Adverse effects of nutritional inadequacy and excess: a hormetic model[1–4]

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ABSTRACT

I address and explain the increased risk of adverse effects from nutrients by using the paradigm of hormesis, the biological and toxicological concept that small quantities have opposite effects from large quantities. To provide necessary background, I categorize, depict, discuss, and contrast hormetic and other dose-response relations. I review some of the different hormetic mechanisms that others have proposed. I then use the hormetic paradigm to explain adverse effects from essential nutrients, including vitamin D. The hormesis paradigm could be useful to nutritional scientists in their consideration of nutritional adverse effects. *Am J Clin Nutr* 2008;88(suppl):578S–81S.

INTRODUCTION

Nutritional scientists might find it useful to consider the concept of hormesis, the paradigm that small quantities can have the opposite effects of large quantities, for explaining many paradoxical effects in nutrition and for formulating nutrition guidelines. According to the hormesis concept, as an investigator reduces the dose of an agent being studied, the response being measured does not necessarily become smaller and smaller, drifting into background noise; instead, the response can actually reverse course and become larger and larger (1).

Hormesis proponents believe that hormesis commonly occurs in both biological and toxicological settings. Hormesis appears to hold for biological model tested, endpoint measured, and chemical class or physical agent used. Everyday examples of hormesis abound. For example, moderate amounts of exercise promote good health, but excessive amounts are debilitating (2, 3). In molecular pharmacology, research has shown that many chemicals have opposite effects at low versus high dosages; for example, the antibiotics penicillin, erythromycin, and streptomycin promote bacterial growth at low doses and have contrary effects at higher doses (4). Investigators have long recognized that mild forms of stress can promote mental and physical function, whereas extreme stress is more likely to cause mental anguish and physical ailments; this is known as the Yerkes-Dodson Law in experimental psychology, which the authors initially formulated in 1908 (5). In stating that "all things are poison and not without poison; only the dose makes a thing not a poison," Paracelsus (the supposed model for Goethe's Dr Faustus) recognized in 1538 that in medicine, the efficacy of toxic chemicals depends on their dosage (6).

According to the Arndt-Schulz Law, which Hugo Schulz formulated more than a century ago, toxic chemicals with inhibitory or lethal effects at high doses have stimulatory and beneficial effects at low doses; thus, low, intermediate, and high doses of the same drug can have different effects (7). Researchers have noted that low doses of vitamin D have stimulatory effects that promote epidermal wound healing (8). In contrast, high doses of vitamin D have inhibitory effects that are useful in treating psoriasis (9). These strong examples of the hormetic effect are in accordance with the Arndt-Schulz Law (10). In the remainder of this review, I address the following topics: hormetic and other dose-response relations, proposed hormetic mechanisms, using the hormetic paradigm to explain the adverse effects of essential nutrients, vitamin D's ability to alleviate DNA damage, and the role of hormesis in nutritional research, particularly in explaining adverse nutritional effects.

HORMESIS: DEFINITION AND DOSE-RESPONSE

The definition of hormesis that I use is adaptive, nonmonotonic, biphasic, dose-response relations characterized by small quantities having opposite effects from large quantities; that is, small doses elicit opposite responses to those of high doses. Note that this definition deliberately avoids the potentially vexing issue of beneficial versus harmful effects, which requires a more detailed evaluation of the biological and ecological response content.

Some representative dose-response forms are provided in **Figure 1**. Researchers usually characterize dose-response relations by using either the threshold model (Figure 1a) or the linear, nonthreshold model (Figure 1b). The most commonly accepted dose-response model in toxicology and pharmacology is the threshold model. This model assumes that dose has no effect until a threshold is reached, at which point response increases linearly with dose.

According to the linear, nonthreshold model, response is directly proportional to dose without any threshold so that some level of response is always present, even at the lowest possible

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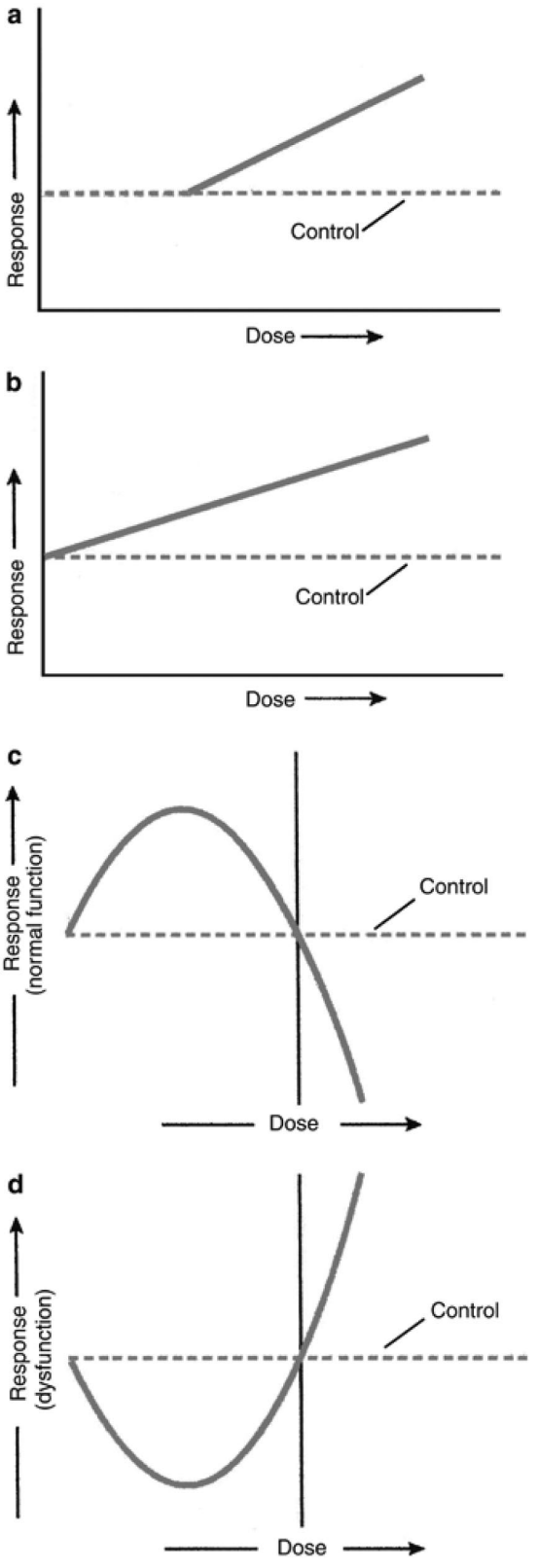

FIGURE 1. Stylized curves for some representative dose-response relations: (a) the threshold model, (b) the linear, nonthreshold model, (c) the inverted U-shaped hormetic model depicting low-dose enhancement and high-dose reduction of normal function effects, and (d) the J-shaped hormetic model depicting low-dose reduction and high-dose enhancement of adverse dysfunction effects. Reprinted with permission from the *European Journal of Clinical Nutrition* (1).

dose level. The linear, nonthreshold model has become the standard model for assessing the health risks of chemical carcinogens and radiation for regulatory agencies in many countries; however, for noncarcinogens, the same regulatory agencies typically make the opposite assumption: that a threshold dose exists and no health risks are associated with doses that are lower than this threshold.

Researchers often depict hormetic dose-responses by using inverted U-shaped curves (Figure 1c) for normal function to show the enhancement associated with low doses when one would expect a reduction (such as for growth, fecundity, longevity, and cognitive function). They use J-shaped curves (Figure 1d) and allied U-shaped curves to show reductions associated with low doses when one would expect enhancements (such as for dysfunction, including carcinogenesis, mutagenesis, and disease incidence). Hormesis not only challenges the threshold and linear, nonthreshold models, which postulate only quantitative changes with decreased dosage, but also, more importantly, suggests that as the dose decreases, not only quantitative changes but also qualitative changes occur in measured responses in contrast with both control (background) and high doses.

The hypothetical dose-response relations that contribute to a postulated hormetic effect, in this case a U-shaped dose-response curve, are depicted in **Figure 2**, which is adapted from a major toxicological reference (11). High doses produce a postulated

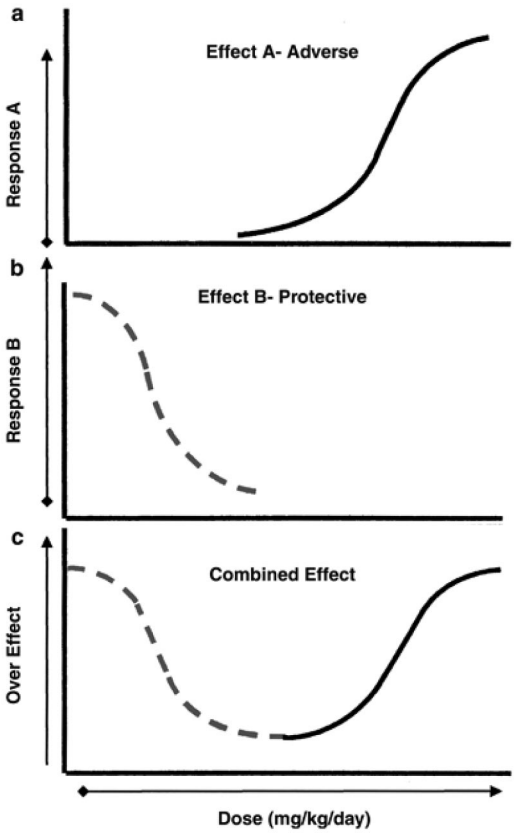

FIGURE 2. Hypothetical dose-response relations depicting hormesis characteristics with dose denominated ($mg \cdot kg^{-1} \cdot d^{-1}$): (a) high doses produce a postulated adverse response, (b) low doses produce a postulated protective response, and (c) the combined effect curve showing a hormetic U-shaped dose response. Reprinted with permission from the *European Journal of Clinical Nutrition* (1).

response labeled "adverse" in Figure 2a, whereas low doses produce a postulated response labeled "protective" in Figure 2b. The "combined effect" curve (Figure 2c) shows a hormetic U-shaped dose-response.

Investigators have reported hormetic-like biphasic dose-concentration responses for numerous endogenous agonists (12) and inorganic (13) and chemotherapeutic agents (14). Some have reported biphasic dose responses in human tumor cell lines (15) and in immunologic studies (16) in response to a wide variety of agents. If one defines stimulation as a response opposite to that observed at higher doses, the maximum stimulatory responses are typically only ≈30–60% greater than those of concurrent controls. Their widths are also modest and typically extend only over a 20-fold dose range (ie, 1/20) or less immediately below the no observed adverse level (NOEL), the highest dose whose effect does not differ in a statistically significant manner from its control (17). In summary, hormetic responses are typically quite modest in both magnitude and width. In addition, researchers have revealed the detected biphasic dose-response relations to be quite common and broadly generalizable; that is, such responses do not appear to be restricted to the biological model, measured endpoint, or agent, and they appear to represent a basic feature of biological response to chemical and physical adversity.

PROPOSED MECHANISMS OF HORMESIS

Researchers have proposed 2 general explanations of hormetic effects. The first is based on the hormetic stress response, or the actions in response to low-intensity stress (the stressor) that, in a living system, initiates a series of countering mechanisms to ensure homeostasis (the maintenance of a constant internal state to ensure efficient functioning and performance). The hormetic stress response is a broad biological strategy, and specific mechanisms unique to each system are simply biological tactics to ensure homeostasis. The specific stress response mechanisms that researchers have proposed to explain hormetic effects include expression of stress response proteins [eg, glucose-regulated proteins and heat-shock proteins (18) that bind to other proteins and thereby protect proteins from damage], elimination of damaged proteins that cannot otherwise be repaired, induction of DNA repair molecules, alteration of chromatin structure to facilitate repair, induction of tolerance toward the same toxin or unrelated toxins, induction of detoxification enzymes, and antioxidative response (19, 20). Hormetic stress response in the form of stress response proteins has been found in laboratory animal studies where dietary restrictions produced anti-aging and life-prolonging effects as well as reductions in neurodegenerative disorders (1).

According to the 2-receptor explanation of hormetic effects, 2 different receptors exist: small numbers of high-affinity receptors and large numbers of low-affinity receptors. Proponents of this perspective argue that the high-affinity receptors are activated at low doses, whereas low-affinity receptors are activated at high doses; the 2 receptors then have different downstream effects. The resulting dose-response morphology takes the form of an inverted U or an upright J or U (as shown in Figure 2).

HORMETIC RESPONSES TO NUTRITIONAL INADEQUACY AND EXCESS

The following review describes the hormetic effects of essential nutrients (vitamins and minerals). Although I do not discuss them, others have described hormetic effects in response to different kinds of adverse circumstances [dietary restriction, alcohol (ethanol), synthetic and natural dietary pesticides (including dichlorodiphenyltrichloroethane), dioxin (including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin), and acrylamide] elsewhere. A recent review has also addressed these hormetic effects (1).

As has been well documented, deprivation levels of nutrients produce adverse effects such as loss of function or overt disease, and excessive levels of some nutrients also lead to adverse effects such as hypervitaminosis, tissue mineralization, and electrolyte imbalance. The 17th edition of *The Merck Manual of Diagnosis and Therapy* (21) describes these effects and discusses and contrasts deficiencies, dependencies, and toxicities of vitamins D, A, E, K, and B-6 and deficiencies and toxicities of 6 macrominerals and 5 microminerals. The dose-response morphology and relations of essential vitamin or mineral nutrients as adapted from a major toxicological reference is depicted in **Figure 3** (11). This figure is conceptually similar to the hypothetical dose-response relation in Figure 2. Many additional examples of essential trace elements producing U-shaped dose-responses on physiologic functioning—ranging from impairment at deficient intakes to optimal functioning at intermediate intakes and toxicity at excessive intakes—have also been given (22).

Nutritional effects on DNA damage may also provide examples of hormesis. Researchers commonly accept DNA double-strand chromosomal breakage as a mechanistic surrogate for carcinogenesis and a major risk factor for cancer. Deficiencies in some vitamins and minerals can mimic radiation-induced chromosomal damage by producing DNA single- and double-strand breaks, oxidative lesions, or both. Vitamin D in vivo in rodent models and in cell culture models prevents endogenously or exogenously induced double-strand breaks, induces apoptosis in most cancer cells, and stabilizes chromosomal structure (23). Investigators have reported that deficiencies of certain vitamins [folate (folic acid), vitamin B-6, vitamin B-12, vitamin C, vitamin E, and niacin] and minerals (iron, selenium, and zinc) appear to mimic DNA damage from radiation (and certain chemicals)

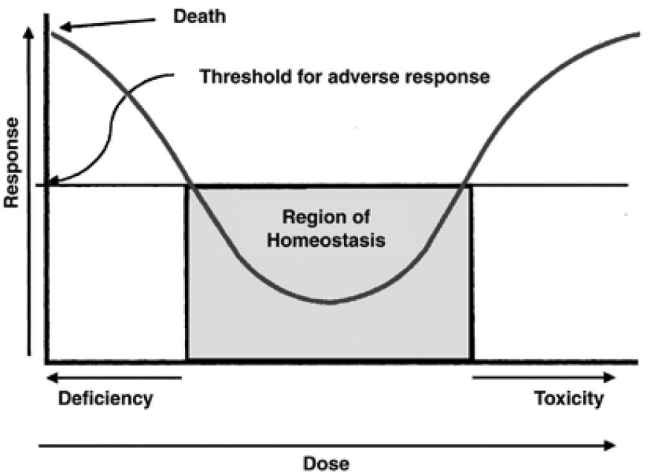

FIGURE 3. Dose-response relations for essential vitamin or mineral nutrients. The U-shaped hormetic response is shown with a region of homeostasis (the dose range with neither deficiency nor toxicity) that lies below the threshold for adverse response and is contiguous with both the low-dose deficiency region (whose base is death) and the high-dose toxicity region. Reprinted with permission from the *European Journal of Clinical Nutrition* (1).

(24). In addition to suggesting that these deficiencies cause many of the same types of qualitative damage as radiation, these deficiencies are suggested to play a more important role in DNA damage compared with radiation quantitatively by orders of magnitude (25). To date, the most complete comparison of radiation-induced and nutrient deficiency-induced DNA damage focused on folate. Laboratory studies of normal human T-lymphocytes in primary culture showed that physiologic concentrations of folate of 12 nmol/L caused more consolidated DNA damage (double- and single-strand breaks) than did radiation doses 100 times higher than the current annual public radiation dose limit (26). Some have also suggested that folate deficiency can synergistically increase cellular radiation sensitivity (27).

SUMMARY AND CONCLUSIONS

In this article, I have discussed the biological and toxicological concept known as hormesis—the idea that small quantities have opposite effects from large quantities. This review showed that hormesis accounts for the adverse effects of excesses and deficiencies of essential nutrients (vitamins and minerals). Note that these hormetic effects are relatively modest, their effects can be double-edged (ie, reduced doses do not necessarily produce subjectively positive effects), and different hormetic endpoints can display either subjectively salutary or deleterious effects at the same dose. Nevertheless, the hormesis paradigm might be able to explain many paradoxical effects, including adverse effects in nutrition and allied fields.

Most of the available evidence is based on in vitro and animal studies. Thus, we need studies in humans to confirm that the hormetic model applies to situations outside the laboratory. In closing, nutritionists might find it useful to be aware of the possible role of hormesis in their research.

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