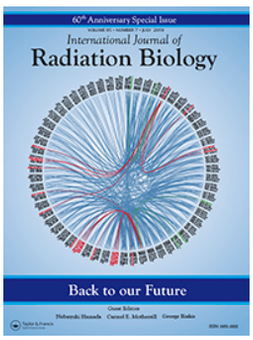

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REVIEW

Sunlight radiation as a villain and hero: 60 years of illuminating research

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ABSTRACT

In the 60 years since the inaugural edition of the *International Journal of Radiation Biology*, much of our understanding of the biological effects of solar radiation has changed. Earlier in the century, sunlight played a 'hero's' role in reducing disabling rickets, while today debate still continues on the amount of sun required before exposure reveals the 'villainous' side of solar radiation. Although knowledge of the ultra violet (UV) component of sunlight as a carcinogen has become widespread, skin cancer rates are still rising yearly. Twentieth century attitudes have seen an about-face in the field of dermatological sun protection, with sunscreens changing from recipes designed to promote a 'healthy tan' to formulations proven to block both ultraviolet B (UVB) and more recently, ultraviolet A (UVA), to minimize premature sun-aging and skin cancer risk. In the early 1960s, DNA was first found to exist within mitochondria, while recently the connections between mitochondrial changes and UV radiation exposure have been expanded. Sixty years ago, understanding of the endocrine systems of mammals was enjoying its infancy. Early discoveries that light, particularly natural light, could have profound effects on functions such as sleep patterns and hormonal balance were made, while today more advanced knowledge has led to lighting improvements having pronounced effects on human wellbeing. Photosensitization 60 years ago was a health concern for both humans and their domestic animals, while today chemically engineered photosensitizing drugs can be administered along with highly directed light to pinpoint delivery targets for drug action. Life on earth is inextricably bound up with solar radiation. This article attempts to outline many of the ways in which our opinions about solar radiation have changed since the journal's inception.

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Sunlight the hero: rickets and vitamin D

In 1959, the first issue of *The International Journal of Radiation Biology* became available. It provided a new forum for exchanging knowledge in the rapidly changing field of radiation's effects on living organisms, both beneficial and detrimental. The same year saw the death of the Nobel Laureate Adolf Windaus, who together with other scientific teams had worked between 1920 and 1940 to isolate cholesterol and then subsequently clarify how UVB wavelengths from sunlight could act upon a fractional component of it to produce biologically active vitamin D (Wolf 2004). It was found that cholesterol from the diet or from cellular metabolism undergoes a chemical reaction when exposed to UVB in the skin to become cholecalciferol, which is then hydroxylated in the liver and kidneys to become the biologically active 25-hydroxyvitamin D, needed to process calcium (Gil et al. 2018) and thus promote normal bone development. Prior to the discovery that exposure to sunlight or dietary supplementation could prevent the disabling childhood deficiency condition rickets (Harrison 1961) and the crippling adult onset of osteomalacia (Nordin 1960) (softening of the bones with similar effects to osteoporosis), these conditions were prevalent in areas where climate or culture prevented sufficient sun exposure to skin (Holick and Chen 2008). Remarkably, in the years following 1959, rickets returned to cities in England and Scotland due in part to the cessation of the fortification of milk and bread with vitamin D, a policy that had been instituted during the Second World War (Benson et al. 1963). Another possible cause for the re-emergence of rickets at this time may have been increased economic migration from sunnier climates to "the smoky pall of a norther city" and the attendant lack of sunshine, according to Arneil, writing in The Lancet (Arneil 1963; Richards et al. 1968). Indeed more recently, it has been stated that the lack of vitamin D amongst the human population is of pandemic proportions (Holick and Chen 2008), with other systemic symptoms often being misdiagnosed, and that depression and lower levels of serum vitamin D are associated (Goltz et al. 2017).

Today the debate has been reignited; does the need for sun exposure to provide adequate levels of serum vitamin D outweigh the peril of overexposure to sunlight as a carcinogen (Reichrath 2006; Vojdeman et al. 2019)? Some authorities argue that moderate sun exposure is beneficial to heath (Holick 2015), while others are adamant that sun exposure must be minimized to prevent cancer risk and that vitamin D supplementation in foodstuffs is the safer course (Pettifor

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2005), particularly for infants. Meanwhile others claim that recommended supplementation levels are inadequate unless augmented by sun exposure (Glerup et al. 2000). As vitamins have been noted as producing the greatest benefit if consumed as part of the diet rather than as processed supplements (Chen et al. 2019), perhaps a holistic solution lies in a varied diet of nutritious fresh food (Abbas and Zaka-ur-rab 2018) and limited sun exposure.

Enter the villain: ultraviolet radiation and cancer

Both the scientific and medical communities have long been in agreement that the UV component of sunlight is the leading cause of skin cancer, in particular non melanoma skin cancer (NMSC) (Bahner and Bordeaux 2013; Berman and Cockerell 2013; Kim and He 2014; Ulrich et al. 2016). In 1958, pigmentation types were divided into three groups; fair skinned with blue or green eyes, olive skinned with brown eyes and dark skinned having dark brown eyes, with a decreasing likelihood of developing skin cancer as skin tone deepened (Mackie and McGovern 1958). The link with sun exposure had previously been made from observational data; sailors and vineyard workers tended to develop lesions on sun exposed skin (Howell 1960), but by 1959, a solid link between ultraviolet light and skin cancer was beginning to be forged, with publications putting forward theories as to the mechanisms of UV-induced carcinogenesis and the results of experimental trials using controlled wavelengths, dosages, and exposure times (O'Neal and Griffin 1957; Blum 1959; Blum et al. 1959).

Today the most common skin classification system is the Fitzpatrick Scale ranging from Type One; very fair skin that always burns and never tans, to Type Seven, dark skin that never burns (Roberts 2009). We also know more about the effects of sun exposure; UV light is a potential mutagen, producing oncogenic DNA mutations; inactivation of tumor suppressors, and also stimulates clonal expansion of cells bearing these defects (Halliday et al. 2008). Particularly vulnerable is mitochondrial DNA (mtDNA) as it has limited repair mechanisms (Cline 2012); however, damage to mtDNA can serve as a marker of sun exposure, with the percentage of genomes carrying several deletions indicative of cumulative damage (Powers et al. 2016). In addition, skin cancer facts, statistics, and prevention advice are more readily available with information technology now accessible with relative ease (Duarte et al. 2017).

However, skin cancer levels related primarily to UV exposure are on the increase in the lighter skinned portion of populations worldwide (World Health Organisation 2015; Irish Cancer Society 2019b). In the US, more people are diagnosed with skin cancer each year than all other cancers combined, at a cost of 4.8 billion dollars per year in the case of NMSC (The Skin Cancer Foundation 2019). NMSC was also the most common form of cancer diagnosed in Australia, costing 127.6 million dollars in 2014 (Institute of Health and Welfare 2016). In the UK, NMSC rates have increased by 61% in the decade between 2005 and 2015 (Cancer Research UK 2015). In Ireland, there were 10816 reported diagnoses of NMSC in 2018 (Irish Cancer Society 2019a). It is not an exaggeration to think of this in terms of a health crisis (Gordon 2013). These escalating numbers may be due to the long-term cumulative nature of UV-induced carcinogenesis (Green et al. 2011) catching up to a generation of young people exposed before information was commonly available, or to the culturally perceived meme that tanned skin is an indicator of health (Nogg et al. 2019). This persists despite each of the above mentioned governments' long-running public information campaigns designed to dissuade their citizens from engaging in UV exposure (Cancer Council of Victoria [date unknown]; Irish Cancer Society 2017). Included in these initiatives is a recommendation, renewed yearly since 2009, that susceptible people receive counselling about the necessity to minimize exposure to UV to reduce the chances of contracting skin cancer (Grossman et al. 2018). The tide does seem to be turning, however, as a search engine query (May 2019) on 'sunscreen' returned 128,000,000 results (Sunscreen - Google Search, 2019), while 'tanning oil' (emollients designed to intensify UV effects on the skin rather than mitigate them) returned only 58,000,000 (Tanning oil - Google Search, 2019).

Attitudes to UVA make an about-face to confront skin aging and cancer

In 1959, the iconic Little Miss Coppertone advertisement modelled on Cheri Brand was first screened. Included in the advert was a partial list of ingredients, including lanolin, cocoa butter and homomethyl salicylate, 'the magic ingredient that screens out harmful burning sun rays' (Brand 1959). This was an improvement on the original formulation based on red petroleum, coconut oil, and cocoa butter, devised to protect service men and women in World War Two by Benjamin Green (Kerin et al. 2013). The thinking at the time was that UVB wavelengths caused sunburn; this was blocked by the aforementioned salicylate or other selective sunscreens, while the desirable tanning rays in the UVA waveband were allowed through (De Navarre 1956). To those whose occupations required prolonged sun exposure, sunscreens were a needed medicament to prevent painful and disabling burning, blistering and possible infection (Daniels et al. 1968). A tanned skin had historically been associated with menial outdoor work in agrarian society; with increasing industrialization, when menial work was carried out indoors with little time for outdoor recreation, a tanned skin denoted membership of the 'leisured classes' (van der Rhee et al. 2016). Little was known about the long-term effects of UVA exposure on skin tone, discoloration, and cancer risk (Ridley et al. 2009).

As with all preparations designed for human use, efforts were balanced between efficacy and consumer acceptability; in the case of the developing sunscreen market, this was an effort to find an equilibrium between erythema reduction and perceptions of odor, 'skin feel' and lack of staining of skin or clothing (Everett et al. 1957). Products under development in the late1950s were generally composed of an

active ingredient chosen as effective at blocking UV wavelengths in the 297–320 nm UVB range (Everett et al. 1957), often a salicylate-based molecule combined with an inert vehicle such as propylene glycol or silicone (La Via 1955) and sometimes a propellant such as dichlorodifluoromethane (Freon). The characterizing of the mechanism of how a tan came about was however, only in its infancy in the 1960s (Quevedo and Smith 1963) with the melanocytes as the origin of pigmentation (Quevedo et al. 1965) but little else.

Although it was known at this time that ultraviolet light caused skin malignancies (Howell 1960), the mechanisms at work had not yet been fully elucidated (Mackie and McGovern 1958); the effects of UV on DNA were only being investigated in the 1960s, with the discovery that UVB produced mutagenic DNA thymine dimers (Setlow and Setlow 1962). Key work in understanding the penetration of light into human skin made it clear that the shorter wavelengths of UVB did not penetrate to the skins germ-cell (sic) layer while the longer UVA radiation could reach subcutaneous tissue where cells were proliferating (Bachem and Reed 1931). The differences between deeper basal cell and squamous cell carcinomas were also being studied (Pinkus 1959), with a focus on the erythemal UVB rays (Macdonald 1959); a connection between adverse effects to skin and 'harmless' UVA had not yet been made (Knox et al. 1960).

At the end of the 1950s, UVA was thought to do no more than facilitate a healthy tan. The dermatological community has come to a consensus that UVA can penetrate to the dermis to cause photoaging (Lim et al. 2001) as well as DNA damage (Zhang et al. 1997). Indeed, the collagen-denaturing effects of all UV irradiation below 400 nm, i.e. both UVA and UVB are now known (Davidson and Cooper 1965), as UVA causes both the breakdown of collagen and reduced collagen synthesis, leading to photoaging, as distinct from chronological aging, with additional features such as dryness, deep, coarse wrinkles and a leathery appearance (Rosi Helfrich et al. 2008), with each UV exposure adding to what amounts to a 'solar scar' *(ibid)*. It is no wonder that the skin care industry has jumped at the chance to include another antiaging component to their marketable products (Garnier 2019; Hawaiian Tropic 2019). In a persuasive change of direction, the tanned look is now being marketed as a poor health choice that is undesirable, with a leader in the educative field, the American Skin Cancer Foundation, headlining their campaign with the slogan 'Go with Your Own Glow' (The Skin Cancer Foundation 2019).

Sunlight to the rescue: sunlight and psychological wellbeing

In 1959, there was little scientific work to connect exposure to natural sunlight with mental wellbeing, although literature and popular thinking have linked the two persuasively (Weill 1987; Denver 2012). Research is ongoing to determine the exact nature of the relationships between the perception of light and the neurotransmitters and hormones responsible for circadian rhythms, mood, and wellbeing (Vandewalle et al. 2009; Shishegar and Boubekri 2016; Chantranupong and Sabatini 2018).

In 1958, melatonin was first isolated by Lerner from beef pineal gland (Lerner et al. 1958) and interest into the pineal was renewed. It is known now that an area in the hypothalamus of the brain controls pineal secretions, and that retinal light perception influences the production of melatonin (Lewy et al. 1980). Melatonin is recognized as the hormone responsible for regulating sleep (Auld et al. 2017), a requisite for life (Steptoe et al. 2008). Unlike nonendogenous tranquilizers such as benzodiazepines with their attendant side effects (Olfson et al. 2015; Soyka 2017), melatonin has been used with good outcome and no adverse carryover as a treatment for sleep disorders (Zhang et al. 2016; Auld et al. 2017; Xie et al. 2017). Interestingly, melatonin exists in abundance in mitochondria (Leon et al. 2004); there it has an important role maintaining homeostasis by acting as an antioxidant, thus promoting efficient energy production (Acuna-Castroviejo et al. 2007).

Another neurotransmitter involved in perceptions of mood and changes in behavior is serotonin; plant manufacture of serotonin points to the earliest evidence of links between early photochemistry at a simpler level and the more complex biochemistry at work in the human brain (Azmitia 2010). Serotonin is directly affected by seasonal changes in sunlight levels, and even by day-to-day weather (Lambert et al. 2002; Praschak-Rieder 2012). In fact, studies show that weather may have such an effect on daily attitudes that life-changing behaviors may result (Lambert et al. 2002; Fredrickson et al. 2005; Kadotani et al. 2014). Serotonin, like melatonin, is synthesized from tryptophan, an essential amino acid that must be sourced as part of the diet (Wurtman and Axelrod 1965; Jenkins et al. 2016). Deficiencies or disorders of serotonin turnover are well known to cause mental health problems such as depression and anxiety (Azmitia 2010), and this neurotransmitter has been studied extensively by those seeking to find both a biochemical cause and cure for seasonal affective disorder (SAD) (Rosenthal et al. 1984), a form of depression linked to reduced photoexposure in the winter months, especially at higher latitudes (Rosen et al. 1990). It is now thought that SAD is caused by an excess of serotonin transporter protein activity during the darker months; this results in the neurotransmitter being removed from the synaptic cleft and recycled more frequently (Willeit et al. 2008; Mc Mahon et al. 2016).

Happily, SAD can be treated effectively in many individuals by replacing the missing sunlight with a bright artificial source (Tyrer et al. 2016), with results comparable to cognitive behavioral therapy for depression (Rohan et al. 2015; Rohan et al. 2016). Symptoms remit as the hours of sunlight increase following the vernal equinox. With the changeable nature of weather from season to season and day to day, it is no wonder that many feel their spirits lift on a sunny day (Fredrickson et al. 2005).

Photosensitivity: from threat to therapy

Skin contact with the sap of certain plants causes phytophotodermatitis, a condition in which a toxin in the sap, often a

furanocoumarin, interacts with DNA in the skin when activated by ultraviolet light (Zajdela and Bisagni 1981), causing cell death. Typically this presents as erythema and often severe blistering, which can persist for days, with hyperpigmentation persisting for months in some cases (Smith et al. 2012). Two of the more common families of plants containing furanocoumarins are the *Umbelliferae* including hogweeds, parsnips and celery, and the *Rutaceae* or citrus family (Pathak et al. 1963).

The parent molecule in the furanocoumarin family is psoralen (Briggs, & Colebrook 1960); as with the other members of the family, the multiple double bonds making up its ring structures are strongly absorptive in the ultraviolet B range of 290–310 nm (Steck and Bailey 1969), potentially increasing its phototoxicity. Between 1958 and 1960, dermatological experiments were carried out using it and another member of the furanocoumarin family, methoxsalen. A trial to determine its efficacy in curing vitiligo when taken orally or applied to the skin produced a variety of results, from limited success to outbreaks of severe itching in sunlight (Elliott 1959). Further experimentation using oral methoxsalen to increase tanning in 25 persons with fair skin who had always burned in the past found that it increased tolerance of sunlight, while one developed a basal cell carcinoma after two weeks at a high altitude, and two children, aged four and five, had to cease therapy due to severe swelling of the lips and feet (Stegmaier 1959). It was later added to suntan lotions, particularly in Europe, until it was found to be carcinogenic when combined with sun exposure (Ashwood-Smith et al. 1980; Zajdela and Bisagni 1981; Autier et al. 1997). Methoxsalen is still used on affected areas topically to treat vitiligo (Oxsoralen (Methoxsalen Lotion): Side Effects, Interactions, Warning, Dosage and Uses, https://www.rxlist.com/oxsoralen-drug.htm#side_effects) and prescribed orally for psoriasis, both in combination with physician-administered UVA treatment (Methoxsalen Oral: Uses, Side Effects, Interactions, Pictures, Warnings and Dosing – WebMD; https://www.webmd.com/drugs/2/drug-6957-1257/methoxsalen-oral/methoxsalen-rapid-oral/details).

Today the site-specificity of photosensitive compounds is also being used to advantage in photodynamic therapy (PDT) to treat cancer (Bolze et al. 2017). Plant extracts are being investigated as photosensitizers, as a number have the required characteristics; they are nontoxic until activated by a physiologically tolerable wavelength and localize preferentially to tumor cells, causing proliferation inhibition (Villacorta et al. 2017). Photosensitizers work because their atomic configuration allows them to interact with oxygen when excited by light of the appropriate wavelength to release superoxide, a reactive oxygen species (ROS) toxic to cells (Abrahamse and Hamblin 2016). Light of the red to infrared wavelengths between 650 and 850 nm is considered the most useful, as longer wavelengths penetrate more deeply into skin yet are still strong enough to produce the desired ROS (Li et al. 2018). As well as naturally occurring compounds, nanoparticles chemically structured to target the lower pH of the cancer environment (due to lactic acid released following glycolysis) have recently been designed and implemented with success (Li et al. 2017). Again, light has taken on the hero's role in the fight for health.

Mitochondrial DNA as a marker of sun exposure

In 1962, Margit and Sylvan Nass were studying the development of embryonic chick cells, and noticed very thin fibers in their mitochondria, resembling the fibers found within the nuclear membrane (Nass and Nass 1962). Then in 1964, Schatz et al. used a high density solution (the radiocontrast agent diatrizoate, aka Urografin) to definitively isolate the mitochondrial fraction of yeast cells; when tested, the mitochondrial layer was found to contain extranuclear DNA (Schatz et al. 1964). Further work found that many species' mitochondria contained DNA (Luck and Reich 1964; Nass et al. 1965a, 1965b; Suyama and Preer 1965), until the Nass group were able to publish their finding that non-nuclear DNA was 'in most and probably all mitochondria' having extracted it from cells from eight phyla of animals (Nass et al. 1965a, 1965b). In the intervening time, the human mitochondrial genome has been sequenced and the genes it encodes deciphered (Anderson et al. 1981), as well as those of diverse other species including the salmon and dog (Davidson et al. 1989; Kim et al. 1998).

It has now accepted that mitochondrial DNA (mtDNA) damage accumulation can act as a record of sun exposure (Birch-Machin and Swalwell 2010). Because the copy number of mitochondrial genomes per cell are estimated at 1000–10,000 genomes per cell (Rooney et al. 2014) and repair mechanisms in mitochondria are limited, damage to mtDNA can be multi-heterogeneous and largely goes unrepaired (Powers et al. 2017). UV light from the sun can damage mtDNA both directly and indirectly; the short, energetic wavelengths of UVB are responsible for direct DNA damage while the longer wavelengths of UVA causes indirect mtDNA damage resulting from the interactions between ROS and DNA. Another form of damage caused by sun exposure is a 4977 base-pair long deletion of mtDNA ($mtDNA^{4977}$). The $mtDNA^{4977}$ deletion has been induced in vitro both by UVA light (Koch et al. 2001) and UVB wavelengths (Hwang et al. 2009) and by UVA between 340 and 450 nm in human skin in vivo, (Reimann et al. 2008) where it was found to persist to the end of testing at 16 months (Berneburg et al. 2004). Indeed, as there is no repair mechanism for $mtDNA^{4977}$, it can persist in viable cells as part of a heterogeneous population of mitochondrial genomes carried forward throughout a person's life (Powers et al. 2016). Similarly, there is also a 3895 base-pair deletion also found more commonly in sun exposed skin than non-sun-exposed skin which acts as a marker of sun exposure (Krishnan et al. 2004). Thus, analysis of an individual's mtDNA can act a record of their past sun exposure history.

The human population has evolved to live on Earth over tens of thousands of years and up until the last few hundred years, skin pigmentation and type was optimal for the geographical location of most people (Jones et al. 2018). More recently, modern lifestyle choices, travel and migration have undone this, with high levels of skin cancers reported in

Australia, with many emigrants from more northerly latitudes with type 1 and type 2 skin suffering the consequences (Anikeeva and Bi 2017). Equally in northwest Europe, may immigrant groups with type 6 and 7 skin suffer from SAD (Kesebir 2018), as pigmentation diminishes the sun-exposed skin's ability to synthesize vitamin D from sunlight (Benson et al. 1963). But just as precautions must be taken against the cold in some of Earth's harsher climates in the absence of the sun, so care must be taken to protect against harmful UV radiation when the sun does shine. We need sunlight radiation, just not too little or too much, and finally we are equipped with enough knowledge to strike the right balance.

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