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Update on hormesis and its relation to homeopathy

Menachem Oberbaum[1,*] and Cornelius Gropp[2]

[1]*The Center for Integrative Complementary Medicine, Shaare Zedek Medical Center, Jerusalem, Israel*
[2]*Psychiatric Service, Shaare Zedek Medical Center, Jerusalem, Israel*

Introduction: **Hormesis is a dose–response relationship characterized by a biphasic dose response to stressors with a low dose stimulation and a high dose inhibition. The first systematic description of hormesis appeared toward the close of the 18th century by the German pharmacology professor Hugo Schulz. The stressor agent can be any agent or factor capable of causing a deleterious effect. The biological systems can be diverse: bacteria, fungi, algae, yeasts, animals, humans, protozoa and plants. The range of endpoints covers longevity, reproduction, cancer, survival, growth, metabolic effects and others. Hormesis is a nonspecific phenomenon, which can occur in any biological system and can be caused by any stressor. It is quantifiable and reproducible. The apparent similarity between the basic principle of hormesis and homeopathy's Similia Principle, together with the homeopathic claim that hormesis validates homeopathy caused its marginalization, and its rejection during the past century by central figures in pharmacology. Recent years have seen a slight renaissance in the conventional scientific attitude towards hormesis.**
Method: **We compared hormesis and homeopathy.**
Result: **There is no convincing evidence of similarity between these two systems. Moreover, there are several crucial differences between them, which seem to refute any idea that they stem from the same root. This paper discusses these differences. The rejection of hormesis on grounds of its similarity to homeopathy is unjustified.**
Conclusion: **The authors suggest exploring the differences between both systems. Such exploration may answer the key question of whether they do indeed share a root or embrace the same principles. Such exploration may also spur research within both systems to answer further open questions.** *Homeopathy* (2015) **104**, 227–233.

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Introduction

The accepted definition of hormesis is divided into two parts: a substance or another stressor agent which, on one hand, causes noxious activity in a biological system when applied in high concentration and, on the other, may reveal an enhancing activity when applied in low concentrations/quantities/doses. The stressor agent can be chemical (heavy metals, trace elements insecticides, pesticides, etc.), physical (electrical, mechanical, heat, cold, etc.), biological (bacterial, viral, etc.) — basically any agent or factor able to cause a deleterious effect. The biological systems can be manifold: bacteria, fungi, algae, yeasts, animals, humans, protozoa and plants.[1] The range of endpoints includes longevity, reproduction, cancer, survival, growth, metabolic effects and others.[2,3] This phenomenon is nonspecific, can occur in any biological system and can be caused by any stressor. It is quantifiable and reproducible. This is the reason that hormesis is recognized as a phenomenon which appears in any area of life.

Historical aspects

As early as the mid-18th century, there were anecdotal reports of the stimulatory effect of low doses of noxious substances.[2] The famed physician and founder of modern

*Correspondence: Menachem Oberbaum, The Center for Integrative Complementary Medicine, Shaare Zedek Medical Center, Jerusalem, Israel.
E-mail: oberbaum@netvision.net.il
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pathology, anthropologist and biologist Rudolph Virchow, described an increase in the motility of ciliae in the tracheal epithelium when exposed to low concentrations of potassium- and sodium hydroxide — motility which is halted by high concentrations of these same substances.[4] The first systematic description of the phenomenon appeared more than three decades later in two papers published by the German pharmacology professor Hugo Schulz toward the close of the 18th century.[5,6] While his first paper[5] was mainly theoretical, his second[6] describes a series of experiments in which he showed that yeast fermentation could be increased by sub-toxic doses of various poisons (iodine, bromine, mercury chlorite, arsenic acid, chromic acid, salicylic acid and formic acid). Low concentrations increased production of carbon dioxide (CO_2) by 10^3–10^6 of the expected value, while higher doses inhibited carbon dioxide production entirely. Schulz concluded from his experiments that the observed reversal response describes a general phenomenon of biological function observable in any biological system.

In 1885, psychiatry professor and passionate homeopathy advocate Rudolf Arndt, also from Greifswald University, published his book *Die Neurasthenie* (*Neurasthenia*)[7] in which he formulated for the first time what he called the Grundgesetz der Biology — the Basic Law of Biology. This law, he claimed, declares that any foreign substance or external stimulus can affect the system in one of two different ways: a weak stimulus promotes cellular activity, often in beneficial ways, while a strong stimulus is inhibitory or toxic to the organism. Schulz acknowledged the contribution of his friend Rudolf Arndt in his writings. It was probably because of his connection with Arndt that Schulz was identified as a homeopathy supporter, although he never presented himself as such.[8] This public perception did no damage to Schulz's scientific reputation: in 1931, he was nominated for a Nobel Prize.[9] His shared observation with Arndt is known as the Arndt–Schulz Law. Initially, the phenomenon they described was supported by a number of prominent scientists, among them, Ferdinand Hueppe, a distinguished German bacteriologist and staff-member of Nobel laureate Robert Koch.[10] Hueppe claimed in his influential book, *Principles of Bacteriology*, to have observed the low-dose stimulation phenomenon in his bacteriological studies.[11] He credited Schulz with first describing it, but because of Hueppe's eminent reputation, it became known as Hueppe's rule.[12] Despite this early recognition, however, the low-dose stimulation phenomenon quickly fell into undeserved disrepute — the main reason being its association with homeopathy. Whereas homeopaths used the Arndt–Schulz Law to prove the homeopathic concept,[13,14] their opponents in the conventional scientific community rejected it because its basic principle was similar to that of homeopathy. Its most notable opponent was the prominent and influential pharmacologist Alfred J Clark, author of several books, including *Applied Pharmacology* (which went into seven editions and was translated into Spanish and Chinese), and his *Handbook of Experimental Pharmacology*, a leading text of the time.[15] Clark's books, which educated generations of pharmacologists, ridiculed hormesis because of the association between hormetic theory and homeopathy.[16] He interpreted the lack of evidence for hormetic responses to pharmacological drugs as proof that hormesis was a useless scientific thesis.[17,18] One reason for the difference in attitude between Hueppe and Clark toward the low-dose stimulation phenomenon may be the difference in their scientific backgrounds. Clark was a receptor pharmacologist who investigated robust sigmoid-shaped responses, dependent on single receptor activation. Hueppe, as a bacteriologist, was acquainted with non-saturable responses linked to growth and survival, which are endpoint-dependent on integration of multiple mechanistic events.[18]

Another factor limiting the acceptance of hormesis in conventional science was the incomplete and problematic definition of the hormetic response.[18] Some researchers, for example, demanded 'beneficial effects',[19] whereas others disconnected 'beneficial effects' from the definition of the hormetic response.[20]

Clark lived and worked at the time when the dose–response concept was developed and established, and an accepted model was urgently needed. Whereas the biphasic dose–response relationship is not adequately described by any model comparable to pharmacology's receptor-occupancy theory and fails to explain underlying molecular and biochemical mechanisms,[18] the competing threshold dose–response model had support in the scientific literature,[21–23] formed the core of Clark's books, and thus had a far better chance of acceptance.[24] Within five decades of the discovery of hormesis, the threshold dose–response was broadly accepted, incorporated into all pharmacology and toxicology textbooks and was the basic dose–response model for government-mandated hazard assessments for chemicals, drugs and radiation. Scientific and academic institutions and governmental regulatory agencies were all satisfied with the threshold dose–response model — disregarding the fact that while it approached the control value, it never went below it; and ignoring any possibility of a hormetic response. According to Edward J Calabrese, the failure of the hormetic research community's scientific leadership is one reason why hormesis was marginalized within the scientific community.[24] There was virtually no engagement on the dose–response issue by researchers in the biological and biomedical communities whose papers demonstrate evidence of hormetic-like biphasic dose responses. This lack of leadership in hormesis resulted in lack of a conventional terminology and, thus, in significant misconceptions. One telling example is the uncertainty regarding even the name of the phenomenon: it is variously known as the Arnd–Schulz Law, the Hueppe rule, U-shaped, inverted U-shaped, J-shape, β-curve, opposite effects and dual effects. The term, hormesis, the best known of them, was coined only in 1943 by Southam and Ehrlich,[25] who described the growth stimulation of wood-decaying fungi in cedar wood induced by low doses of natural antimicrobial agents.

Despite strong opposition and even contempt among scientists toward hormesis, however, the idea of the biphasic