Stress, Longevity & Health – the concept of hormesis in a modern world

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In the last 100 years, for the average person, absolute life expectancy has risen in the developed world from less than 50 years to almost 80 years, with women tending to live longer. This has largely been due to improved hygiene, the use of antibiotics, and a more even distribution of good quality food amongst all social classes, as well as better health care and the widespread adoption of scientific breakthroughs by mainstream medical practitioners.

It is thought that the absolute life expectancy is nevertheless no more than 120 years. Unfortunately, despite the euphoria expressed in the 20th century that we would all be living to 100 years or more in the 21st century, the average life expectancy is either flattening off or, in some countries (notably the USA) it is actually showing signs of reducing. Moreover, for many the extra years of life are dogged by ill health. This has prompted scientists to develop measures of a healthy life expectancy (HLE) and years lived without disability (YLD). In effect, a healthy life expectancy is the amount of time you live for without major illness. This is, therefore, not just a medical indicator but also an important measure of the quality of life.

The actual HLE figure arrived at varies greatly between countries and between the sexes, and is closely related to a country's wealth. [1] In very poor countries, it can be as low as 40 years. In Japan, it can be more than 78 years. Generally, across the globe, the YLD varies from 6.2 to 11 years.

Healthy populations tend to display "morbidity compression"; in other words, the individual lives most of their life in good health but then all their illness is compressed into their last few years. Implicit in this is the notion that the longer our healthy life span, the longer we will live.

However, the latest data analysis (from global data collected in 2010) shows that although absolute life expectancy has risen across the world, HLE has not kept pace. Consequently, whilst we may be living longer, we are living for longer in ill health. As the greatest increase in life expectancy is due to a reduction in child mortality, the failure to reduce YLD is seen as a failure to tackle many preventable diseases and is thus a wake-up call to the global health community.

In the 21st century the biggest problem facing modern man in the developed world, despite all our medical breakthroughs, is an increasing prevalence of what can best be described as life-style induced disease. One of the worst culprits is the emergence of a largely sedentary life-style combined with, for more than a billion souls, an almost unlimited supply of cheap

[1] Measured in terms of *per capita GDP* (Gross Domestic Product)

calories. Emerging data suggests that not only are people becoming more unfit and sedentary, they are also getting fatter.

A modern affliction; the Metabolic Syndrome

Accelerated mortality is linked to a cluster of conditions we refer to collectively as "Metabolic Syndrome". Clinically, it is defined in a number of ways, but generally speaking, if you have a least three of the following: a high waist to hip ratio, high blood pressure, a low level of "good" cholesterol (HDL-c), or a high blood glucose level, you are said to have it. All of this is associated with increased levels of oxidative stress and inflammation. Data suggest that increased levels of body fat do in fact increase inflammatory tone.

To date, the condition is clearly associated with a greater risk of developing type 2 diabetes, coronary heart disease, kidney failure, cancer, cognitive decline and reduced sexual function. In short, it is an accelerated ageing syndrome.

Metabolic Syndrome and hormesis; what doesn't kill you makes you stronger and smarter

By contrast, an individual's life expectancy can be modulated by adjusting the relationship between calorie intake and calorie consumption. This is borne out by the very simple observation that most species so far studied display an interesting property; if you calorie restrict them, they tend to slow down or stop reproduction, but their life expectancy increases. This can be understood if we reflect for a moment on the process of natural selection.

One of the most important dilemmas of life is where best to spend your precious and hard-won energy; in reproduction or in maintenance mechanisms that enable your cells to last a long time? Clearly, if you have an energy surplus, it is much better to invest it in your offspring, as this ensures the survival of your genes. However, if there is not much energy about, then it is more important to survive to breed again another day.

During fasting and calorie restriction, cells start to more vigorously digest damaged cellular components in a process called "autophagy", effectively liberating energy and reprocessing them to ensure that all cellular components are at their most efficient. This also includes improving DNA protection and the fidelity of the DNA during replication, and reprogramming the expression of genes to ensure this process continues. Part of this process includes producing more efficient mitochondria[2] that can produce energy with fewer free radicals,

[2] **Mitochondria**. These are tiny organelles found in virtually every cell of the body. They were once free living bacteria billions of years ago, but ended up cohabiting inside other cells as they provided an enormous benefit; they could use oxygen to liberate far more energy from food – this allowed multicellular life forms to evolve. The price for this was that they produced free radicals, which, if left unchecked, could induce oxidative stress. However, this oxidative stress induced anti-oxidant adaptation in the cell to protect it, in particular, its DNA. Generally speaking, longevity is associated with lots of healthy mitochondria that produce energy with little oxidative stress; conversely,

while upping the innate anti-oxidant defences. In effect, fasting/calorie restriction reprograms most of the cells in the body to burn energy as efficiently as possible, which means using fat or its derivatives, while minimising oxidative stress and ensuring that all components of the cell are working at peak efficiency and DNA damage is kept to a minimum. This also tends to suppress inflammatory responses (which induce oxidative stress). However, some cells have different jobs depending on where they are. For instance, as soon as energy is stopped being delivered to fat cells, they start to releases fatty acids and glycerol; the liver can use the glycerol to produce more glucose (essential, at least initially, for the brain), while starting to produce fatty acid-derived molecules called ketones that the brain can also use as fuel. As muscles use up their fuel stores, they become more sensitive to insulin (so enabling them to be ready to soak up any energy if food is found). There are also subtle changes in the immune system that downgrade to some extent its ability to induce oxidative stress.

There is also another rather interesting change, and this involves the brain; calorie restriction and fasting not only is highly neuroprotective, but it enhances the generation of new brain cells (neurogenesis). Effectively, a small amount of non-lethal stress produces adaptation. Without stress, most cells will slowly revert to their lowest energy efficiency setting. Thus, when challenged, organisms don't only become tougher, they become smarter. This is the concept of hormesis; a small amount of stress can induce adaptation that improves your ability to resist that stress. Too much is damaging – in effect hormesis is a biphasic response.

The best way to think of it is like a self-adapting car that starts off with a small engine and weak brakes, with little awareness of its environment. If you make it work hard, it slowly grows its engine and improves its brakes, while better sensing its environment. If you don't drive it hard, it slowly shrinks its engine and brakes. If you overdo it, it eventually breaks down or blows up. But work it just right, it will not only go faster, stop quicker, but it will also be better able to withstand bumps and learn how to avoid pot holes.

Calorie restriction is clearly one way of inducing stress, but it is not the only one: exercise is also really good as it rapidly induces cellular (oxidative) stress by using up energy stores and causing a local deficit of oxygen. Interestingly, heat and cold also have this effect. All of these things force the cell to adapt – as long as you don't overdo it. We evolved in a highly competitive and stressful environment. To put it another way, without a challenging environment, we would have never evolved, and without the constantly changing environment during the lifetime of an individual, we would have never developed systems to balance somatic maintenance against the need to reproduce. In terms of evolutionary timescales, an individual's life is but a blink, so removing agents that cause a system to adjust to its stressor and restore the status quo during an individual's lifetime will have little effect on evolution, but it will have an effect on the individual.

inflammation suppresses their function. It is now thought that the basis of hormesis is related to mild induction of mitochondrial stress that induces an adaptation to improve their function.

So what are the implications for each of us in our daily lives?

Humans have been the only (sentient) animal to reach a significantly high enough level of intelligence to alter their environment; this effect has been dramatically accelerated in the last 3-4 generations with the advent of advanced technology. It has enabled at least a billion people to live without the fear of starvation, of being too cold (or too hot) and critically, removed the need to move. And herein lies the rub: because of our evolution in a hormetic environment that was constantly changing, with a constant battle to find food, we have developed the ultimate survival technique – environment-induced intelligence.

It can therefore be said that we have become the victims of our own success: we have now removed the very stressors (exercise and fasting, and probably, temperature extremes and high level plant compounds) that are necessary to maintain our systems towards longevity.

However, there is a second and third whammy; we are also supplying ourselves with almost unlimited calories, which is being stored as fat tissue, and the very food we eat has not been stressed either, so it does not provide our bodies with the necessary polyphenols (which are mostly produced by plants under stress). Hence, not only are we increasing our stores of inflammatory fat, we have removed a potent anti-inflammatory agent. But it gets worse.

Because of this imbalance, we are tipping ourselves into a negative spiral; because of the low level inflammation, we become increasing insulin resistant, which inhibits our ability to store fat safely, which itself becomes toxic because it gets deposited in the wrong places.

Thus, not only have we switched off the longevity programme, we are activating a programme that accelerates the aging process and makes us dumber, and very likely, reduces our incentive to exercise as we start to become more depressed. We have hit a tipping point and many are now in a vicious downwards spiral.

The inescapable conclusion

The simple fact is that we require physical activity, and other stressors, to stimulate our systems to reach optimum health. If you want a long and healthy life, exercise is not a “nice-to-have”, it is essential, as it stresses our mitochondria and that induces an adaptive response that makes us tougher.

….. / The lessons for each of us

The lessons for each of us are clear:

1) Get fit; the science and data is unequivocal on this – the fitter and stronger you are, the better your chances of living a long and healthy life. Exercise, and using your muscles, is anti-inflammatory (as long as you don't overdo it)

2) Keep moving. Overall fitness is important, but data is also showing that lounging around all day, without moving for long periods, is also bad.

3) Don't over-eat and occasionally, calorie restrict for 4-5 days per month (reduce your calories on the occasional day to 40 % or less than you might normally eat – you need to feel hunger; then eat normally on other days)

4) Avoid foods containing lots of saturated fat and excessive sugar: your body reacts to excessive saturated fat as it is the kind of fat found in bacteria – excess sugar overloads the system and gets converted into fat! Excess body fat is inflammatory!

5) Switch to using unsaturated fats and reduce intake of red meat

6) Eat lots of coloured fruit and vegetables; they contain compounds that mildly stress your system and also contain fewer calories. They toughen you up from the inside

7) Turn the thermostat down; cold is a powerful stressor, make your body work a bit to keep warm

8) In short, reintroduce some hormesis into your life; there is a very simple evolutionary reason why excess and comfort shorten life, and why a bit of the right kind of stress lengthens it. You cannot argue with natural selection!