids</td>
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<td>Depressed appetite and PCM1</td>
<td>Low serum zinc</td>
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1 PCM, protein-calorie malnourished.

TABLE 3
Common immunological denominators for zinc deficiency and protein-calorie malnutrition among humans and higher animals

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After having this methodology in hand, the next step was to demonstrate that zinc deficiency rapidly depleted the B-cell compartment of the marrow (Fraker et al. 1995, King et al. 1995). Recent work showed that zinc deficiency caused a 50–70% decline in precursor B cells (B220\(^+\)CD43\(^+\)IgM\(^-\)IgD\(^-\)) with somewhat similar declines noted for immature B cells (B220\(^+\)IgM\(^-\)IgD\(^+\)) (King et al. 1995, Osati et al. 1998). Conversely, pro-B cells (B220\(^-\)CD43\(^+\)6C3\(^-\)) exhibited no change in their distribution, gradually becoming a greater proportion of the marrow as the compartment was depleted of precursor and immature B cells (Osati et al. 1998). Mature B cells (IgM\(^+\)IgD\(^-\)) were also fairly resistant to zinc deficiency. The explanation appears to be that pro-B cells, which are just beginning gene rearrangements and are not yet a problem or a threat, all express higher levels of bcl-2 than precursor B cells and thus are more protected against apoptosis created by zinc deficiency (Merino et al. 1994). When expressed at high levels, bcl-2 is a proto-oncogene that can block a variety of death cues (Mignotte and Vayssier 1998). Conversely, because precursor B cells have a >90% chance of generating nonsense clones and must be eliminated apoptotically (a few percent also became anti-self clones), their expression of bcl-2 is quite low (Merino et al. 1994). Mature B cells, on the other hand, which have made acceptable rearrangements, also express high levels of bcl-2. Thus, the pattern of survival of B cells during zinc deficiency paralleled bcl-2 expression and suggests that apoptosis is indeed a component of the zinc deficiency-induced depletion of the B-cell compartment. Nevertheless, because apoptotic cells are quickly phagocytosed, it has been difficult to directly prove that precursor T and B cells are eliminated apoptotically in the zinc-deficient mouse. Evidence provided by other laboratories indicate that zinc deficiency causes apoptosis in embryos and enhances DNA strand breaks in zinc-deficient infant rhesus monkeys (Olin et al. 1993, Rogers et al. 1995) and that calorie restriction can also enhance apoptosis (Luan et al. 1995). Apoptosis clearly plays a role in nutritional deficiencies that must be better understood.

Thus, it is becoming evident that zinc deficiency has a substantial and rather specific impact on the lymphocytic branch of the immune system. The rapid depletion of the marrow and the thymus of precursor T and B cells as zinc deficiency advances reduces the ability of the immune system to replenish the peripheral blood and secondary immune tissues with adequate numbers of lymphocytes. Thus, a significant factor in the thymic atrophy and lymphopenia that accompany zinc deficiency is an alteration in the production of lymphocytes and loss of precursor cells via an apoptotic mechanism. Therefore, a reduced ability to replenish the lymphocyte population by the primary tissues of the immune system is a key player in the observed lymphopenia that reduces host defense. The rapid and dramatic decline in the proportion of precursor T and B cells in the marrow and thymus is another clear example of the tight link of segments of the immune system to zinc status.

Potential resistance of myeloid cells

We noted that there was a ≥50% increase in the Mac-1-positive population in the marrow of zinc-deficient mice that would include cells of the myeloid series such as neutrophils, macrophages-monocytes, basophils, eosinophils and others (King et al. 1995). It is important to remember that these cells are the first line of defense, providing protection against most pathogens and malignant and aging cells. They are at work at all times and require the assistance of lymphocytes only if overwhelmed. Unlike precursor lymphocytes, the early myeloid cells appeared to survive during zinc deficiency (Fraker and King 1998). As the lymphocyte compartment became depleted, the neutrophil compartment increased by as much as 40% in the marrow of zinc-deficient mice, with even greater increases noted in the monocytic compartment (Fraker and King 1998). Interestingly, there is precedence for this. Human neutrophils exposed to Gc in vitro not only survived but also had an extended half-life (Liles et al. 1995, Meagher et al. 1996). Could this also occur in the zinc-deficient mouse? It would constitute another mode for conserving zinc because turnover of the neutrophils would be reduced. Moreover, immunologists have known for years that if they want to promote myelopoiesis in in vitro cultures, they need only add a small amount of corticosterone (Dexter et al. 1977). Thus, this important discovery will be further evaluated to determine the functional status of the granulocytes because a number of investigators noted deficits in the function of these cells in zinc deficiency and PCM (Chandra and Newberne 1977, Fraker et al. 1993, Hill et al. 1995, Vruwink et al. 1991, Wirth et al. 1989). Whether myeloid cells became more resistant to apoptosis or zinc deficiency is also important to understand. Surprisingly, several experiments indicate that the total or absolute number of nucleated cells remained normal in the marrow of both moderately and severely zinc-deficient mice (King et al. 1995, Osati et al. 1998). Thus, it was the composition of the marrow that changed as zinc became more limiting and chronic levels of Gc became more prevalent.

The question then arose as to whether this change in the composition of the marrow was also apparent in the peripheral immune system. Preliminary studies revealed a rather remarkable twofold to threefold increase in the proportion of neutrophils in the blood of both moderate and severe zinc deficiency. Thus, there is a clear dichotomy in the effects of suboptimal dietary zinc on lymphopoiesis versus myelopoiesis that is rather striking and may represent a purposeful regulatory change in response to zinc deficiency.

A working hypothesis emerges from these findings. As zinc becomes limiting, choices have to be made. Collectively, the marrow may be the largest tissue of the body. Regardless of the substantial amounts of zinc are needed to produce billions of lymphocytes each day. They are the second line of defense and often live and die without being gainfully used in an immune response. This and the >90% error rate in their production (Tarlinton 1994) make them nutritionally expensive to maintain. As zinc deficiency advances, it seems that lymphopoiesis is put on the chopping block to be reduced in part by Gc-mediated apoptotic mechanisms. Conversely, myelopoiesis survives at least for a time, perhaps to provide some basic or minimal immune protection.

Role of zinc status in cell survival and death

Beyond its ability to induce the chronic production of Gc, suboptimal zinc itself should also affect the integrity of the immune system because of the many critical roles zinc plays in cell function (Chester 1997). For example, zinc is critical to the function of >100 enzymes and an equal number of zinc finger–dependent transcription factors (Hallock & Vallee 1993, Vallee and Falchuk 1993). Some investigators also argue that zinc is key to membrane integrity, although specific roles remain to be identified (Bettiger and Odell 1993). The same can be said for the nucleus and for chromatin, which are thought to have high concentrations of zinc (Chester 1997). It is evident from the work of Chester and others that zinc is very...
Apoptosis begins with a death signal, which could be a change in the activity of an enzyme like protein kinase C or binding of Gc to the Gc receptor with translocation to the nucleus and the induction of death genes (Schwartzman and Cidlowski 1993) (Fig. 1). In the case of the pathway used by steroids and γ-irradiation (and, we believe, zinc), the expression of bcl-2/bax is a checkpoint in the pathway (Chao and Korsmeyer 1998, Ucker 1997). As discussed earlier, high expression of bcl-2 generally provides enhanced protection, whereas low levels lead to cell death (Chao and Korsmeyer 1998, Ucker 1997, Webb et al. 1997). Thus, it is important to identify substances that can modulate apoptosis, and zinc may be such a candidate. Moreover, it is our belief that apoptosis plays important roles in the changes in embryogenesis, reproduction capacity, growth and immune integrity brought about by nutritional deficiencies; these must be given greater consideration, and a better understanding of the interplay between zinc and apoptosis is critical.

A number of laboratories have shown that very high concentrations of zinc (500–1000 μmol/L) inhibited apoptosis in a variety of cells, cell lines and so on and suggested that these inhibited endonuclease activity (Cohen and Duke 1984, Telford and Fraker 1997). However, it was suspected that zinc could inhibit other sites in the death pathway. Indeed, zinc also binds to the vicinal cysteines in the ligand binding region of the Gc receptor, thereby blocking the binding of steroid both in vivo and in vitro (Telford and Fraker 1997). Thus, zinc could block the death signal itself in such cases. However, high levels of zinc are potentially toxic. Concerned that such high levels of zinc could have toxic effects at later time points, we examined the survivors of dexamethasone (Dex)-treated cultures that were presumably "protected" by zinc (700 μmol/L). It was found that cells thought to be protected from apoptosis by these high levels of zinc "survived" for only a short period of time, with ~90% being dead in a few hours (Fraker and Telford 1997). After a 6-h exposure to 1 μmol/L Dex, thymocytes exhibited 61% apoptosis, which was held to background levels of 16% by high concentrations of zinc "survived" only for a short period of time, with ~90% being dead in a few hours (Fraker and Telford 1997). After a 6-h exposure to 1 μmol/L Dex, thymocytes exhibited 61% apoptosis, which was held to background levels of 16% by both high zinc and the Gc antagonist RU38486 (Fraker and Telford 1997). The cells were then washed free of all reagents, recounted and placed into regular RPMI 1640 with 5% fetal bovine serum. At 16 h after exposure to Dex, cells treated with Dex alone or Dex plus RU38486 exhibited a viability of ~64% (Fraker and Telford 1997). However, in Dex-treated cultures, the cells "protected" by high zinc exhibited ~5% survivors, with 95% of the cells being in an apoptotic state. As an extra check, 700 μmol/L Zn was added again at the 6-h mark to untreated cells, and the Dex plus-zinc–treated cells with losses of >80% were still noted at 16 h with no viable survivors. Thus, we found that the high concentrations of zinc (700 μmol/L) used by previous investigators did not provide long-term protection of cells.
Ability of zinc to induce apoptosis

Because of the above finding, a series of experiments was begun to determine whether more physiological levels of zinc could affect apoptosis, taking advantage of the precision of flow cytometric methods for quantification of cell death (Telford et al. 1994). To our surprise, zinc salts at 80–200 μmol/L added exogenously to standard RPMI 1640 cultures for 8 h could induce 30–40% apoptosis in thymocytes (1 μmol/L corticosterone = 60% apoptosis) (Telford and Fraker 1995). Cell cycle profiles, DNA gels and phase contrast morphology all indicated that zinc had induced a classic form of apoptosis. Moreover, the most sensitive population was the CD4\(^+\)CD8\(^-\)TCR\(^h\)CD3\(^+\) precursor T cells (47% apoptotic), where mature CD4\(^+\)CD8\(^-\) and CD4\(^-\)CD8\(^+\), which express higher levels of bcl-2, exhibited little apoptosis beyond background levels (Telford and Fraker 1995). Copper, iron and nickel did not induce apoptosis, but gold, cadmium and selenium induced necrosis. Splenic B cells (IgM\(^+\)) also responded to zinc-induced apoptosis, as did marrow B cells, with ~25% apoptosis observed for each population (Telford and Fraker 1998). Because these concentrations of zinc were still high, we wanted to determine the actual intracellular levels of zinc. Atomic absorption indicated that 6–7 ng Zn/10\(^9\) cells was all that was entering the cell in a typical 8-h experiment (1–1.5 μg Zn/10\(^9\) in control cells) (Fraker and Telford 1997, Telford and Fraker 1995, 1998). These concentrations are more within the realm of physiological relevance, given recent evidence that metallothionein can donate zinc to surrounding proteins (Maret and Vallee 1998), along with growing evidence that there may be pools of intracellular zinc that could provide a flux of zinc (Palminter et al. 1996).

Future studies of modulation of cell death by zinc could lead to the identification of important new roles for zinc. Clearly, small changes in cellular zinc may play a role in the loss of precursor cells in the immune system. Perhaps suboptimal zinc and the chronic production of Gc act in synergy to heighten levels of apoptosis in precursor T and B cells as zinc deficiency advances, thereby causing lymphopenia, as discussed earlier. Likewise, cells under stress or cells in a dysregulated or an aging system may experience fluxes in zinc that might promote apoptosis.

Impact of zinc supplementation on immune integrity

The evidence that adequate zinc nutriture is of paramount importance to a properly functioning immune system is now substantial, yet there is little evidence of any ongoing effort to further explore the efficacy of zinc supplementation on the immune integrity of young pregnant women, the aged or those with any of the many diseases just discussed in which malnutrition and wasting are components. However, studies from Sazawal et al. (1988) clearly show that zinc supplementation significantly reduces diarrhea and the incidence of infection in children in developing nations (Table 4). Infants with marasmus showed weight gains and increased host defense responses after 60 d of supplementation with 2 mg zinc (kg/d) (Castillo-Duran et al. 1987). Seventy-year-olds supplemented with zinc for 1 mo had improved DTH. Despite these and other dramatic successes, the efficacy of zinc supplementation in reducing the impact of diseases and disease states is not being given the priority that it deserves.

However, the public has readily accepted the premise that zinc supplementation can prevent or at the least shorten the duration of colds. A subset of the public apparently has been purchasing and taking so-called zinc cold lozenges, despite the fact that the science that supports the efficacy of this use of zinc is problematic at best. One wonders what the public response would be if they were aware that zinc supplementation is on record as having had a positive impact on persons with AIDS, aging, sickle cell anemia, burn patients, elderly persons and children with diarrhea. One worries that if physicians, nutritionists and immunologists do not begin to lead the way on these important health issues, they will be forced to follow the public and the nutritional supplement industry.

Important areas of need

The need to address the value of supplementation of zinc and other nutrients on chronic diseases is evident and long overdue for greater attention. Although animal models can contribute valuable information in this area as well, it is clear that human studies are of paramount importance. It is much preferable that such studies be performed by competent professionals under properly controlled conditions. In the absence of professionally supervised studies, the “experiments” will be done by the public in conjunction with the nutritional supplement industry. The public’s interest in nutritional, herbal and holistic alternatives to drugs is keen and should be duly noted by all of us.

With regard to the interactions between the immune system and nutrients such as zinc, the surface has been barely scratched. Most of the immunological studies performed to date have centered around the peripheral immune system. We know little about the effect of zinc deficiency and the use of zinc supplements on the mucosal immune system. Changes in gut immunology created by malnutrition no doubt contributed to the ongoing high mortality rates of children in developing nations created by infections with Escherichia coli, Salmonella, dysentery, cholera and others that create havoc in the intestine. Also, few details are known about the impact of nutritional status on pulmonary immunology and the resulting incidence of pneumonia, bronchitis, allergy or tuberculosis. We know little about the relationship of nutritional status to the acute phase response regardless of whether one considers its protective or inflammatory mode. How does suboptimal nutriture affect the fetal-neonatal immune system, and how readily is repair of immune integrity manifested when dietary status is improved? Is there a subset of elderly persons who would truly benefit from zinc supplementation, and how do we identify them? We also know little about the impact of marginal zinc status on viral or cancer defense systems. Supple-

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**TABLE 4**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Zinc supplement</th>
<th>Immune parameter(s)</th>
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<tbody>
<tr>
<td>6–35 month old(^1) infants in India</td>
<td>10 mg/d</td>
<td>Lower respiratory infections were reduced 45%</td>
</tr>
<tr>
<td>32 infants(^2), &lt;80% of normal weight</td>
<td>6 m</td>
<td>Doubled responders to DTH(^4)</td>
</tr>
<tr>
<td>Elderly &gt;70 years(^3), 15 subjects</td>
<td>440 mg zinc</td>
<td>Improved numbers of T-cells</td>
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<td></td>
<td>One month</td>
<td>Improved DTH (2X)</td>
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<tr>
<td></td>
<td></td>
<td>Improved tetanus response</td>
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</tbody>
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1 Sazawal et al. 1998.
4 DTH, delayed type hypersensitivity.
mentation with zinc might reduce the impact of these diseases and conditions.

Clearly, the mouse model shows that zinc is essential to lymphopoiesis and that when zinc is suboptimal, there is significant depletion of precursor lymphoid cells from the primary tissues of the immune system. The dramatic effect of zinc deficiency on marrow function is another indication of the dynamic link between immune status and zinc status. This is no doubt an underlying cause of the lymphopenia, thymic atrophy and reduced cell- and antibody-mediated responses associated with zinc deficiency. This could well be the case for PCM and other nutritional deficits and thus provides a path for others. Moreover, subsets of developing B cells in the marrow varied in sensitivity to zinc deficiency, with those expressing high levels of bcl-2 being the most resistant. This, along with other data, strongly suggests that apoptosis is one of the seminal causes of these losses. No doubt apoptosis plays a role in many of the physiological changes created by zinc deficiency. Consequently, apoptosis in the marrow, in particular neutrophils and monocytes, exhibited substantial resistance to zinc deficiency. This is an incredible dichotomy in the effects of zinc deficiency on regulation within the marrow and is the first study to demonstrate the impact of a nutritional deficiency on marrow function. Understanding the nature of the changes in marrow function created by zinc deficiency opens the way for therapeutic intervention.

Studies also now exist that demonstrate that changes in zinc status can modulate apoptosis, providing new roles for zinc. Fluxes of zinc in the cell; synergy between zinc and Gα; and dysregulation of cellular zinc during stress, aging, autoimmune disease, ischemia, Alzheimer’s disease and others may therefore affect cell survival. Demonstration of the ability of zinc to modulate cell survival would, we hope, prompt other nutritionists to also examine the role apoptosis may play in altered growth, development, reproduction and senescence during deficiency states.

LITERATURE CITED


