I mentioned (...) the work of the 2009 Nobel Prize winners, Blackburn and Greider (...), who, in their press conference on telomerases, told us: (...) We will live between 300 and 600 years. I say this in front of an audience of bosses who burst out laughing. (...). Would you take these capsules? Of course I would take them. Of course I would! Roselyne Bachelot (former Minister of Health) in 2016. Why does Google want to make us immortal?

Theme of the month:

Will something that doesn't kill you make you stronger? Hormesis.

Hormesis (also known as preconditioning, conditioning, pretreatment, cross tolerance, adaptive homeostasis, and rapid stress hardening) is a biological principle that allows us to naturally improve the functions of our body, its resistance, its immunity... It is a valuable aid in fighting the adverse effects of aging.

It is a particularly topical subject given the importance of good immune defenses to avoid or limit the impact of viral infections. Still poorly characterized, hormesis has been the subject of numerous scientific studies over the last twenty years.

Hormesis: how does it work?

Basically, hormesis is a stimulation of the biological defenses of an organism in response to a low dose of toxins or other stress-generating agents. This exists in all living beings, starting with the single cell.
In practice, the rule is simple: Subject your body to an optimized level of stress, typically of short duration, followed by a period of rest and recovery, and it will strengthen itself, to adapt and better resist next time. This illustrates Nietzsche's quote: "What does not kill, makes you stronger".

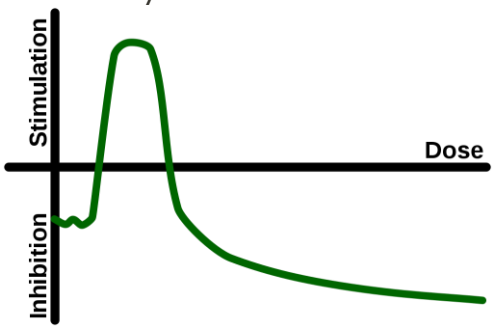
This stress can be a toxic substance, an exposure to extreme temperature or radiation, unusual muscular effort, physical or psychological constraints, deprivation of nutrients or oxygen, or other factors that directly affect the functioning of cells.

The paradoxical consequence of hormesis is that the increased comfort of our daily life does not always improve our health. For example, permanent environmental comfort, sanitized food, motorized travel, aseptic environment... Our modern comfort can weaken us.

First of all, hormesis improves our functions of adaptation to the environment and to external constraints: regulation of body temperature, muscular resistance, use of nutrients, production or storage of energy within our cells...
Moreover, it strengthens other major vital functions (circulatory, immune, repair, nervous...).

It is important to not confuse short-term stress, rather beneficial, with chronic stress which accentuates aging and often leads to illness (especially permanent psychological stress, which is common nowadays).

Below there is an illustration of the phenomenon. Under a certain threshold, the stimulation by stress is too weak to induce a strengthening of the organism, conversely above a second threshold, there is a risk of toxicity or degradation.



The "hormetic zone" varies from one individual to another and depends in particular on their physical and psychological state of fitness.

The dose (or intensity) of a biological stress or nutrient is essential in determining whether it will have beneficial or toxic effects. Paracelsus' famous quote from the 16th century "All is poison and nothing is without poison; only the dose makes something not poison" was completed in the 19th century according to Arndt-Schulz's law: "For any substance, low doses stimulate, moderate doses inhibit, too high doses kill".

Until now, it is not completely understood how hormesis can increase life span. Many so-called "anti-ageing" processes do, in fact, act through the mechanism of hormesis (e.g. caloric restriction or rapamycin).
Does hormesis apply to any substance or toxic action in high doses? Probably not. For example, for hormone disruptors, studies seem to show that there is an accumulation of toxic effects even at very low doses.

Phytochemicals in plants

Phytochemicals such as alkaloids, polyphenols and terpenoids activate the same processes as caloric restriction, fasting and exercise. Many of the beneficial effects of fruits and vegetables may therefore be due to the activation of stress resistance pathways by substances that plants secrete to protect themselves.

Caffeine, EGCG (green tea), curcumin, glucosamine, polyphenols, polysaccharides, quercetin (onion), resveratrol (grape and wine), spermidine (soy, mushroom) and sulforaphane (broccoli) are molecules that produce hormetic effects.

For example, a low dose of sulforaphane protects cells from oxidative stress, a higher dose of this compound has toxic effects on cells that lead to cell death. Similarly, a low dose of resveratrol (2 mg/kg) reduces inflammation-induced stomach ulcers in mice, while higher doses (5 and 10 mg/kg) increase the formation of ulcers and markers of inflammation.

Hormesis and pollutants

PFAS chemical molecules, also known as perfluorinated pollutants or eternal pollutants, are part of our daily life. It has been shown since the 2000s that these elements contaminate ecosystems, even in areas far removed from human activities, such as the Arctic regions.

However, a study by the Center for Biological Studies in Chizé and its Norwegian partners has shown that exposure to these pollutants is associated with lower telomere erosion and increased survival in a seabird from this area. These surprising results were published in July 2020. This study is the first to make the link between telomeres (a significant mechanism of ageing) longevity and contamination by these pollutants, which are increasingly present in the Arctic.

Hormesis and radiation

According to the hypothesis of radiation hormesis, low doses of radiation can stimulate the activation of repair mechanisms that protect against disease and that are not activated in the absence of ionizing radiation.
Low dose here means small additional doses comparable to normal background radiation (10 µSv = average daily dose from the natural background). Since at high doses the negative effects are irrefutable, there must be a threshold between the beneficial and negative effects of radiation. This threshold is known as the Zero Equivalent Point (ZEP).

Hormesis and increased immunity

Our immune system strengthens with repeated exposure to microbial agents (for example, children playing in the dirt have fewer infections than those living in a more "sanitized" environment).

The hormesis principle is also found in allergy desensitization or vaccination treatments. Subjects are exposed to a very small amount of the pathogen so that their bodies learn to resist it. Kind of like King Mithridate who, fearing being poisoned, drank a small amount of poison every morning.

It has been shown that the hormesis triggered by exposure to heat (e.g. a sauna) can improve general immunity. The one triggered by brief exposure to cold may make the immune system better able to respond to infections and bacterial toxins. Some drugs have a protective action against infectious diseases by increasing resistance to infection. Infectious damage to body tissue is then reduced, without the substance having any direct action on the microbe.

So-called "adaptogenic" remedies (such as ginseng) would act in this way, requiring the body to make an effort to adapt to the product, which will be followed by a strengthening of immunity and a general improvement in the ability to adapt to stress.

Production of muscle fibers

Intense effort, even of short duration, will stimulate muscle production. This muscular synthesis, which atrophies with age and its hormonal modifications, will be reinforced by hormesis.

Blood and lymphatic circulation

Hormesis can counter the progressive decrease in circulating blood volume which is linked to aging and a source of disease and degeneration. If we most often speak of brief and repeated physical or intellectual efforts as triggers, the intake of certain nutritional substances (especially vegetable and called "hormetins"), induce digestive stress that can also initiate hormesis by requiring a special effort to our digestive tract simply because they are difficult to digest.

Hormesis and cognitive abilities

Phenomena related to hormesis fight against neurodegeneration of aged patients. Under certain conditions, smoking could have a protective effect against neurodegeneration such as Parkinson's or Alzheimer's diseases. Of course, this example is extreme and the negative effects of more than a tiny amount of tobacco smoking far outweigh the positive effects.

The production of reactive oxygen substances during oxidation reactions can also trigger a beneficial hormesis. We know that oxidation is linked to aging, but we should, a priori, make the difference between punctual and what is called "oxidative stress". In the latter case, the body defends itself with its anti-oxidants. ROS (Reactive oxygen species) induced hormesis is the result of several metabolic factors including the stimulation of autophagy (a regenerating process of our cells which is triggered in particular during fasting). In fact, there are many hormesis factors that stimulate autophagy: fasting, intense exercise, adaptogenic substances.

Hormesis and nutrition

Fasting is now classified as a hormesis inducer. At the cellular level, our bodies have powerful mechanisms for adapting to nutrient deprivation.
Caloric restriction or protein restriction are methods to improve healthy longevity. In a situation of nutrient deprivation, the body adapts itself by involving several metabolic pathways, including autophagy, and accordingly strengthens itself.
Stress generated by a reduced diet (without going as far as malnutrition), or by periods of fasting can improve health and longevity, at least partially, through hormetic processes.

The effects of dietary restriction, however, seem to be more important in short-lived animals and are likely to be quite limited in humans, in addition to the fact that caloric restriction is very difficult to follow.

Hormesis and breathing

On one hand, depriving our cells of their vital oxygen creates great stress for them. If, however, it does not last too long, hormesis will trigger very interesting mechanisms for health. Paradoxically, hyperventilation increases the blood oxygen level, and can also activate hormesis.
It has also been shown that momentarily reducing blood circulation (as is often done before heart surgery) can protect the heart and the brain.

Hormesis and aesthetics of the body

We all want to improve our skin quality with beauty care. Various exfoliating treatments (such as peelings) with repeated micro traumatisms, by stings and facial slaps, are proposed to cope in particular with skin slackening, but should not be applied without explicit permission.

Hormesis in practice

Practicing hormesis means getting out of your comfort zone in an optimized fashion, then recovering with a period of rest.
For example :

- Exposure to cold: some people will take a 3-minute ice bath, others will shower in cold water.
- Exposure to heat through the sauna or hot tub.
- High intensity exercise: The effort is different from one person to another, depending on their physical abilities and their current fitness. It is the same idea for aerobic exercise and yoga.
- Diet: Some people will skip a meal (intermittent fasting), others will not eat for several days. For others, alcoholic beverages in small doses have a positive effect.

Conclusion and Outlook

The proverb "What doesn't kill you, strengthens you" contains a grain of truth if applied wisely, but is false and even cruel if the right doses are not respected.
For example, the descendents of people who survived the famine of the last winter of World War II in the Netherlands had poorer health. Too much adversity is harmful, exemplified today by people who have suffered severe COVID, who will almost certainly have a shorter life expectancy.

Your grandmother may have already told you: Not too much, not too little. But the dosage, the "fine tuning" of substances and actions useful for longevity requires considerable research.

It is very important to determine optimized hormetic dosages of toxic substances prior to administering them, because there are considerable financial, political and ideological interests at stake.

The precautionary principle should join the "proactive" principle. It is not just a question of preventing what could be dangerous, but of determining what could be useful and exactly how. This is made possible by massive health data (big data), rigorous new experiments with informed volunteers, and the scientific and medical study of physical, physiological, genetic mechanisms, etc. We thus progress towards a longer healthy life.

This month's good news: Financial support for citizen research and books related to the fight against aging

---

The "Unlock Longevity" donation campaign organized by the SENS Foundation has raised more than $2 million in private donations to support the most promising research!

Two books defend the advances for rejuvenation. In the English-speaking world, the book Ageless: The New Science of Getting Older Without Getting Old by Dr. Andrew Steele was reviewed in The Guardian. In French-speaking world, the book La mort de la mort. Les avancées scientifiques vers l'immortalité by José Cordeiro and David Wood, was widely discussed in the French-speaking press.

For more information, please visit:

- *heales.org*, *sens.org*, *longevityalliance.org* and *longecity.org*.
- Source of the image.