



**Sylvia R. Karasu M.D.**  
The Gravity of Weight

# The Scientific Coming of Age of an Old Concept: Hormesis

When a small dose has the power to heal

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Winslow Homer's "Snap the Whip," 1872, one of Homer's favorites. Parents should not overprotect children from the small stresses of life. There can be a "blessing in a skinned knee."  
Source: Metropolitan Museum of Art, Public Domain

"If parents rush in to rescue them from distress, children don't get an opportunity to learn that they can suffer and recover on their own," writes Wendy Mogel in her book aptly titled, *The Blessing of a Skinned Knee*. (2001) She continues, "Parents need to prepare children for rough conditions by teaching them to tolerate some stresses and extremes." Mogel's sentiment is similar to Friedrich Nietzsche's 1888 motto, "...even in a wound there is power to heal...vigor grows through a wound" (*Preface to Twilight of the Idols*) and his more commonly quoted maxim, "What does not destroy me makes me stronger." (*Maxims and Arrows*, from *Twilight of the Idols*) Exposure to some degree of stress, (i.e., a disturbance of homeostasis) with which a child or adult can cope successfully, is a

mark of resilience. (For a more thorough discussion of stress, see my previous blog, *The Obliterative, Dislocating Effects of Stress*, <https://bit.ly/2C7UeWO>.)



Paracelsus, alchemist and physician born in 1493, who believed that alchemy was meant to be used to prepare medications.  
Source: Wellcome Trust Images, Public Domain

Quantifying exposure involves the concept of dose and has been described throughout history. The ancient Greeks wrote "Nothing in Excess" on the Temple of Apollo at Delphi. (Tsatsakis et al, *Toxicology Reports*, 2018), and the 16th-century alchemist and physician Paracelsus famously wrote, "All things are poison, and nothing is without poison; only the dose makes a thing not a poison." (quoted in Gohlke and Allison, *Obesity*, 2013; Pai-Dhungat and Parikh, *Journal of the Association of Physicians of India*, 2015). It was, though, mid-19th century physiologist Claude Bernard who first wrote of dose response. (Tsaksakis et al, 2018)

Later in the 19th century, professor of pharmacology Hugo Schulz, working with yeast, noted that about a dozen disinfectants seemed to stimulate the yeast at low concentrations while inhibiting its metabolism at higher concentrations. (Calabrese, *Mutation Research*, 2002; Calabrese, *International Journal of Molecular Sciences*, 2018) Schulz interpreted this biphasic response to be the "explanatory principle" of homeopathy. (Calabrese, *Microbial Cell*, 2014.)

Homeopathy is a branch of study, first proposed by physician Samuel Hahnemann (1755-1843), whose main tenets are "like cures like" and substances are able to retain their biological effectiveness even after

substantial repetitive dilutions. (Ernst, *British Journal of Clinical Pharmacology*, 2002) Now considered a pseudoscience with results no better than placebo, it was immensely controversial and a major threat to traditional medicine then. (Ernst, 2002) Schulz, by identifying his biphasic response with homeopathy, made a career-ending mistake. He became completely discredited and marginalized by his medical colleagues, and with it, his discovery. (Calabrese, 2014) For decades, researchers and clinicians accepted that drug dose followed a linear pattern, "generating enormous ignorance in the knowledge of responses in the low-dose range." (Bhakta-Guha and Efferth, *Pharmaceuticals*, 2015)



Samuel Hahnemann, physician and founder of Homeopathy, now considered a pseudoscience with results no better than placebo. This bronze statue by Charles Henry Niehaus, was dedicated in 1900 and is a memorial to him at Scott Circle, Washington, DC.

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Not until researcher Charles Southam, working on a thesis on forestry (1941) was the concept of what came to be called a *dose-response curve* resurrected. Southam, who later became a physician, studied the effects of an extract from the Western red cedar tree on invasive fungi. He found that a hot water extract from this tree was toxic to the fungi, but after several dilutions (i.e., a very low concentration), this same extract actually stimulated the fungi's growth. His original thesis, in which he first used the term *hormesis*, from the ancient Greek, *eagerness, urge, set in motion*, (Tsatsakis et al, 2018) is available on the internet (see Stone et al, *Dose Response*, 2018 for the link) and more easily available than the paper he published with John Ehrlich in the journal *Phytopathology* in 1943. (Still awaiting interlibrary loan!)

The concept of hormesis had a "resurgence" in the 1980s when the Environmental Protection Agency (EPA) and other regulatory agencies became interested in estimating cancer risks and used hormesis to question, after toxic contamination, "How clean is clean?" (Calabrese, 2002)

Though some researchers maintain that there is not a clear definition of hormesis (Mushak, *Science of the Total Environment*, 2013; Tsatsakis et al, 2018), most accept that it "defines a two-phase dose-response relationship" in which low doses stimulate a beneficial effect and high doses have an inhibitory or toxic effect. (Zimmermann et al, *Microbial Cell*, 2014) But not all agree that low-dose stimulation

necessarily is a beneficial effect and "stimulation should not be conflated with benefit." (Mushak, 2013) For example, when bacteria are treated with a "sub-lethal" dose of antibiotics, they can develop "a surge of resistant populations." (Zimmermann et al, 2014)



"The Dance of Death: the Apothecary," colored aquatint by Thomas Rowlandson, 1816. 'I have a secret to cure each malady...'

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Hormesis, in general, though, is considered a *eustress*--good stress--and can be applied not just to toxins, but to other disruptions of homeostasis, including those from chemical, thermal, and radiological stresses. (Murugaiyah and Mattson, *Neurochemistry International*, 2015; Gems and Partridge, *Cell Metabolism*, 2008) For example, it reflects the *acquired resilience* (analogous to the concept of *acquired immunity*) (Stone et al 2018) that develops with low doses of sunlight, phytochemicals, exercise, and caloric restriction with adequate nutrition, i.e., "the stresses of everyday life" (as differentiated from very high doses of these same stresses that are toxic.) It may even help to explain the so-called *hygiene hypothesis*, namely that allergies and asthma are more common today because children are initially

less exposed to some pathogens. (Gems and Partridge, 2008) Hormesis creates a typical U-shaped or J-shaped (or an inverted U-or J-shaped) dose-response curve (Stone et al, 2018), sometimes referred to as a bimodal or bidirectional curve.

This dose-response relationship of hormesis has been called "the most important aspect in toxicology" and its being ignored for so many years a "historical blind spot in toxicology." (Calabrese, *EMBO Reports*, 2004) But since it has "widespread and significant implications" for drug development and resistance to disease, it has finally "come of age scientifically." (Calabrese, 2018) For example, many medications, including those used to treat anxiety, epilepsy, and Alzheimer's Disease, display hormetic features. (Calabrese, 2018) So does our body's cortisol production: there are biphasic effects of our glucocorticoids, including a role in enhancing synaptic function and adaptive plasticity (e.g. mediating dendritic remodeling.) (McEwen, *Chronic Stress*, 2019)

The most predictable aspect of hormesis is that its low-dose stimulatory effects are "typically modest," but the response is independent of the biological model, endpoint, or inducing agent. (Calabrese, 2018) Because of the modest response, hormesis may not be detected or may be difficult to replicate and detecting it depends on the quality of the research design, number of doses/concentration, the dose-spacing when administering the low



The largest known Western Red Cedar. It was on an extract of the Western Red Cedar that Southam experimented on fungi and found low-dose stimulation and high dose inhibition, the pattern he called "hormesis." Photo by Wsiegmund. Source: Wikipedia Commons/GNU Free Documentation License, Creative Commons, Attribution-Share Alike 3.0 Unported

dose, and the statistical power of the study. (Calabrese and Mattson, *Nature Partner Journals*, 2017) Further, there are multiple types of dosing, including the exposure dose, the absorbed dose, the administered dose, and the biologically effective dose. (Tsatsakis et al, 2018)

*Bottom line:* The dose-response curve of hormesis, reflective of beneficial low-dose stimulation and high-dose inhibition (i.e., toxicity), was often overlooked or ignored for years because of its initial association with the pseudoscience of homeopathy. Though research involving a diluted extract from a tree and its effect on invasive fungi in the early 1940s renewed interest in the phenomenon of a dose-response, it was not until the 1980s, in the context of environmental pollutants, that hormesis became widely studied. Today there are literally thousands of examples of hormesis. The concept can even have relevance to child-rearing: allowing children to experience a little stress, such as a skinned knee, can enable them to withstand exposure to much greater stresses in life. Sometimes vigor does grow through a wound and a small dose has the power to heal.



A patient suffering the adverse effects of arsenic treatment. Colored lithograph, ca. 1850. Sometimes a very small dose of a substance can be therapeutic whereas a large dose can be toxic. Credit: James Morison. Source: Wellcome Trust Images/Public Domain



Drug jar for mercury pills, Italy, 1731-1770. Years ago, mercury was used to treat syphilis, but clearly in high doses it is quite toxic. Source: Wellcome Trust Images, Science Museum, London.

## About the Author



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