

HORMESIS

EMERGING HOTLY DEBATED CONCEPT

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IN a practical class at the Bridgewater State College (US), sometime in 1966, the instructor told the students to perform an experiment on the growth-inhibiting effect of phosfon (a chemical substance having growth retarding effect) on the peppermint plant. The students, to their utter astonishment, found that instead of showing stunted growth, the phosfon-treated plant was growing almost 40% taller and leafier compared to the control. A thorough inquiry into the probable reason behind the unusual finding revealed that a highly diluted solution of the growth-retardant was used by mistake for the experiment.

History of science is replete with many happy accidents that led to remarkable discoveries. In this case, also, the inadvertent mistake of the students was ignored by all but one student. His name was Edward J. Calabrese. Following completion of his graduation from the Bridgewater State College in 1968, he got his MS and PhD degrees from the University of Massachusetts, Amherst. The mistaken experiment left an indelible impression on his mind. He pursued it later and championed the concept of a biological phenomenon called hormesis.

Hormesis is a biphasic response of a living cell or an organism to a physical agent (temperature, pressure, radiation) or a chemical substance (acid, alkali, salt, various toxic substances) that shows an inhibitory response at high dose but a stimulatory response at low dose. The physicochemical factors that

induce hormetic response are known as hormetins.

There is no single mechanism that can explain the mechanism by which all the hormetins work. Different hormetins work following different *modus operandi*. But in general the stimulation at low dose by the hormetins is found to be confined within the range of 30% to 60% higher compared to the response in the control group.

Looking Back

During the late 1880s, the German pharmacologist Hugo Schulz was looking into the effect of several compounds on the metabolism of yeast at the University of Greifswald in search of improved disinfectants that would be useful in surgery. While observing a dose-dependent decrease in the metabolism induced by all the agents, he was highly surprised to note that the addition of the same chemical substances at a low dose had a stimulatory effect on the metabolism of the yeast. After repeating the same experiment several times, when he became convinced that his observation was not an experimental artifact, he inferred it as a part of the biological response of the yeast to a wide range of low level stress factors.

However, because of the unusual findings, his paper failed to impress scientists at a medical conference in 1884. The ability of various physicochemical factors to induce low dose stimulation and high-dose response in living cells or organisms

was subsequently confirmed by a number of investigators mostly from the area of microbiology and plant biology. Stimulatory effect of the extracts of the Red Cedar tree on the metabolism of some fungi at low concentration was also observed by Chester Southam and John Ehrlich in 1943. They coined the term hormesis (Greek meaning “to set in motion”) to describe the seemingly paradoxical phenomenon.

But the interest of the scientific community in hormesis was largely the outcome of the untiring efforts of Dr Edward J. Calabrese. He presented hormesis “as a fundamental evolutionary concept with profound biological and medical implications”. Ultimately he was successful in establishing hormesis as a topic of extensive multidisciplinary research. It also found a place in the leading textbooks of pharmacology and toxicology.

Hormetic response plays an important role in evolution. Toxic metals (copper, cadmium) leach from the ores into soil and water. Terrestrial and aquatic microorganisms that appeared early in the course of evolution got exposed to them. Only because they adapted to the low dose toxicity caused by the metals, they could survive and sustain their existence. Cadmium in low concentration is also known to improve growth of some soil bacteria and decomposers.

Herbicides are used to inhibit the growth of plants. However some herbicides are found to stimulate plant growth at low concentration.

Glyphosphate, for example, is a herbicide that is used as hormone at low concentration in different plants. Fenoxaprop-P-ethyl is another herbicide that is found to stimulate plant growth and production capacity at low concentrations.

Problems With Hormesis

Hormesis bears the potential to enhance the resistance of crops to damages caused by the environment, pests and microorganisms. It may also help in enhancing the agricultural yield. However, the approach involves considerable amount of risk. Improper application of the hormetins may prove counter-productive. The plant may turn more sensitive to the stressors. Its productivity may also fall. Regulatory affairs and environmental issues also must be taken into the account while applying hormetic techniques in agriculture.

During physical exercise, the rate of metabolism is substantially enhanced leading to the production of some metabolites (reactive oxygen species, various types of aldehydes, acids) that are damaging to the cell. But following limited and programmed physical exercise on a regular basis, our body cells are exposed to these harmful chemicals in a limited concentration. These chemicals are believed to trigger hormesis and thus precondition our body cells to the exposure to the harmful substances. The overall benefit of regular physical exercise thus obtained, appears to be manifested by delayed aging and increased longevity.

Extreme caloric restriction (not taking food) is harmful to our health. But regulated caloric deprivation in the form of fasting and mild exercise is believed to delay aging by interfering with the biochemical processes related to senescence.

Antibiotics are powerful arsenals in our crusade against the infectious bacteria. However, indiscriminate and injudicious use of antibiotics provides opportunity to the bacteria to get exposed to low doses of these anti-infective drugs. In the process, the bacteria get adapted to them.

Thus, imprudent use of antibiotics is aggravating the problem of antibiotic resistance that has assumed the shape of a major crisis all over the world during the past few decades.

Food materials are preserved in the freezer compartments. Low temperature slows down the growth-rate of bacteria that occur in the food materials as contaminants. Further, salt and organic acids (mostly in the form of lemon juice) are added to the food to ensure complete prevention of bacterial growth. If these growth inhibitors are used in high concentration, bacteria cannot grow. But if they are applied in sub-inhibitory concentration, the bacteria present in the food get adapted to the inhibitors and become competent to tolerate them in high concentration. Moreover, they develop tolerance also to some other growth-inhibitory agents (e.g., antibiotics). Thus, exposure to sub-inhibitory concentration of inhibitors also promotes antibiotic resistance.

Some anti-cancer drugs take a very long time to get degraded and excreted from our body. Hence, the tumor cells get exposed to low concentration of the chemotherapeutic agents. It may provide an opportunity to the tumor cells to grow further.

In order to minimize the damage caused by oxygen deprivation during cardiac surgery, sometimes heart muscles are pre-conditioned by inducing artificial oxygen deprivation before the surgical operation.

Favorable medicinal effects are associated with some compounds that mimic the effect of various hormetins. Extensive research of various medicinal effects of hormetins and hormetin-mimics is in progress. The importance of low dose of medicines in therapeutics is beginning to be appreciated. The scope of low-dose chemotherapy for various types of cancer is also under investigation.

Debate on Radiation Hormesis

Despite a surge of interest in the different aspects of hormesis during the last few decades, it continues to be a debated issue. Many scientists argue

that the beneficial effect at low dose is not a general phenomenon and some chemical and physical agents are always damaging to the biological systems irrespective of the dose at which they are used.

A raging debate is going on at present on the hormetic effect of ionizing radiation (e.g., X-ray, gamma ray). According to the linear non-threshold model (LNT), the health risks associated with exposure to radiation increase with the dose in a linear fashion and there is no minimum dose (threshold) that must be exceeded to generate the effect. So the model does not leave any scope for “a safe dose of radiation” having beneficial effects. Death caused by cancer following low-dose radiation exposure was observed in an international study involving 308297 participants.

On the other hand, the proponents of radiation hormesis claim that the studies on harmful effects of low-dose radiation were biased and existence of thresholds in the low range of biological radiation was supported by experimental evidence. They also emphasize that humans and other living organisms are always exposed to some amount of radiation in the natural environment. Thus, it is obvious that the effects of low dose radiation on biological systems need more extensive studies before we reach a definite conclusion on this issue.

Hormesis is a phenomenon observed in all forms of life. The transformation of hormesis from its highly marginalized and neglected status till the middle of the last century to a topic of intensive research today, depicts the never ceasing enthusiasm of scientists to explore the uncharted waters in order to unveil the mystery of nature.

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