

The hormetic (biphasic) dose response: a little bit of a bad thing can be good

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Long intriguing to me has been the concept of using “optimal stress” to provoke recovery – a manifestation of the hormetic (or biphasic) dose response in action, whereby an environmental agent (a stressor) generally thought to be toxic or inhibitory at a high dose will prove to be therapeutic or stimulatory at a lower dose. In fact, the term “hormesis” derives from the Greek “hormo,” which means, literally, “to excite or stimulate.”

Although a controversial topic and often marginalized in the toxicological literature (which has historically embraced a linear “no-threshold” dose-response model whereby toxins are thought to be toxic at whatever their dose and to become ever more toxic at ever higher doses), hormesis is now slowly gaining acceptance in some scientific circles, largely through the extraordinary research efforts [1-3], an avant-garde Professor of Toxicology at the University of Massachusetts.

Over time, Calabrese has come to believe that there is not always a simple linear relationship between the dose of a stressor and the clinical response. Rather, his contention is that a biphasic response (“cost” at a high dose but “benefit” at a lower dose) is an almost universal biological phenomenon – whatever the stressor, whatever the biological system, whatever the endpoint being measured.

More specifically, Calabrese hypothesizes that a hormetic dose response is the manifestation of a system’s adaptation to stress, a “modest overcompensation” in the face of threatened disruption to its homeostatic balance.

Along these same lines, the noted 16th century Swiss physician is credited with having written that the difference between a poison and a medication is the dosage thereof. So a poison is not always toxic, and nor is a medication always therapeutic [4].

What this means is that if a depressed patient on 20 mg of fluoxetine is responding, but only suboptimally, perhaps – counterintuitively – 10 mg of the selective serotonin reuptake inhibitor (SSRI) will be the more optimal dose and not ever higher doses. And whereas mild to moderate exercise will stimulate and energize the body, excessive or prolonged exercise may ultimately deplete the body of its nutrient and energetic reserves, thereby doing more harm than good.

Stressful input, therefore, is inherently neither bad (poison) nor good (medication).

By way of a further example, it has been found that depriving oneself of half a night’s sleep once a week (preferably the second half of the night) can provoke a rapid, even if short-lived, restabilization of mood and recovery from depression [5]. As another example, intermittent fasting (for example, 36 h water fast once a week) can so significantly reduce the total

body burden that mental clarity and focus can be improved dramatically and a sense of overall well-being restored [6].

In fact, superimposing an acute injury on top of a chronic one is sometimes exactly what the body needs in order to heal [7]. Is not this situation of “controlled damage” a manifestation of the hormetic effect? More specifically, consider the practice of wound debridement, which is used to accelerate healing. Not only does debridement prevent infection by removing foreign material and damaged tissue from the site of the wound but also it promotes healing by mildly aggravating the area, which will in turn activate the body’s innate ability to self-heal in the face of challenge.

Another example of causing physical irritation or injury to provoke recovery is the practice of prolotherapy, a highly effective treatment for chronic weakness and pain in such vulnerable areas as the lower back, the shoulder, the hip, the knee. This technique involves injecting a mildly irritating solution (for example, a relatively innocuous substance like dextrose, a local anesthetic like lidocaine, and water) into the affected ligament or tendon in order to induce a mild inflammatory reaction, which will then activate the body’s healing cascade, resulting ultimately in overall strengthening of the damaged connective tissue and alleviation of the pain.

Actually, prolotherapy is believed by many holistic practitioners to be significantly more effective than cortisone injections because these latter treatments, although sometimes able to provide immediate short-term relief of pain, will cause destruction of tissue and exacerbation of pain because of their catabolic effect over the long run.

Just as with the body, where a condition might not heal until it is made acute, so too with the mind. Indeed, I have come to appreciate that the therapeutic provision of “optimal stress” – against the backdrop of an empathically attuned and authentically engaged therapy relationship – is sometimes the magic ingredient needed to overcome the seemingly intractable resistance to change so frequently encountered in many psychiatric patients [8-10]. In essence, manageable stress can “optimize” by provoking “heightened functionality,” a result of the body’s “adaptive upregulation.”

The hormetic dose response will probably remain a controversial – and be experienced by many as a divisive – issue in toxicology for a long time to come because it challenges the time-honored view of the linear no-threshold dose-response model of mainstream toxicology. But with ever mounting evidence that many environmental stressors do indeed elicit a biphasic dose response, it behooves the scientific and medical communities to become more knowledgeable about the concept so that they can appreciate both that “a little bit of a bad thing can be good” and that “more of a good thing is not necessarily better.”

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Stark

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