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Ageing, science and the cosmetics industry

The micro-inflammatory model serves as a basis for developing effective anti-ageing products for the skin

Paolo U. Giacomoni

During the twentieth century, public health, improved hygiene and the widespread use of antibiotics dramatically reduced mortality in the Western world. Other technological improvements to our living conditions, such as the use of refrigerators to cool food or the transition from animal to mechanical means of transportation, have also helped to ease the burden of infectious diseases that plagued our ancestors only a century ago. These medical and technological developments have resulted in a massive increase in general life expectancy and consequently the number of people living to a comparatively old age, such as healthy centenarians. Together with a birth rate that has been in decline since the 1950s, this has led to a situation in which the elderly make up nearly half of the population. Western societies are now faced with the medical, social and financial consequences of a population distribution that is skewed towards older people. But the increase of the so-called greying population has also created a huge market for consumer goods that are palatable to active people in their fifties and sixties, including nutritional additives, sports, fashion and cosmetics.

While politicians, demographers and geriatric professionals begin to address the immediate social consequences, biologists, gerontologists and the pharmaceutical industry are looking for ways and means to achieve successful ageing—to improve the quality of life in older age. Two different trends of academic discourse and endeavour have emerged from these efforts. Whereas some scientists believe it is possible to extend the maximum human lifespan and try to find ways to increase longevity, others have more modest expectations. They focus their work on applications that make it possible to grow older while avoiding age-associated pathologies or annoying physiological impairments. In view of this divergence in academic discourse, many scientists now consider ageing and longevity as two different fields of research. To use a current aphorism: some want to add years to our lives, others want to add life to our years. When I am asked about the possibility of increasing longevity, I usually recall the Greek myth of Tithonos, a young mortal man who fell in love with the immortal goddess Eos. Afraid that she would outlive her love, Eos asked Zeus to grant Tithonos eternal life—but realized later that she should have asked for his eternal youth. He grew older and older until he was so worn and withered that only his voice was left. A treatment to increase longevity may not necessarily improve quality of life.

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In this way, we have come to regard geriatrics as something different than gerontology. The former discipline involves caring and curing the specific ailments of the elderly, whereas gerontology is a research field that emerged from the analysis of the process of ageing in an integrated fashion. By comparing the ageing of organisms with the ageing of organs and cells, and by studying the molecular phenomena associated with those processes, scientists wanted to understand the ageing process and why an organism is prone to so-called age-associated diseases. Based on these studies it became necessary to define ageing in an operational way, such that the definition allowed scientists to assess quantitatively whether a treatment has the capacity to provoke, accelerate, hinder, slow down or even reverse the ageing process.

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A now widely accepted definition of ageing is the accumulation of molecular damage with time (Giacomoni, 1992). This has largely helped the study of ageing based on observations made with cell cultures, organ explants and some easily accessible organs of the body, such as skin. It has also facilitated the search for effective rejuvenating treatments. But even if successful, such interventions may not be entirely beneficial, even for the individual who receives the treatment. Returning to the myth of Tithonos, the curse of ageing may be cured by an endogenous and unflagging capacity for mitigating molecular damage, but it may be replaced with a different, even worse, curse. According to what we know about the physiology of memory, the consequence of solving Tithonos' problem by

mitigating undesirable change would probably be that eternal youth is accompanied by the helpless inability to learn and acquire new experience. This double-sided blessing is the odious characteristic of the gods' gifts in Greek mythology. Given this conjecture, I would therefore advocate mitigating the effects of ageing without seeking to prevent it completely.

Together with the ageing of muscular and skeletal systems, ageing of the skin is a process with very direct effects on the daily life and psychological and social well-being of an individual. It is also a form of ageing whose effects may be mitigated, thus helping our putative Tithonos, without incurring another curse caused by a lack of neurological plasticity. Lastly, the skin is a major sensory organ, it is the body's first line of defence against infectious organisms and physical harm, and it plays a very important role in controlling body temperature. Slowing down the ageing processes of the skin will therefore not only help us to keep a more youthful appearance but will most likely have beneficial effects for the whole organism.

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In fact, skin is an ideal paradigmatic model to study the onset of ageing, because it is the easiest organ to observe and ageing of the skin is not in itself a life-threatening process. The physiological knowledge about skin ageing that has been gathered in the past years has resulted in the so-called micro-inflammatory model to explain how both internal factors and external results cause skin ageing (Giacomoni & D'Alessio, 1996a; Giacomoni & Rein, 2001, 2004). Some scientists are even applying this model to the aetiology of other ageing-associated pathologies such as rheumatoid arthritis or Alzheimer's disease (McGeer & McGeer, 1998, 1999; Combs *et al*, 2000).

The micro-inflammatory model of skin ageing is based on the observation that all causes that are known to accelerate skin ageing share a common feature: the ability to trigger the synthesis of intercellular adhesion molecule-1 (ICAM-1) in endothelial cells. These causes are as diverse as infections, tractions, cigarette smoke, ultraviolet radiation, trauma, hormonal imbalance, electromagnetic fields, ethanol ingestion, psychological stress, anoxia and advanced glycation end-products. Most scientists in the field now accept that everything that provokes the synthesis of ICAM-1 can be considered a factor for skin ageing.

After ICAM-1 is synthesized, it is transported to the surface of the endothelial cells that line the capillary vessels in the dermis. There it acts as a signal to circulating monocytes and macrophages to attach to the capillary vessels' surface, where they perform diapedesis—they squeeze through the capillary walls—and migrate into the dermis. These last two steps are mediated by the release of pro-oxidants such as hydrogen peroxide and singlet oxygen, and by hydrolytic enzymes, including proteases and elastase, which damage the surrounding extracellular matrix and even nearby cells. If this occurs, the damaged cell triggers the arachidonic-acid cascade, which releases prostaglandins and leukotrienes that then signal resident mastocytes to release histamine and tumour necrosis factor 1 (TNF-1). These two molecules have the ability to induce even more endothelial cells of the skin capillaries to synthesize ICAM-1, and thus to bind circulating monocytes and macrophages.

A simple thought experiment shows how this self-maintaining and self-amplifying micro-inflammatory process is thought to be responsible for skin ageing through the production of highly reactive oxygen species (Giacomoni & D'Alessio, 1996a). Breathing oxygen and eating sucrose—in the complete absence of other environmental factors or of genes able to induce ageing processes—cause cellular ageing. The superoxide produced by phosphorylative oxidation can damage mitochondrial DNA, obstruct cellular energy production, harm cellular physiology such as membrane potential and provoke the arachidonic-acid cascade and the ensuing inflammatory reactions. Any self-amplifying inflammatory process in the skin that leads to the production of reactive oxygen molecules will therefore cause skin ageing.

An interesting insight afforded by the micro-inflammatory model is that it demonstrates how even a minor injury to a single cell can provoke harm to the surrounding tissue by several orders of magnitude larger than the initial insult. Considering that the fibroblasts in the adult dermis are unable to arrange newly synthesized collagen fibres in an orderly three-dimensional lattice during wound healing, this model gives us a framework for understanding how major changes can take place in the dermis even after insults, such as cigarette smoke or anoxia, which otherwise would not be able to act on the elastic and rheological properties of the skin.

Of course, the micro-inflammatory model of skin ageing has its limitations. Although it is able to explain the sagging and thinning of skin in older people, and the onset of wrinkles, it fails to predict the appearance of so-called age spots—the darkening of small regions of the epidermis 10–100 mm^2 in size. Indeed, if anything, the model would predict a homogeneous darkening of the epidermis, since it is known that irritants provoke pigmentation and the micro-inflammatory model does not accommodate such an asymmetric, local and discrete variation of inflammatory mediators. The model also fails to predict the decreasing capability of the skin to retain water in the dermis. Nevertheless, since this is mainly dictated by the hormonal equilibrium in women, it might be a problem linked mainly to development and not to ageing *per se*.

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Despite such limitations, the merit of the micro-inflammatory model is to provide a rational basis for the design of treatments against skin ageing. As it suggests, one simply ought to identify the major environmental or lifestyle factors that cause the skin to age and wither—and just avoid them. Unfortunately, whereas it is relatively easy to avoid cigarette smoke or change other behaviours, it might be more difficult, if not completely unhealthy,

to escape environmental factors such as oxygen. Furthermore, the sun is still is the single greatest environmental factor that accelerates human skin ageing. Luckily, one can avoid the sun without being obliged to live a solely nocturnal life. There are many defences available against the sun's rays, such as the classic ones afforded by clothing, hats, umbrellas and sunglasses, as well as modern high-tech barricades. Sunscreens—photostable, skin friendly, nonirritant and nonphototoxic substances—are able to absorb ultraviolet (UV) radiation with high extinction coefficients before it can penetrate the skin and cause cellular damage.

Indeed, the search for effective, stable and safe sunscreens has prompted intense cooperation and mutual exchange between scientists in industry and academia. The science of photobiology, of which the study of sunscreens is but one domain, is possibly the one scientific field where this collaboration has been most fruitful. In this particular case, the interaction was driven by the needs of the cosmetics market. Consumers want to avoid the uncomfortable feeling caused by UVB—the short-wavelength part of solar UV radiation which is mutagenic, erythemogenic and carcinogenic—when outdoors. There is also considerable interest within the cosmetics industry in the production of sunscreens that are able to absorb UVA, the long-wavelength part of solar UV radiation that creates reactive oxygen species that damage DNA, proteins and lipids. Since UVA constitutes at least 95% of the total solar UV radiation on earth, the overall contribution to damage by UVB and UVA is comparable even if the quantum yield of the UVA damage is smaller compared with UVB.

Whereas UVB radiation is absorbed by common glass and its intensity changes with latitude, season, time of day and meteorological conditions, UVA rays can traverse clouds as well as glass and the intensity of this radiation varies only slightly with the hour of the day. This is why many cosmetics companies have suggested the use of broad-spectrum sunscreens in daily skincare products, which has increased the market's demand for UVA/UVB sunscreens. This is where the scientific problem of solar exposure in ageing ends, and political problems for cosmetics begin.

First, sunscreens are subject to different legislations in different regulatory jurisdictions, which has led to a situation in which products that are freely available in one country may be banned elsewhere. In the USA, sunscreens are classed as drugs, although they can be obtained over the counter without the need for a prescription. This means that any sunscreen to be sold in the USA needs the approval of the US Food and Drug Administration (FDA), even if it is an ingredient of a cosmetic product, such as a daily skincare cream or a lipstick. Consequently, there are sunscreens available in Europe that are not yet allowed in the USA by the FDA. On the other hand, the European Union has banned some products, for instance, those containing zinc oxide particles, which are freely available in US pharmacies. Second, even if it might appear scientifically sound to say that sunscreens are anti-ageing agents, if only because they reduce the amount of photons hitting epidermal cells and therefore reduce the generation and accumulation of molecular damage, European and American legislators have established a policy of closely scrutinizing any anti-ageing claims for cosmetic products.

These legal and regulatory details notwithstanding, the search for real anti-ageing products for the skin continues. One extremely effective tool would be a product that helps cells to repair DNA damage. Such a product does exist: it is industrially manufactured and its activity has been proven beyond doubt, reproduced in several laboratories and documented in a number of publications. It is a liposome-like vesicle containing either T4 endonuclease V or a photolyase from cyanobacteria. The former has been approved as a drug in the USA and Japan to treat people affected by the genetic disease *xeroderma pigmentosum*. This disease is characterized by the inability of the DNA repair system to perform the first nick near the site of DNA damage to initiate the process that cleaves and replaces the damaged part. The drug

provides help through the topical application of an agent that penetrates the epidermis, enters keratinocytes or other epidermal cells and releases an enzyme that nicks the DNA and thus triggers the whole repair mechanism (Yarosh *et al*, 2001). Photolyase could also be used to accelerate the removal of UVB-generated pyrimidine dimers by topical application of vesicles that penetrate epidermal cells and deliver the enzyme followed by blue light or UVA radiation, since photolyase uses light energy to remove cyclobutane-type pyrimidine dimers (Stege *et al*, 2000).

Other products could also be envisioned to support skin repair in the long term. Wound healing, for instance, often results in scars that consist of entangled collagen fibres. This chaotic arrangement of fibres is the consequence of a quick healing process, governed by inducers of collagen synthesis such as TGF-1. Researchers have observed that antibodies against TGF-1, or antagonists against its receptors, slow down the healing process and prevent scar formation (Shah *et al*, 1995; O'Kane & Ferguson, 1997). Electron-microscopy analysis of such healed tissue reveals that the fibres in the connective tissue are neatly aligned and endowed with three-dimensional order. Mechanical stretching of healed tissue indicates that when healing was slowed down by TGF-1 antagonists, the force necessary to re-open the wound is larger than when the healing occurred in their absence. Since the repair processes occurring in the dermis after UV irradiation are reminiscent of wound healing (Giacomoni & D'Alessio, 1996b), these observations seem to indicate that there may be ways to maintain the elastic and rheological properties of the skin when growing older.

Such products to support DNA repair mechanisms and to help maintain the orderly arrangement of collagen fibres in the dermis would be great tools for the cosmetics industry in overcoming ageing processes in the skin. Applied with sunscreens or daily care creams, they could reduce the accumulation of direct damage, the amount of secondary damage provoked by the subsequent inflammation, and the loss of order in the arrangement of newly synthesized fibres. As pointed out above, such products would not only have cosmetic value for the skin but would surely benefit the rest of our bodies as well.

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Paolo U. Giacomoni is Executive Director of Clinique Laboratories, Melville, NY, USA.
E-mail: pgiacomo@estee.com

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