Invited Review

A History of Ultraviolet Photobiology for Humans, Animals and Microorganisms¶

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INTRODUCTION

Ancient civilizations understood that sunlight provides visibility, warmth, health and vitality. Their understanding of *how* sunlight provides these life-sustaining influences was immersed in mythology and cultural traditions. Offspring, dissatisfied with the intellectual power of their ancestors' explanations, sought new mythologies in their search for a better understanding of the cosmos and their relationship with it.

Starting in the late 17th century, a new mythology arose in Europe that was based on scientific principles and provided the basis for a more reliable understanding of the relationship between humans and sunlight. By the start of the 19th century, the application of these principles led to the realization that sunlight is not a single stimulus but, rather, a collection of stimuli of different wavelengths (*e.g.* infrared, visible, ultraviolet). This realization inspired additional studies aimed at determining whether different wavelengths might be responsible for the different effects of sunlight. As this review documents, indeed they are.

This review focuses primarily on studies before 1920 that were involved in the discovery of UV radiation, its properties and its influences on living organisms. After 1920, the number of UV-related publications grew rapidly, reaching at least 275 for the years 1920–1927 alone (1). Between 1960 and 2001, there are 37 466 publications on the subject "ultraviolet radiation" listed in PUBMED, a U.S. government-supported computer database of health-related research. Due to the extent of the literature, this review covers only the most important studies between 1920 and 2001. The selection of these studies was made solely by the author, and any omissions and shortcomings are his responsibility. There are a number of excellent reviews on UV photobiology written between 1920 and 2001, and these should be consulted for more in-depth analyses (*cf.* [1–20]).

We begin with the discovery of UV radiation, its properties and relationship with sunlight. These discoveries were unveiled through a series of serendipitous observations coupled with

improvements in instrumentation and careful experimentation. This is followed by a more detailed discussion of the evidence linking sunlight and UV radiation with physiological and pathological changes in humans, nonhuman animals and microorganisms. Each group has its own unique narrative relating it to UV radiation. A recurring theme is that UV radiation has both beneficial and harmful effects depending upon the type of organism, wavelength region (UVA, UVB or UVC) and irradiation dose (intensity × duration).

THE DISCOVERY OF UV RADIATION, ITS PROPERTIES AND RELATIONSHIP WITH SUNLIGHT

The discovery of UV radiation and its properties was a gradual process that spanned three centuries and involved scientists from many countries (21–24). In 1614, Sala made a seminal observation. He noticed that sunlight turned silver nitrate crystals black. In 1777, Scheele found that paper soaked in silver chloride solution darkened when exposed to sunlight. When he directed sunlight through a prism onto the paper, the violet end of the spectrum was more effective than the reddish end.

In 1801, Ritter made the hallmark observation. He noticed that invisible rays just beyond the violet end of the spectrum were even more effective at darkening silver chloride–soaked paper. He called them "deoxidizing rays" to emphasize their chemical reactivity and to distinguish them from the "heat rays" at the other end of the visible spectrum. Over time, the simpler term "chemical rays" was adopted to describe these invisible rays along with the adjacent violet-blue rays. The terms chemical and heat rays remained popular throughout the 19th century, but they were eventually dropped in favor of the more restrictive terms ultraviolet and infrared radiation, respectively.

Initial studies of the chemical rays focused on their ability to stimulate chemical reactions. In 1809, Gay Lussac and Thénard demonstrated that concentrated sunlight was capable of converting a mixture of hydrogen and chlorine gases into hydrochloric acid. In 1815, Planché noted that chemical rays darkened many kinds of metallic salts. Between 1826 and 1837, Niépce and Daguerre found that silver iodide was especially light-sensitive, and they used this discovery as the basis for their early work in photography. In 1842, Becquerel and Draper independently showed that when sunlight was passed through a prism onto a daguerreotype plate (a gelatin emulsion containing silver iodide), wavelengths between 340 and

400 nm induced a photochemical reaction. This was the first indication of the spectral extent of UV radiation.

During the 19th century, physicists made several important theoretical and empirical contributions that helped to clarify the properties of UV radiation. In 1802, Wollaston expanded on Newton's earlier observation that sunlight was composed of different colors by showing that sunlight possesses discrete bands of light rather than a continuous spectrum. In 1814, Fraunhofer mapped over 500 bands of sunlight, later called "Fraunhofer lines," some of which are within the UV region. In 1859, Kirchoff and Bunsen invented the spectroscope and demonstrated that different atoms absorb and emit different wavelengths of light. They speculated that the gaps in the solar spectrum are the result of selective absorption by atoms in the Earth's atmosphere.

A major breakthrough in photophysics came in 1865 when Maxwell proposed a theory that light and sound are part of a larger spectrum of energy with wave-like properties. He called them "electromagnetic waves" because he believed that they were generated by the interaction of electric and magnetic fields. In 1882, Maxwell's theory was confirmed by Hertz who developed a means for measuring microwaves, the first empirical evidence for radiation beyond the UV–visible–infrared spectrum. His results reinforced the belief that electromagnetic radiation travels in waves at discrete frequencies (or wavelengths).

The development of artificial lighting provided another source of UV radiation, although this was not appreciated at first. In 1808, Davy invented the "open" arc lamp using charcoal electrodes attached to a large Voltaic battery. Unfortunately, the charcoal electrodes deteriorated in the process. In 1843, Foucault tried carbon electrodes that were more stable, but the arc was dim. In 1876–1877, Jablochkov and Brush bolstered the power of carbon electrodes using the Gramme dynamo and generated the first useful electric arc lamps. In 1898, Bremer introduced fluoride salts into the carbon electrodes that further enhanced their brightness. In 1850, Stokes used aluminum electrodes to produce a "closed" arc lamp in a quartz tube that emitted UV rays to 185 nm. In 1835, Wheatstone invented the mercury (Hg) vapor lamp, which was brighter than previous arc lamps, but it was prone to flicker and deterioration. It would take the contributions of many inventors over the next 66 years before Cooper-Hewitt would produce the first commercially viable Hg vapor lamp.

In 1802, Davy showed that artificial light was produced by passing electrical current through a platinum wire. Although simpler than the open arc lamp, it was not as bright. Nevertheless, in 1820, De La Rue turned Davy's observation into the first incandescent light bulb. In 1879, Swan enhanced the brightness by using a thin carbon filament instead of platinum wire. The same year, Edison patented an incandescent lamp based on a thin cotton filament encased in a partly evacuated tube. His lamp burned brighter and longer (50 h) than any other incandescent lamp, and it soon replaced arc lamps as the most popular form of artificial lighting. In 1906, Coolidge invented the tungsten light bulb. Tungsten is more malleable than other metals, allowing it to be coiled; with more wire, it burned brighter and longer than other incandescent bulbs. Tungsten also emits a broader spectrum than carbon-based filaments, yielding a whiter (and more UV-intensive) light.

Another significant development in photophysics was the invention of devices for quantifying radiation. In 1829, Nobili invented the thermopile, and it was improved in 1852 by Melloni. In 1876, Crookes invented the rotating vane radiometer, and in 1878 Langley invented the bolometer. All three inventions used blackened metal to absorb radiation, but each device differed as to how the radiation was quantified. The thermopile used a stack of tightly packed metal plates to amplify the photoelectric signal. The radiometer measured light intensity by the number of revolutions induced over time, and the bolometer measured a decrease in electrical resistance upon absorption of radiation. Each provided an effective means of measuring radiation throughout the UV–visible–infrared spectrum.

Early in the 20th century, new discoveries in photochemistry and photophysics improved both theoretical and empirical understandings of the behavior of electromagnetic radiation. In 1900, Planck theorized that radiation is composed of tiny packets of energy called "quanta." In 1905, Einstein theorized that Planck's quanta were massless particles of energy (named "photons" in 1928 by Lewis) that are released from atoms and molecules upon absorption of light. In 1913, Bohr proposed that electrons absorb the light energy and reemit it at wavelengths that correspond to the electron's energy. In 1926, Schrödinger developed a theory of wave mechanics that treated electrons as waves rather than particles. These theories provided a new conceptual framework for studies of radiation.

About the same time, experimentalists were devising new ways to measure the extent of UV radiation. In 1903, Schumann used a carbon spark discharge lamp and fluorite prism placed in a vacuum chamber (called a "vacuum spectrograph") to detect the emission of hydrogen at 120 nm. In 1906–1908, Lyman used the vacuum spectrograph to detect emission of helium at 50 nm. He also demonstrated that oxygen, but not nitrogen, absorbs radiation between 127 and 176 nm. In 1920, Millikan used a high-intensity nickel spark lamp in a vacuum spectrograph to measure the emission of hydrogen at 20 nm. He also detected the emission of weak X-rays indicating that there was no natural cut-off between UV and X-rays.

Atmospheric scientists helped to establish the relationship between sunlight and UV radiation. In 1902, Langley showed that the Earth's atmosphere reduces UV radiation by approximately 40 per cent. Based on Lyman's results, Miethe and Lehman proposed in 1909 that oxygen in the upper atmosphere absorbs most of the UV radiation. They determined that the lower limit reaching the Earth's surface was between 291.21 and 291.55 nm. In 1921, Fabry and Buisson measured the spectral composition of sunlight and the absorption characteristics of ozone. They surmised that ozone in the upper atmosphere is responsible for filtering most of the solar UV radiation. In 1919, Dorno demonstrated that the intensity of UV radiation penetrating the atmosphere varies throughout the day (greatest when directly overhead) and with the seasons of the year (greatest in summer).

By 1920, the existence of UV radiation, its properties and relationship with sunlight was well established. The potential for commercial and industrial applications shifted the focus to development of new sources (fluorescent lamps, photoflash lamps, stroboscopes, lasers, advanced photon source) and better devices for measuring it (filters, detectors, spectrometers). Research on the interaction of UV radiation with atoms, molecules, solutions and the atmosphere continued. An example of the latter is the work of Molina, Rowland and Crutzen, who have studied the destructive effect of industrial pollutants on the ozone layer. There was also increasing interest in understanding the effects of UV radiation on living organisms, especially humans. The connection between sunlight and UV radiation raised the possibility that many of the effects of sunlight that had been observed over the centuries might

be due to these invisible rays. As revealed in the following sections, there is ample evidence supporting such a connection.

(Note on terminology: During the 20th century, the study of UV radiation led to the development of different terminologies. Physicists developed a terminology based on the physical properties of UV radiation. They adopted the term "near UV" to refer to solar UV that reaches the Earth's surface, *i.e.* 290–400 nm. They used the term "vacuum UV" for the region that required a vacuum to measure it, *i.e.* below 180 nm. They used the term "far UV" for the region between the near and vacuum UV regions, *i.e.* 180–290 nm. Biologists developed a different terminology that emphasized the effects of solar UV on living organisms. They used the term "UVC" to refer to the solar region that was absorbed by the ozone layer in the Earth's upper atmosphere, *i.e.* below 290 nm, and therefore had no biological effect. The term "UVA" was used for the region 320–400 nm that penetrated window glass and had physiological effects on organisms. The term "UVB" was applied to the region between the UVC and UVA, *i.e.* 290–320 nm, and this region was believed to be responsible for the deleterious effects of sunlight on living organisms.)

HUMANS, SUNLIGHT AND UV RADIATION

Human fascination with sunlight undoubtedly began before the dawn of civilization (25–30). Our hominid ancestors must have recognized its importance for vision and warmth and, eventually, agriculture. Given the sun's importance and our ancestors' primitive understanding of the cosmos, it is not surprising that they worshiped the sun. Hieroglyphic-, cuneiform- and alphabet-based writings indicate that the sun was revered as a god by the Egyptians, Assyrians, Persians and Babylonians between 3000 and 500 BCE. Archaeological and anthropological evidence suggests that the sun was also deified by other ancient civilizations including the Druids, Aztecs, Incas and American Indians. Even the ancient Greeks, who were the first to write about the importance of sunlight in human health, worshiped the sun god Helios.

Around 400 BCE, two events of scientific importance occurred in Greece. The Ionian philosopher Anaxagoras was put on trial for promoting the idea that the sun is a big fiery rock, rather than a deity, and the Athenian physician Hippocrates prescribed heliotherapy (sunbathing) for both medical and psychological purposes. These events initiated a change, albeit a slow one, in human understanding of the relationship between sunlight and living organisms.

The practice of heliotherapy continued throughout the Greco-Roman era, and it appears in the writings of Herodotus (5th century BCE), Cicero and Celsus (second century BCE), Vitruvius (first century BCE), Pliny the Elder (23–79 CE), Galen (130–200 CE), Antyllus (third century CE) and Oribasius (325–400 CE). After the fall of the Roman Empire, the practice apparently fell into oblivion. It reappeared during the Early Middle Ages, documented by the Persian scholar and physician Avicenna (980–1037 CE). Sunbathing for medical and cosmetic purposes has continued to the present time due to a pervasive cross-cultural belief in the healing power of sunlight. As outlined in the following section, early scientific studies supported and reinforced this belief.

The health-promoting influence of sunlight

Although heliotherapy has been practiced for at least 2400 years, there was very little objective evidence supporting its purported therapeutic influence. By the 18th century, reports began to appear in the medical literature indicating that sunlight ameliorated different skin diseases. In 1735, Fiennius (cited in 31) described a case in which he cured a cancerous growth on a patient's lip using a sunbath. In 1774, Faure (cited in 30) reported that he successfully treated skin ulcers with sunlight, and in 1776 LePeyre and LeConte (cited in 28) found that sunlight concentrated through a lens accelerated wound healing and destroyed tumors.

There were also reports that sunlight had beneficial effects on internal maladies. In 1782, Harris (cited in 31) used irradiated mollusk shells to improve a case of rickets (fragile bones). In 1815, Loebel (32) used facial irradiation to heal a case of amaurosis (partial blindness caused by disease of the optic nerve), and in 1845, Bonnet (33) reported that sunlight could be used to treat tuberculosis arthritis (bacterial infection of the joints). In 1879, Martin (34) used stripes of blue and white light to treat progressive degeneration of the optic nerve.

Additional observations indicated that sunlight was capable of altering basic human physiology. In 1843, Scharling (35) measured reduced production of CO_2 in subjects at night, and in 1866 von Pettenkofer and Voit (36) reported that serum bicarbonate levels were lower at night. In 1850, Berthold (37) found that hair production was greater in the daytime, and in 1888 Feré (38) noted that breathing and pulse rate were reduced under red light. These results were supported by similar data from animal studies (see below), but it would be well into the 20th century before the notion of daily (circadian) rhythms would take hold.

Probably the most remarkable claim during this period was the positive influence of sunlight on mental health. This idea can be traced back to Hippocrates (cited in 39) who recognized that depression was more common in the winter months in Greece when there was less sunlight. In 1806, Pinel (39) identified two types of seasonal depression, one occurring in winter and another in summer. By 1845, his student Esquirol (39) documented several cases of both types of depression. In 1876, Ponza (40) reported that light therapy was beneficial for treating patients with mental illness. In particular, he found that violet-blue light was useful for reducing mania, whereas red light improved depression. During the 20th century, phototherapy would be rediscovered several times as an effective means for treating seasonal affective disorders (41–43).

One of the earliest indications that sunlight might have detrimental effects involved cases of smallpox. It had been known for centuries that sunlight aggravated smallpox, although the origin of this connection is unknown. By the time the son of Edward I of England (1239–1307 CE) contracted the disease, it was standard practice to cover patients and windows with scarlet sheets and blankets (29). This remedy was widely known and documented as far away as China and Japan during the Middle Ages. Nevertheless, there was virtually no scientific assessment of its effectiveness until the 19th century.

In 1832, Picton (44) was the first to document the detrimental effects of sunlight on patients with smallpox. He reported that soldiers confined to dungeons during a smallpox epidemic contracted the disease but recovered without suppuration or scarring. In 1848, Piorry (45) recommended keeping patients with the disease in darkened rooms until the disease passed. In 1867, Black (46) found that exclusion of sunlight slowed the development of the pustules of smallpox and prevented pit formation. By 1871, Waters (47) and Barlow (48) independently confirmed the positive results of light deprivation on patients with smallpox under

controlled conditions. They noted that the treatment was more effective if started early in the disease before eruptions. In 1898, Chatiniére (49) used similar red light therapy to treat measles.

Despite the widespread success of red light therapy, there was no agreement as to how it worked. In 1893, Finsen (50) speculated that the chemical rays were detrimental to smallpox patients, although he provided no evidence for this or offered any explanation as to how such rays might aggravate the disease. Four years later, he showed that chemical rays had the opposite effect in the treatment of lupus vulgaris (cutaneous tuberculosis). In this case, he demonstrated that the chemical rays from sunlight or an arc lamp had antibacterial actions (see section below on microorganisms) and that, under appropriate conditions, it cured the disease. For this accomplishment, he was awarded the 1903 Nobel Prize in Physiology or Medicine and endowed with financial support for the Finsen Light Institute in Copenhagen.

Diagnostic uses of light

The prospect of using light for diagnostic purposes was initiated by Richardson in 1868 (cited in 51). Using various light sources, most notably a magnesium arc lamp, he showed that light was transmitted through the more lucent structures of living and dead bodies. Absorption of light by internal structures allowed him to view the obscure outlines of bones of the hand and foot and structures within the cheeks, neck, chest and abdomen. Even pulsations within blood vessels were visible although the vessels themselves were indistinct. In an extremely emaciated young subject, the beating of the heart was faintly discernable although the motions of the heart valves were not. He also made similar observations of structures in a frog, chick and carp. In 1870, Nicholson (51) succeeded in viewing internal organs of the human body using a calcium lamp.

In 1898, Gebhard (52) used an arc lamp and daguerreotype plate to show that light can penetrate the human body. He placed the plate in the palm of his hand and shielded it from light with plaster of Paris. When the back of his hand was exposed to the lamp, the plate darkened demonstrating that light had passed completely through his hand. In 1901, Darbois (53) demonstrated that a piece of photographic paper, placed between two glass slides and inserted into the mouth and then irradiated with an arc lamp through the cheek, became blackened after 1 min. The previous year, Kime (54) showed that sunlight was capable of producing an image on a photographic plate after passing completely through the thorax. Despite these successes, the discovery of X-rays by Röntgen in 1895 and its incredible resolution shifted attention away from light as a diagnostic tool. It would reappear in the late 20th century, however, with the invention of optical coherence tomography (55).

The dark side of sunlight and arc lamps

Despite numerous observations on the growth-promoting and healing effects of sunlight, the underlying physiology was poorly understood. For centuries, conventional wisdom assumed that the warmth of sunlight simply accelerated the natural growth and healing powers of the body. Negative effects, like sunburn (erythema) and blindness caused by sungazing (solar retinopathy), were believed to be due to excessive exposure to the sun's heat. In 1821, Home (56) was the first person in the modern era to openly question this assumption. He argued that sunburn to the back of his hand was not caused by the heat rays of the sun because covering the opposite hand with a black cloth prevented the response even though the air temperature under the cloth was 6–8°F warmer. Furthermore, he found that illumination of the hand of a Negro failed to elicit sunburn even though the temperature of the Negro's skin increased by the same amount as his own.

Home was clearly puzzled by his results. He mentioned that he had experienced a severe burn on the back of his legs 40 years earlier during a voyage to the West Indies. This occurred despite the fact that he was wearing a thin pair of linen trousers. He stated "I could not image how it happened, always suspecting it to be the effect of the bites of insects; but I never satisfied myself upon that subject." Armed with his new results, he surmised that both burns were caused by the sun but not by the heat rays. He reasoned that black skin somehow provided a protective shield against sunburn. When he asked Sir Humphrey Davy for his interpretation of the results, Davy concluded that the radiant heat of sunlight was absorbed by black skin and converted into "sensible" heat. There was no indication as to what Davy meant by sensible, but this was likely an attempt to bring Home's results in line with the conventional wisdom.

Evidence that UV rays could be harmful to people came initially from scientists working with arc lamps. In 1843, Fizeau and Foucault (57) reported problems with their eyes after experimenting with a carbon arc lamp, and they suspected that it was caused by the chemical rays. In 1859, Charcot (58) noted that arc lamps caused skin burns, and he too believed it was due to the chemical rays. In 1889, Maklakoff (59) reported that welders experienced irritation of the eyes and skin within a few hours of exposure to high-intensity welding arcs. He noted a progression of effects including acute flu-like symptoms, erythema, pain and delayed pigmentation.

In 1889, Widmark (60,61) published his landmark studies confirming that UV rays from arc lamps were responsible for skin burns. He showed that burns were induced by the chemical rays of a carbon arc lamp transmitted through a prism and filtered through water to remove the heat rays. Furthermore, burns were avoided if the lamplight was filtered through window glass, indicating that rays below 320 nm were the primary culprits. These results were extended in 1891 by Hammer (62), who found distinct differences between sunburn caused by chemical and heat rays. He showed that heat rays caused redness of the skin that appeared quickly and disappeared shortly after exposure (within minutes). Chemical rays, on the other hand, caused redness that appeared several hours later, was persistent, and was followed by desquamation (loss of skin) and eventually increased pigmentation. These results were confirmed by Hausser and Vahle (63) in 1927, and they produced the first detailed action spectra for erythema and pigmentation.

Other investigators documented changes in skin attributed to the chemical rays of sunlight. In 1885, Unna (64) found that sun-exposed skin was thicker and displayed enhanced keratinization. In 1890–1892, Berliner (65) and Wolters (66) declared that chemical rays were responsible for sunburn, xeroderma pigmentosum and Hutchinson's summer eruptions. By 1894, Unna (67) was convinced that UV and, possibly, the violet-blue rays of sunlight were responsible for increased skin thickness, pigmentation and skin cancer in sailors. In 1896, Dubreuilh (68) reported that people with outdoor (rural) occupations were more prone to skin cancer than those with indoor (urban) occupations.

There were also reports of people who were unusually susceptible to sunburn. In 1886, Veiel (69) reported a case of

a woman who became sunburned through a window glass. Because she was protected by a red veil, Veiel concluded that it was caused by the sun's chemical rays. In 1898, Anderson (70) reported that two patients exhibiting seasonal sunburn (hydroa aestivale) possessed an unusual porphyrin-like pigment in their urine. Ehrman (71) suggested that this pigment was hematoporphyrin, although Günther (72) noted that not all patients with porphyrinuria were light-sensitive. In 1913, Meyer-Betz (73) confirmed the photosensitizing properties of hematoporphyrin by administering it to himself.

The safety of arc lamps and sunbathing is debated

By the start of the 20th century, additional reports questioned the safety of arc lamps and the healthiness of sunbathing. Moeller (74) demonstrated that continuous exposure of skin to an arc lamp caused a sequence of changes that included vasodialation, swelling of the extracellular space, hyperplasia of the epidermis and an abnormal horning process. Hyde (75) described similarities in the damaging action of UV rays, X-rays and radium exposure on skin, and he presented epidemiological data suggesting that sunlight causes skin cancer.

In 1916, Burge (76) argued that glass blower's cataracts, caused by arc lamps, are due to absorption of UV rays by the lens proteins leading to their precipitation. The same year, Verhoeff and Bell (77) showed that cataracts are caused by an indirect process initiated by the heat rays of the arc lamp. They found that absorption of heat caused damage to the ciliary body leading to malformation of the lens. In 1920, Van der Hoeve (78) showed that absorption of UV rays had the same effect, *i.e.* damage to the ciliary epithelial cells, interfering with the nutrition of the lens. By 1922, Schanz (79,80) argued that both infrared and UV rays are responsible for the cataracts of glass workers.

Despite these observations, many health professionals, especially those working at the Finsen Light Institute, continued to extol the virtues of heliotherapy as long as protective eyewear was used. Their advice was bolstered by a growing list of diseases that could be treated with heliotherapy including verrucose tuberculides, lupus erythematosus, alopcia areata, acne vulgaris and naevus vascularis planus (50). In addition, investigators from outside of the Finsen Institute obtained positive results with light therapy. Schouli (81) and Festner (cited in 82) used red light to reduce the severity and duration of scarlet fever and skin inflammation (erysipelas). Bernhard (cited in 83) and Rollier (83) used Alpine sunbaths to heal wounds and surgical (extrapulmonary) tuberculosis. Hasselbalch and Jacobaus (84) used a carbon arc lamp to treat cardiac afflictions, and Huldschinsky (85) used sunbaths and UV rays from an Hg arc lamp to treat rickets. By 1924, Hess (86,87) and Steenbock (88) and their colleagues had independently shown that sunlight cured rickets by inducing vitamin D production in the skin.

Light was also used successfully to treat diseases of the eye. Nesnamov (cited in 89) used sunlight through a collecting lens to treat corneal ulcers. Nicolas (90) used sunlight to treat conjunctival tuberculosis and an Hg arc lamp to treat scrofula and tuberculosis of the outer eye. Schanz (80) confirmed Nicolas's results and added eyelid eczema to the list of eye diseases treatable with light. Duke-Elder (91) showed that UV rays were effective for treating tubercular and inflammatory eye conditions involving the conjunctiva, cornea, iris, ciliary body, choroids and retina. By 1923,

Wright (92) recommended using concentrated sunlight or artificial light to treat trachoma and corneal ulcers.

Although the above studies focused on the therapeutic effects of light therapy, other investigators studied the body's natural adaptive responses to sunlight. In 1901, Ehrmann (93) reported that skin tanning arises from local stimulation of melanin production inside specialized skin cells (melanoblasts). In 1916, Jüngling (94) showed that melanin production was enhanced by light rays longer than 330 nm, whereas sunburn was induced by rays below 330 nm. In 1920, With (95) argued that skin thickening helps protect against the damaging effects of UV rays, and Rollier (83) reported that heliotherapy for surgical tuberculosis was more effective in tanned people. These results were interpreted as evidence that the body is endowed with natural mechanisms for regulating the amount of light exposure.

Rollier also noted that heliotherapy was accompanied by increased lymphocyte production (lymphocytosis) suggesting a potential beneficial effect of sunlight on the immune system. This observation was consistent with evidence obtained by Wickline (96) and Chamberlain and Vedder (97) between 1908 and 1911 that showed that lymphocytosis developed gradually over many months for Americans living in the Philippines. In 1919, Taylor (98) reported that 25 of 38 adults at a summer retreat in Massachusetts (USA) displayed an increase in lymphocyte production. Although these studies did not control for other environmental variables (*e.g.* climate and lifestyle changes), Aschenheim (99) demonstrated that exposure of infants to direct sunlight, for as little as 1 h, resulted in lymphocytosis. There was also compelling evidence from animal studies that supported these claims (see below).

By 1920, the overriding consensus was that sunlight had a positive influence on health. According to Laurens (1), "at one time there was considerable argument as to whether ultra violet radiation could act directly on deep seated organs, and there are still some who believe that this is the case. The only reasonable conclusion, however, is that following ultra violet irradiation some photochemical substance formed in the skin is carried by the blood stream to these various organs, there bringing about the observed changes." He continued "the sun bath by dilating the capillaries activates the circulation and may induce a continuous tonic action on the sensory nerve terminals in the skin, thus restoring tone to muscles and promoting physiologic processes throughout the body. This is the probable explanation of the increased metabolism of the body, of the improvement in general health and of the increased resistance to disease."

The possibility that sunlight and its associated UV rays might be harmful to humans did not take hold until later in the 20th century. This change in attitude was influenced by four main factors. First, experimental studies using animals and microorganisms provided compelling evidence of the damaging effects of UV rays, as described in the following sections. Second, evidence emerged that other kinds of radiation (*e.g.* X-rays, gamma rays) had deleterious effects on living organisms fostering the belief that all forms of *radiation* are harmful. Third, governmental agencies were established with the responsibility of supporting health-related research, and they took a proactive role in funding investigations that studied the pathological effects of UV radiation. Fourth, additional epidemiological data indicated a correlation between skin cancers and excessive exposure to sunlight. The collective influence of these four factors eventually shifted the opinion of the scientific community and the public. By the end of the 20th

century, exposure to direct summer sunlight for extended periods was considered a health risk.

ANIMALS, SUNLIGHT AND UV RADIATION

Physiological effects

Experimental investigation of the influence of sunlight on animals began in the early 19th century. As with the human studies, the earliest observations indicated that sunlight exerted a positive influence on animal health including enhanced growth, development, respiration and metabolism. In addition, there were physiological studies of the effect of light on contractile tissues, skin pigmentation, immune response and biological rhythms. There was much interest in whether these effects were mediated directly through the skin or indirectly through the central nervous system (CNS) *via* the eyes. There was only occasional mention of phototoxic or photophobic responses, although this possibility was vigorously investigated during the 20th century.

Growth and development. In 1824, Edwards (100) reported that sunlight enhanced the rate of development of frog eggs. Twenty-six years later, Higginbothom (101) showed that development of frog and salamander eggs progressed normally in the dark as long as temperature was controlled. In 1858, Beclard (102) found effects of light that were not as easy to explain. He noted that eggs of the common house fly, *Musca*, developed faster under violet-blue light compared with green, yellow, red or white light; furthermore, green light inhibited their development. In 1874, Schnetzler (103) found that green light also hindered the development of frog eggs. In 1878, Yung (104) reported that violet-blue light increased development and metabolism of frog, turtle and snail eggs, whereas red and green light hindered them. In 1880, Schenk (105) found that tadpoles obtained from eggs incubated under red light were more motile than those obtained from eggs incubated under blue light.

In addition to studies of egg development, there were reports on the effect of light on the growth of animals. In 1871, Pöey (106) reported that General Pleasanton had performed experiments showing that piglets grew faster under violet light compared with white light. In 1874, Hammond (107) noted that a 20 day old cat kept in the dark for 10 days weighed less than its littermate even though it had weighed more initially. After 5 days in normal lighting, the light-deprived cat weighed the same as its littermate. In 1900, Borissow (108) found that dogs and rabbits grown in light weighed more at the end of a month than those grown in dim light. In 1924, however, Degkwitz (109) was unable to show any effect of light on the growth of puppies so long as their diet and exercise were carefully controlled.

In general, the above studies indicated that light had a stimulatory effect on growth and development, although it depended upon the color of the light. The most consistent stimulatory effects were obtained with violet-blue light, although the quality of the filters (usually liquids) and the intensities of the light were not addressed. Nevertheless, additional studies demonstrated other positive effects of chemical (UV and violet-blue) rays on living organisms, as described below.

Respiration and metabolism. In 1858, Beclard (102) noted that violet-blue light enhanced CO_2 production in adult frogs but not in the birds or mammals he tested. In 1870, Selmi and Piacentini (110) reported that yellow light enhanced CO_2 production in a dog, hen and turtle. In 1872, Chassanowitz (111) confirmed Beclard's results using frogs and further showed that it was not due simply to

enhanced motor activity during illumination. In 1875, Von Platen (112) found that illumination of the frog retina stimulated oxygen uptake, CO_2 production and increased metabolism. The same year, Pott (113) showed that an individual mouse produced more CO_2 under green or yellow light than under violet, red or sunlight. It also produced less CO_2 at night.

In 1879, van Pesch (114) found that pea beetles exposed to light consumed more oxygen than those in the dark. Two years later, Fubini (115) reported that frogs illuminated after lungectomies generated less CO_2 than normal frogs, indicating that the effect was not just a local skin response. The same year, Moleschott and Fubini (116) reviewed the literature and concluded that violet-blue light enhanced CO_2 production in amphibians, birds and mammals. They surmised that blinded animals produced less CO_2 during illumination and that both the respiratory rate and tissue respiration were affected. In 1885, Moleschott (117) reported that light-induced CO_2 production in frogs was mediated locally through the skin as well as through the visual system. By 1887, Fubini and Spallitta (118) showed that all colors were effective at increasing CO_2 production, though not to the same degree.

Vision and CNS involvement in light responses. In 1883, Lubbock (119) showed that ants are able to see UV rays, and in 1914 Van Herwerden (120) found that *Daphnia* (water fleas) responded to rays shorter than 334 nm. In 1924, von Frisch (121) demonstrated that bees can perceive rays at 300 nm, and Lutz (122) confirmed that bees, wasps and fruit flies see UV rays. In 1924–1925, Schiemenz (123) and Wolff (124) provided evidence that fish can see the 365 and 340 nm lines of an Hg arc lamp. Recent evidence indicates that some birds are also capable of UV vision (125) and that insects (126) and fish (127) are endowed with the ability to perceive UV polarized light.

In 1922, Shoji (128) measured the extent of UV absorption by the cornea in 11 different kinds of animals (including man) and showed that it absorbs UV rays shorter than 300 nm. He found the average peak absorption of the lens was 366 nm and that substantial UV rays were transmitted to the retina in some animals. Mayer and Dworski (129,130) used UV rays from a Hg vapor lamp to treat experimentally induced corneal tuberculosis in rabbits and guinea pigs. Under virtually identical conditions, they found the treatment effective in the rabbits but not in the guinea pigs, indicating species differences in the effectiveness of the treatment.

Although the importance of the retina in vision and its anatomical connection to the CNS were well known by the 19th century, the visual transduction process was not understood. In 1866, Schutze (cited in 31) demonstrated that vertebrate eyes possess two kinds of photoreceptors: rods for dim vision and cones for color vision. In 1877, Boll (131,132) and Kühne (133,134) independently published their classical studies on visual purple (rhodopsin), the photoreceptor pigment of rods, and established that it was involved in the detection of light. Sixty years later, Hosoya (135) showed that rhodopsin absorbs UV as well as visible rays. Although UV rays are substantially absorbed by the cornea and lens, recent evidence indicates that they can affect mate choice, communication, foraging for food and circadian rhythms (136; also see Indirect Effects [Photosensitization], below).

Several investigators studied the influence of light on blinded animals. In 1876, Fubini (137) showed that blinded frogs put on more weight than normal frogs when both were raised under identical lighting conditions. Both groups displayed accelerated weight gains when light exposure was discontinued. In 1878, Bert (138) confirmed Fubini's results, and in 1879 Wedensky (139)

demonstrated that blinded frogs oriented their heads towards the light source so that both halves of their body received equivalent exposure. Upon decapitation, he showed that frogs experienced heightened spinal reflexes on the side facing the light. In 1888, Wedensky (140) reported that Golowin had discovered that light and heat enhance spinal reflexes in the frog.

In 1883, Graber (141) showed that blinded salamaders and naturally blind ringworms avoided UV and violet-blue light, and he suggested that the response was mediated through the skin. In 1890, Dubois (142) confirmed that blinded salamanders displayed an aversion to shorter wavelengths of light, and, in 1895, Finsen (50) extended the results to frogs, earthworms, woodlice, beetles and flies. Around the same time, Loeb (143) and Hesse (144) reported that planarians (flatworms) move away from intense visible light, and Parker and Burnett (145) showed that even blinded planarians are negatively phototaxic. Agreeing with Graber, they believed that the response was mediated through the skin.

Contractile tissues. Several studies showed that light stimulated the motility of contractile tissues. Between 1844 and 1859, Arnold (146), Reinhardt (147) and Brown-Sequard (148) observed that artificial light induced contraction of the iris muscle in the extracted eyes of eels and frogs. Brown-Sequard further demonstrated that it was due to a direct effect of light on the pupillary sphincter muscle. In 1892, Steinach (149) extended these results to fish and amphibians by showing contraction of the papillary muscle in response to light in isolated eyes even after carefully removing the optic and oculomotor nerves.

In 1857, Marmé and Moleschott (150) found that communication across the frog neuromusclular junction was enhanced by light. In 1879, Uskoff (151) noticed that spontaneous ciliary movement of isolated frog epithelial cells was momentarily stopped when illumination of the cells was changed from violet-blue to red light but not by red light alone. In 1905, Dreyer and Jansen (152) reported that UV rays caused capillary stasis in the frog's web, tongue and mesentery. In 1924, Campbell and Hill (153) obtained similar results using mesenteries of the frog and mouse.

Other studies demonstrated wavelength-dependent responses in excitable cells. In 1919, Adler (154) showed that UV, but not visible, rays stimulated smooth muscle contraction in the frog, rabbit and guinea pig. In 1954, Giese and Furshpan (155) showed that low-intensity UV rays increased the frequency of discharge of the stretch receptor of a crayfish muscle, whereas high-intensity UV rays decreased it. In 1957, Pierce and Giese (156) found that high-intensity UV rays reduced the amplitude of action potentials in the axons of frogs and crabs, but irradiation with blue light immediately afterwards reversed the effect (photoreactivation). In 1971, Fork (157) used violet-blue and green laser light to stimulate action potentials in slug neurons without causing permanent damage to the cells. Recently, Yuste and colleagues (158) have achieved the same result in mammalian neurons using an infrared laser and two-photon absorption in the violet-blue region.

Skin pigmentation. It is well known that chameleons become darker when exposed to direct sunlight. In 1852, Brücke (159) showed that this was the result of pigment cells moving to the surface, and he surmised that the response was mediated through the visual system. Shortly thereafter, Wittich (160) reported that frog skin became lighter in sunlight, the opposite of chameleons. In 1858, DuBois-Reymond (161) found that the skin of the electric catfish, like frog skin, became brighter in sunlight and turned black in the

dark. In 1874, Pouchet (162) found similar results with other types of fish raised in darkness. He also noticed that fish with cataracts (clouded corneas) were darker than their peers, suggesting involvement of the eyes in the production of pigmentation. In 1875, Bert (163) confirmed Brücke's observations on chameleons, but he proposed that it was caused by a local effect on the skin rather than mediated through the eyes (*i.e.* CNS). Bert (163) and Hoppe-Seyler (164) both showed that chameleons are more responsive to blue light than red or yellow light, indicating that changes in pigmentation were unlikely to be due to changes in skin temperature.

Immune system. The effect of light on the immune system was first reported by Kondratieff (165), who showed that violet and white light enhanced recovery of sepsis-induced infection in rabbits. Furthermore, he found that light increased the severity of sepsis-induced cramps as well as caused an increase in body temperature. When sepsis was severe, he noticed that violet and white light paradoxically decreased the animal's body temperature.

As with humans, sunlight stimulates lymphocytosis in animals. In 1908, Polito (166) detected lymphocytosis in rabbits exposed to direct sunlight for as little as 15 min. In 1921, Clark (167) found similar results with rabbits whose ears were shaved and irradiated with an iron arc lamp for 1 h. She showed that there was an initial transient drop in lymphocytes within the first few hours after irradiation, followed by an increase that reached a maximum 5 days after exposure, followed by recovery by the ninth day. Although all wavelengths between 230 and 750 nm induced the initial transient decrease, the subsequent increase was obtained only with rays between 230 and 320 nm. Whole blood irradiated outside the body and reintroduced showed no such effect. She proposed that UV rays produced a "cutaneous reflex" that stimulated lymphocyte-producing organs *via* the blood stream.

Some investigators speculated that lymphocytosis helps to explain both the positive and negative effects of heliotherapy in humans. In 1919, Murphy and Strum (168) demonstrated that mice with lymphocytosis show a high degree of immunity to certain transplantable tumors as well as enhanced resistance to bacterial infection. Around the same time, Levy (169,170) and Gassul (171) reported that UV irradiation of mice between 10 min and 56 h caused progressive engorgement of internal organs (especially the spleen) with blood. Clark (167) suggested that this may explain the lung hemorrhaging that was frequently seen after heliotherapy for tuberculosis.

Biological rhythms. The first evidence of biological rhythms originated with the study of plants. In 1729, De Mairan (cited in 172) showed that leaves display periodic movements even in complete darkness that corresponded to day–night cycles. Further studies by many investigators confirmed and extended these results, as reviewed by Bunning (173). The earliest evidence of light-dark cycles in animals was provided by Kiesel (174) in 1894. He described cyclical changes in arthropod pigmentation that persisted in the dark. Thirty years later, Marcovitch (175) found that the sexual development of aphids is dependent upon the length of daylight.

Between 1926 and 1932, Bremer (176) showed that pupation in insects is dependent upon light–dark cycles, Beiling (177) demonstrated that the activity of bees is dependent upon the time of day, and Bisonette (178) showed that the breeding behavior of ferrets is dependent upon the length of daylight. Rowan (179) reported that increased daylight enhances gonad development in the migratory junco bird. These results and others led Bunning (180), in 1936, to propose the concept of an endogenous biological

clock in animals modulated by daily cycles of light and dark. In 1959, Halberg (cited in 181) coined the term "circadian rhythms" to describe these cycles.

Until recently, most scientists believed that circadian rhythms in mammals were modulated only by visible rays. In 1987, Brainard and colleagues (182) demonstrated that UVA rays suppressed the nocturnal production of melatonin in mice, and in 1994 (183) they showed that UVA rays altered murine neuroendocrine and circadian rhythms. In 1995, Amir and Robinson (184) showed that UVA rays are capable of inducing phase shifts in the expression of a transcription factor (Fos) in the hypothalamus of the rat. Very recently, Berson, Yau and colleagues (185,186) have demonstrated that rat retinal ganglion cells are photosensitive, due to the photosensitive pigment melanopsin that absorbs throughout the UV and visible spectrum, and that these cells are responsible for setting the circadian clock.

Cultured cells. During the past decade, several groups have shown that irradiation of cultured cells with UV rays activates genes that influence cell division and immune responses. The activatable genes include plasminogen activator (187), interleukin-1 (188), c-fos (189), small proline-rich proteins (190), growth arrest and damage-inducible proteins (191), multi-drug resistance one gene (192) and p53 (193). Many of the UVC-inducible genes are activated by a transcription factor complex involving either AP-1, NFkB or p53 protein (194). In some cases, UVB and UVA rays induced similar responses. It remains unclear, though, whether these responses reflect physiological responses to UV rays or pathological effects due to cell injury.

Pathological effects

The possibility that sunlight and artificial sources of UV radiation might be harmful to nonhuman animals did not arise in force until the 20th century. Nevertheless, there were isolated reports in the previous century of inhibitory effects of light. As mentioned above, Beclard (102), Schnetzler (103) and Yung (104) noticed that green light inhibited the growth and development of both vertebrate and invertebrate eggs, although the spectroscopic properties of the filters were not described. Graber (140), Loeb (143), Hesse (144) and Finsen (50) reported that various vertebrate and invertebrate animals avoided UV and violet-blue light if the intensity was too high. In 1882, Marshall (195) noticed that the motile larvae of sponges accumulated on the side of the tank with less light, and 3 years later Ultzmann (196) found that isolated sperm survived for 48 h if protected from cold and light.

Early in the 20th century, the debate in the literature over the healthiness of heliotherapy and arc lamps provided the motivation for testing these ideas using animal models. The following studies are examples of pathological responses in animals that were induced by exposure to UV rays. In most cases, the investigators employed high-intensity artificial lights (arc lamps, fluorescent lamps, lasers) whose spectral emissions were enriched in UV rays. In these cases, the relevance of the results to sunlight is often unclear.

Circulatory and immune system damage. Campbell and Hill (153) reported that UV rays from either a carbon arc lamp or a Hg vapor lamp projected through a lens onto frog or mouse mesentery caused localized stasis in capillaries independent of temperature changes. Similar results were obtained with visible light if the tissue was bathed in eosin or hematoporphyrin. The latter induced the formation of thrombii and localized leukocytosis, whereas UV rays alone induced only leukocytosis.

Chronic low-dose solar-simulated UV radiation can cause both local and systemic immunosuppression (197,198). This has been shown using either UVA or UVB rays. Suppression of the immune system may permit the outgrowth of UV-induced skin tumors.

Reproductive system damage. In 1928, Altenburg (199) demonstrated that UV rays cause mutations in fruit flies if the rays reach the reproductive organs. One can only wonder whether other insects that are equally unprotected from sunlight and UV radiation are susceptible to similar damage and whether solar-induced mutations contribute to evolutionary changes.

Skin cancer. In 1928, Findlay (200) reported that skin tumors developed in depilated albino mice exposed for 8 months to UV rays from a quartz Hg vapor lamp. Exposure of mice to the combination of UV rays and coal tar produced skin tumors in only 3 months. In 1934, Roffo (201) demonstrated that skin cancer could be induced in rats by exposure to either sunlight or Hg arc lamps. In 1936, Funding *et al.* (202) found that 290–320 nm (UVB) was the region of sunlight most responsible for inducing tumors in experimental animals. These results coincided with Latarjet's (203) proposal that changes in atmospheric ozone levels could increase the risk of skin cancer.

In 1941, Blum and associates (204,205) reported that skin cancer could be reproducibly induced in the ears of mice exposed to UV rays from arc lamps. A single exposure was insufficient, and cancer developed over time in a predictable fashion. Total irradiation dose was important but not the exposure interval (reciprocity held). Only wavelengths below 320 nm worked. Unlike humans, dermal tumors in mice were common. The authors speculated that this could be due to the greater UV penetration of mouse skin. In 1943, Bain and Rusch (206) showed that UV rays are more effective in producing tumors in mice when given at low intensities over long periods rather than at high intensities over short periods.

In 1975, Freeman (207) irradiated mice with a monochrometer at intervals between 290 and 320 nm and produced the first action spectrum for skin cancer. Using daily dosages equivalent to the threshold dose for erythema production in untanned human skin, he found that the peak carcinogenic response occurred at 310 nm. His results supported the hypothesis that the carcinogenic effectiveness of UV rays is proportional to the erythema effectiveness. He speculated that the two effects may have a common or similar site of action.

In 1976, Zigman and colleagues (208) showed that longer wavelength UV rays from a "black light" are capable of inducing skin cancer in mice, a result confirmed by Strickland (209), who also noted that UVA rays were far more carcinogenic when combined with UVB. In 1993, Setlow *et al.* (210) reported that UVA and violet light (420 nm) from high-intensity lamps are capable of inducing cutaneous malignant melanoma in fish. In 1994, De Gruijl and van der Leun (211) calculated that skin cancer in hairless mice and humans occurs over a broad region of the solar spectrum with peaks at 300 and 380 nm, the shorter wavelength region approximately 1000-fold more effective.

The possibility that sunlight can cause mutations in skin cells leading to skin cancer has been supported by studies of tumor biopsies in humans and animals. Brash and colleagues (212,213) found mutations in the p53 gene in nonmelanoma tumors in humans, and De Gruijl and associates reported similar mutations in mouse skin irradiated with UVB rays (214). Quantitative studies suggest that this mutation is present in approximately 50% of human basal cell carcinomas and 15% of squamous cell carcinomas (212,215). The incidence of tumors with p53 mutations

is much higher in mice exposed to UVB rays, but approximately the same in mice exposed to UVA rays (216). Because the p53 gene controls cell cycle regulation, a loss of function mutation in this gene could be an early event in the initiation of nonmelanoma skin cancers.

Damage to cultured cells. Several investigators have noted that illumination of cells through a microscope caused deleterious effects. In 1879, Uskoff (151) noted that isolated white blood cells displayed greater outgrowth of processes during microscopic examination with red light compared with violet-blue light. In 1915, Lewis and Lewis (217) found that the mitochondria of embryonic chick cells degenerate after 15 min of microscopic observation. They also noted that the mitochondria-specific dye Janus green was toxic even in the absence of light. In 1916, Macklin (218) reported that cultures of embryonic chick heart degenerate quickly when illuminated through a microscope using daylight, tungsten globe or a Welsbach burner. Degeneration was exacerbated in the presence of dyes (gentian violet, Janus green), a result reported previously by Churchland and Russell (219) using cultured frog pericardial cells. As described in Indirect Effects (Photosensitization) (below), the result with the dyes probably involved the generation of toxic photoproducts due to the interaction of light with the dyes.

Macklin (218) and Kite (220) showed that placing a filter between the light source and condensor reduces phototoxicity in cultured plant and animal cells. The filter consisted of a glass vessel filled with a solution of dye (copper sulphate or copper acetate) that restricted transmission to wavelengths between 450 and 670 nm (actually 280–670; see ref. 221). In 1922, Goodrich and Scott (222) found that illumination of embryonic chick heart cells with a tungsten–halogen lamp was not harmful if the intensity was kept below 280 foot-candles. In 1958, Frederic (223) showed that 90 foot-candles was damaging to cells when using violet-blue light (436 and 511 nm) but not green, yellow or red light (556, 571 and 625 nm). In the presence of Janus green, he noted that even 4 foot-candles was toxic. Curiously, these authors failed to cite the substantial literature on the toxic effects of light and dyes on other tissues and organisms. It is unclear whether they were unaware of this literature or whether they felt that it was so well known that it did not need to be cited.

Between 1932 and 1934, Kemp and Juul (224) and Mayer and Schreiber (225) reported that UV rays retard division of cultured mammalian cells. In 1944, Carlson and Hollaender (226) used grasshopper neuroblasts to show that the effects of UV rays on cell division depend upon the cell cycle. Early prophase was the most sensitive period, resulting in slower division. In 1974, Wang *et al.* (227) reported that UVA rays killed cultured mammalian cells, although they suspected that it was due to toxic photoproducts induced in the culture medium. Between 1978 and 1980, Parshad, Sanford and colleagues (228,229) determined that UVA and violet-blue light had a lethal effect on cultured mammalian cells even when irradiated in saline. They provided direct evidence of single-strand DNA breaks and indirect evidence that production of hydrogen peroxide was involved. Peak and Peak (230) confirmed these results and demonstrated that DNA–protein crosslinking also occurs.

Damage to excitable cells. Between 1931 and 1957, many investigators demonstrated that exposure to UV rays decreases the excitability of neurons including Audait (231), Hutton-Rudolph (232), Lüthy (233), Booth *et al.* (234), Boyarsky (235), von Muralt and Stämpfli (236), Gasteiger (237), Lüttgau (238) and Pierce and

Giese (156). The absorbance of UV radiation by nerve cells differed from the action spectrum of the response (*i.e.* wavelength dependence). The absorption peak was between 240 and 270 nm, whereas the peak of the action spectrum was around 310 nm. This disparity led Booth and his associates to suggest that thiamin may be involved in the response. Lüttgau's results indicated that UV rays induce a decrease in membrane sodium permeability, consistent with the possibility of membrane injury. Chalazonitis (239) showed that the photodynamic action of dyes on nerve cells resembled the effect of UV radiation alone, suggesting a common mechanism.

Blindness. In 1916, Verhoeff and Bell (77) studied the effect of UV rays (below 305 nm) from an Hg arc lamp on the eyes of rabbits. They found dose-dependent effects on the conjunctiva, cornea, iris and lens. At low doses, there was a slight conjunctival hyperemia but no effect on the other ocular tissues. At medium doses, haziness of the cornea developed. At high doses, there was edema and purulent exudation in the cornea and iris. Upon microscopic examination, the lens capsular epithelium was swollen, and there was a ring of densely packed cells surrounding the exposed region. Some changes emerged 24–48 h after irradiation including shedding of the corneal epithelial cells and leukocyte infiltration of the damaged areas. There was evidence of repair after 3–10 days, and by 5 weeks all tissues exhibited marked recovery. There was no noticeable damage to the retina even with very intense exposures.

In 1976, Ham *et al.* (240) exposed the retinae of monkeys to high-intensity laser lines from eight monochromatic sources between 442 and 1064 nm. The violet-blue lines, but not the others, caused histological damage similar to that found in retinae from patients who gazed voluntarily at the sun for 1 h before submitting to enucleation for malignant melanoma. Because light transmission through the lens peaks at 470 nm, they argued that solar blindness is most likely caused by the shorter wavelengths of sunlight with possible thermal enhancement induced at longer wavelengths. Over the next two decades, many investigators would lend support to their hypothesis that violet-blue light is the primary cause of solar retinopathy (241).

Indirect effects (Photosensitization). There are reports in the literature describing enhanced light sensitivity in ancient Egyptian and Indian cultures caused by injestion of certain fruits and vegetables. There were, apparently, even attempts to treat various medical conditions using diet and light (242). Nevertheless, the first scientific reports for such a relationship were noted by Dammann (243) in 1883 and by Wedding (244) in 1887. They reported that animals that ate buckwheat in the sunlight developed bubble-forming rashes on their skin only in areas lacking pigmentation. Wedding hypothesized that sunlight caused a chemical reaction with the buckwheat as it traversed the cutaneous blood vessels in nonpigmented areas. This caused quite a stir and even the famous scientist Virchow expressed reservations about this interpretation (244). Over time, additional experiments supported Wedding's idea, and eventually the scientific community embraced it.

The first kind of supporting evidence came from an unlikely source. Raab (245) found that *Paramecia* stained with the fluorescent dye acridine red were killed when exposed to visible light. He also showed that animals treated with eosin and exposed to visible light suffered from edema and necrosis in the irradiated area. While investigating the cause of the toxicity, he found that neither the light nor the dye was toxic when given alone. Furthermore, the dye was nontoxic if exposed to light separately

and then applied. He concluded that it was the combination of dye and light that was responsible for the effect.

Between 1900 and 1910, von Tappeiner (Raub's mentor), Jodlbauer and their colleagues went on to show that this toxic effect (which they called "photodynamic sensitization") could be produced using any fluorescent dye and any wavelength (UV or visible) that excited the dye. This led von Tappeiner (246) to propose that it was the emitted light that was responsible for the toxicity.

In 1932, Blum (3) reviewed the results of 121 papers related to this topic, and he concluded that it was not the light but rather some chemical toxin produced by the interaction of light with the dyes. This effect, he pointed out, was clearly distinct from the direct effect of UV rays on cells. Photodynamic actions required a dye or some other chemical to interact with the light, and the response was dependent upon the presence of oxygen. The latter was demonstrated by Straub (247), who hypothesized that the photodynamic effect was due to direct oxidation of cellular constituents. Blum (3) surmised that cellular damage was an indirect effect caused by photooxidation of the dye, resulting in the generation of a toxic by-product, probably a peroxide. He also ventured that the photosensitivity of range animals feeding on either buckwheat or St. John's wort was due to the same kind of photochemical reaction.

In 1910, Hausmann (248) sensitized mice to visible rays by injecting them with hematoporphyrin, a natural blood-borne molecule that absorbs violet-blue light. He noticed lympocytosis especially near the surface muscles and speculated that damage to the blood vessels was the primary cause of the sensitization. In 1919, Adler (249) showed that visible light stimulated skeletal muscle if the muscle was sensitized with eosin. In 1928, Earle (250,251) found that illumination of cultured mammalian cells (fibroblasts and white blood cells) through a microscope was toxic if red blood cells were present. He presumed that the red blood cells produced a toxic by-product when exposed to light. In 1937, Büngeler (252) showed that photoactive compounds, which were not inherently carcinogenic, could enhance the carcinogenicity of light.

Based upon Raub's observations, von Tappeiner (253) predicted that the interaction of light with chemicals could be a useful tool in medicine. To test this idea, von Tappeiner and Jesionek (254) used topical eosin and light exposure to treat human skin tumors. Although they reported some success, it would take most of the 20th century to verify the utility of "photodynamic therapies" (255).

MICROORGANISMS, SUNLIGHT AND UV RADIATION

Microorganisms are single-celled animals that range in size from 100 μm to less than 1 μm in diameter. Their existence and role as mediators of infectious diseases were established during the 19th century. Improvements in microscopy allowed scientists to visualize their morphology and behavior as well as to investigate the conditions under which they propagated. It was during this period that scientists discovered the influence of light on these tiny creatures. Unlike the narratives for humans and nonhuman animals described above, the damaging effect of sunlight (and UV rays) on microorganisms was noticed early on.

Pathological responses

In 1845, Schmarda (256) reported that microorganisms found in stagnant water displayed different responses to light. Some searched for it; others fled from it; some grew in it; others were damaged by it. None lived exclusively in the dark. In 1875, Lessona (257) observed that marine pteropods and heteropods avoided sunlight and only approached the ocean surface at night. In 1879, Engelmann (258,259) obtained results that supported Schmarda's observations. He showed that the amoeba *Pelomyxa* became immotile upon illumination, whereas the photosynthetic alga *Euglena* was attracted to light.

About this time, Downes and Blunt (cited in 260) made one of the most influential discoveries in all of photobiology. They noticed that direct sunlight inhibited the growth of microorganisms in test tubes containing Pasteur solution. Illumination for several hours resulted in test tubes free of bacteria for several months (if the tube was subsequently sealed with a sterile cotton plug). Additional tests revealed that the bactericidal action was dependent upon the intensity, duration and wavelength of sunlight (violet-blue being the most effective), as well as on the availability of oxygen. Over the next 20 years, their results were confirmed and extended by numerous investigators who employed various types of bacteria, growth media and light sources.

In 1878, Tyndall (260) was the first to confirm Downes and Blunt's observations, but he suggested that it might be due to suppression of bacterial growth rather than a killing action. In 1882, Jamieson (260) agreed that sunlight had a bactericidal effect, but that it was most likely due to temperature elevation of the medium rather than a direct effect on the bacteria. In 1885, Duclaux (260) and Arloing (260) demonstrated that sunlight had a direct killing effect on pure cultures of *Tyrothrix scaber* and *Bacillus anthracis*, respectively. Duclaux noted different sensitivities to light between strains. In 1887, Roux (260) confirmed that oxygen was required for the bactericidal effect of sunlight on *B. anthracis* and its spores. In 1888, Gaillard (260) found that sunlight was damaging to many kinds of bacteria and spores but not to molds or yeast. He agreed that the rate of destruction was dependent upon the intensity of sunlight, the composition of the medium and the presence of oxygen.

In 1890, Janowski (260) showed that direct sunlight killed *Bacillus typhosus* in either liquid or gelatin medium. In addition, the effectiveness of sunlight was dependent upon the initial concentration of bacteria and independent of any effect on the medium. Koch (261) reported that sunlight killed the tubercle bacillus. In 1891, Tizzoni and Cattani (262) found that exposing the tetanus bacillus to 1 month of sunlight eliminated its lethal effect when injected into rabbits. This result was obtained only when the irradiation occurred in the presence of air (oxygen). Dandrieu (263) showed that sunlight had a sterilizing effect on water, and he recommended using artificial light as a means of sterilizing drinking water. In 1887, Klebs (264) noted in his "General Pathology" textbook that bacteria and other microorganisms grew best when shielded from light, especially sunlight. He recommended having bushes removed from pastures suspected of harboring anthrax because bushes shield the bacillus from sunlight.

In 1892, Geisler (260) used a prism and heliostat to show that sunlight and electric lamps were lethal to *Bacillus typhosus*. Using quartz test tubes, he demonstrated that UV rays were the most lethal, although longer wavelengths were damaging at higher intensities. Buchner (260) developed a very sensitive assay for cell death that allowed him to detect the killing action of direct sunlight in as little as 10 min. He ruled out any contribution of infrared rays by exposing the cultures through 0.5 m of water. This led him to

speculate that sunlight has a natural sterilizing effect on rivers, streams and lakes.

Between 1893 and 1895, Ward (260) performed a remarkable series of experiments demonstrating superb technical skill and ingenuity. Using improved versions of Buchner's assay and Geisler's apparatus, he showed that violet-blue and near UV (UVA) rays were the most damaging part of sunlight on bacteria. He also noted that pigmented fungi were resistant, consistent with the notion that pigments serve as protective filters. Finsen (50) showed that sunlight concentrated by a lens and passed through the ear of a white rabbit was capable of bactericidal action. In 1896, Westbrook (265,266) showed that the bactericidal effect of sunlight was greatest at the surface of cultures, whereas bacterial growth was facilitated deeper in the medium due to elevated temperature and decreased oxygen availability.

In 1893, Richardson (267) showed that sunlight had a sterilizing effect on human urine and that irradiation of urine in the presence of oxygen resulted in the generation of hydrogen peroxide. D'Arcy and Hardy (268) showed that UVA and violet-blue rays from a high-intensity electric arc lamp stimulated production of an oxidizing substance in water, possibly ozone. This, they suggested, might explain the bactericidal action reported by Ward. In 1927, Bedford (269) showed that UV light stimulated hydrogen peroxide production in culture medium. This led him to suggest that the destructive action of UV light on bacteria is caused by the interaction of light with photosensitizers in the medium resulting in hydrogen peroxide production leading to irreparable damage to the bacteria.

Between 1900 and 1904, Bie (270,271) used a carbon arc lamp and liquid filters to confirm that violet-blue and UV rays were lethal to bacteria. He also noted that oxygen was not required for the UV effect (272). In 1901, Strebel (273) showed that UV rays from cadmium and aluminum arc lamps were more powerful than sunlight for killing bacteria. Bang (274,275) reported that *Bacillus prodigiosus* exhibited different sensitivities to UV rays from metal arc lamps. He recorded lethality with 340–360 (UVA) and 200–300 nm (UVC + UVB), although the latter region was more effective, and lethality increased at warmer temperatures. In 1903, Barnard and Morgan (276) used a prism and several types of arc lamps to confirm that the greatest bactericidal action occurred at emission lines between 226 and 328 nm (UVC + UVB).

Between 1904 and 1905, Hertel (260) performed the first rigorous quantitative assessment of the effects of light on microorganisms. Using a thermopile and galvanometer, he demonstrated that UV rays from an arc lamp are several orders of magnitude more lethal than visible rays. The order of potency was UVC > UVB > UVA > visible rays. He also observed some interesting cellular behaviors in response to UV rays including avoidance, strange locomotory behaviors (circular, screwing and rotatory motions), cell contractions and death.

Between 1906 and 1907, Thiele and Wolf (277,278) used carbon and Hg arc lamps to confirm Bie's observation that the bactericidal action of UVB and UVC wavelengths did not require oxygen, whereas killing by UVA–visible rays did. They also noted that lethality to the longer wavelengths was more pronounced at higher temperatures (30–40°C). In 1910, Cernovodeanu and Henri (279,280) argued that the UV action of arc lamps on bacteria was independent of temperature. In 1914, Henri and Moycho (281) determined that 280 nm was the most lethal emission line of the arc lamps, and they calculated that an emission energy of 2×10^5 erg/cm^2 was needed to kill the bacteria. Henri and Henri (282) showed that sublethal doses of UV radiation modified the metabolism of *B.*

anthracis so that, unlike the original bacilli, it was able to obtain nitrogen from ammonium salts or amino acids as well as grow in sugar-containing media. This was the first demonstration of the mutagenic effects of UV rays.

In 1917, Browning and Russ (283) found no germicidal effect of a tungsten arc lamp with emission lines longer than 300 nm, although no intensity measurements were reported. Bovie and Hughes (284) found that a sublethal dose of UV rays at 280 nm inhibited cell division of *Paramecia*. They noticed that upon removal of the irradiation, cell division was often accelerated. Henri (285) found that egg albumin absorbs rays in the UV region leading him to suggest that the bactericidal effect of sunlight is proportional to protoplasmic absorption. Burge (286), however, killed bacteria with UV rays, extracted their enzymes and found that the proteolytic enzymes were unharmed.

In 1923, Bayne-Jones and van der Lingen (287) demonstrated that the absorption spectrum of a bacterial emulsion correlated with the wavelength-dependence of the bactericidal action between 185 and 350 nm. They found no bactericidal action at wavelengths longer than 350 nm even at 40°C or pH 4.6, conditions that accelerated killing at shorter wavelengths. Coblentz and Fulton (288) calculated the total energy needed to kill a single bacterium was 19 pW from an Hg arc lamp emitting at 170–280 nm. They demonstrated that continuous and intermittent exposures were equally effective (reciprocity). Wykoff (289,290) reported that the energy required to kill bacteria with X-rays was 100 times less than that required with even the most potent UV rays (*i.e.* 265 nm). He calculated that only one in four million absorbed UV photons is capable of causing cell death.

In 1929, Gates (291–293) measured an action spectrum for the bactericidal effect induced by an Hg arc lamp. The action spectrum corresponded to the absorption spectrum of nucleic acids with a peak response at 265 nm. He proposed that the bactericidal effect was caused by UV-induced damage to nucleic acids. He also noticed that cell division was more sensitive to UV rays than to cell growth. In 1945, Tatum and Beadle (294) used Hg arc lamps to induce mutations in *Neurospora*, supporting a direct effect of UV rays on nucleic acids.

In 1943, Hollaender (295) reported that *E. coli* were killed with light of 350–490 nm (UVA + violet-blue), but it required 10 000–100 000 times more incident energy than at 265 nm (UVC). The response at longer wavelengths was also different in that it displayed a threshold, temperature coefficient (Q_{10}) of 2 and caused retarded growth and other sublethal effects. Jagger and colleagues (296) confirmed Hollaender's observation that UVA rays inhibited bacterial growth as well as cell division in the absence of exogenous sensitizing agents. Webb and Bhorjee (297) demonstrated that UVA and violet light as low as 5 kJ/m^2 completely inhibited the induction of an enzyme in *Escherichia coli* (b-galactosidase).

Webb (15) reviewed the literature showing that UVA rays cause lethal and mutagenic effects in microorganisms even in the absence of exogenous photosensitizers. Unlike UVB effects, UVA effects are oxygen-dependent. In 1980, D'Aoust and colleagues (298) showed that flavins are endogenous photosensitizers that underly the damaging effect of visible light in bacteria. Hartman (299) reported that irradiation of *E. coli* with UV rays (300–400 nm) induced hydrogen peroxide production, a process that probably involves flavins (300).

In 1960, Beukers and Berends (301) demonstrated that irradiation of frozen solutions of thymine with UVC resulted in

the formation of thymine dimers, and this eventually led to the discovery that dimers could be formed between adjacent pyrimidines (302). Hanawalt and Setlow (303) showed that DNA synthesis rate in bacteria recovers after UV exposure. In 1964, Setlow and Carrier (304) and Pettijohn and Hanawalt (305) independently found that DNA is spontaneously repaired in bacteria after UV exposure. This eventually led to the notion of nucleotide excision repair (306).

In 1949, Kelner (307) found that the survival of bacteria exposed to UV rays is higher if they are illuminated with visible light immediately afterwards (called "photoreactivation"). This led to the discovery of the enzyme photolyase, a flavin-based enzyme activated by violet-blue light that repairs pyrimidine dimers (308). Studies of DNA repair mechanisms in bacteria have contributed to unraveling the basis of certain human disease including xeroderma pigmentosum and Cockayne syndrome (309,310). There is also emerging evidence that binding of transcription factors to the promoter regions of genes can inhibit repair and create hotspots for UV photoproducts (311,312).

Physiological responses

The physiological response of microorganisms to light was first noticed by Schmarda (mentioned above), but the first rigorous studies were performed by Engelmann. In 1879, he found that *Euglena* was attracted to light (*i.e.* positively phototaxic) and that the light sensitivity resided at the base of its flagellum (258,259). In 1883, he demonstrated that phototaxis of other protozoans toward *Euglena* was due to light-induced production of oxygen in the latter (313). In 1888, he showed that photosynthetic (purple) bacteria congregated in the near infrared region of the spectrum, *i.e.* 800–900 nm (314). He inferred that this was a region of absorption by a pigment with properties similar to chlorophyll (he called it "bacteriochlorophyll") that was important for the photosynthetic growth of the bacteria.

In 1888, Loeb (315) proposed that phototaxis of *Euglena* is due to differential stimulation of their pigmented eyespots (stigma), rather than direct activation of the flagellum. In 1911, Mast (316) reported experiments indicating that phototaxis involves both the eyespots and the flagellum. In his model, flagellar motion causes the bacterium to rotate; rotation, in turn, causes alternating exposure of a photoreceptor adjacent to each eyespot (which periodically shades the photoreceptors) producing a succession of on–off responses. The latter allows alignment of the axis of the bacterium to the light. In 1915, Buder (317) determined that *Euglena* oriented toward a light source in the direction of the light rays, rather than to the light-intensity gradient. Brucker (318) observed that the threshold for phototaxis in *Euglena* was raised by light adaptation. Links (cited in 319) proposed a model for bacterial phototaxis which hypothesized that light-induced elevation of intracellular ATP activates the flagellar motor.

In 1902, Beijerinck (320) reported that chromogenic bacteria are attracted to light. Pieper (319) found that blue-green algae were attracted to light greater than 575 nm but were negatively phototaxic to light below 500 nm. Between 500 and 575 nm, he found that the reaction was positive in dim light and negative in bright light. In 1919, Metzner (321) showed that nonphotosynthetic spirilla became phototactic when impregnated with the photo-senstizing dye eosin. In 1948, Manten (322) proposed that phototaxis in purple bacteria results from the sudden decrease in the rate of photosynthesis upon leaving the light. In 1956, Schlegel

(323) showed that purple bacteria, which are normally attracted to light, are negatively phototaxic if the intensity is too high. In 1959, Clayton (324) reported that phototaxis of purple bacteria occurs in the absence of oxygen and carbon dioxide.

In 1955, Zalokar (325) found increased photocarotenogenesis in *Neurospora* (fungus) exposed to violet-blue light. Curry and Gruen (326) demonstrated positive phototropism to violet-blue light using *Phycomyces* (fungus). In 1960, Delbrück and Shropshire (327) showed that the action spectrum for phototropism in *Phycomyces* corresponded to the absorption spectrum of flavinoids. Sargent and Briggs (328) demonstrated that violet-blue light altered the circadian rhythm of *Neurospora*. Diehn (329) confirmed Curry and Gruen's observation using *Euglena*. In 1979, Bialcyzyk (330) reported that motile cells of *Physarum* (slime mold) avoided violet-blue light. Recently, Selbach and Kuhlmann (331) found that *Chlamydodon* (a ciliated bacterium) is capable of sensing the direction of light and that it is likely mediated by a photoreceptor excited by UVA and violet-blue rays.

Most studies of UVA and violet-blue light responses have implicated carotenoids and flavins as molecular photoreceptors. In 1935–1937, Castle (332) and Bünning (333) proposed that carotenes were involved in phototropism in the fruiting bodies of *Phycomyces* and *Pilobolus* (fungi) and in the coleoptiles of the plant *Avena*. In 1950, Galston (334) proposed the alternative "flavin hypothesis" in which riboflavin acts as a photosensitizing agent in the photooxidation and stimulation of the growth hormone (auxin) indole acetic acid. Forty years later, Galland (335) reported that flavins are still regarded as the most common photoreceptors in blue light responses, although carotenoids and pterins have been implicated in some cases.

One of the more controversial discoveries is the observation that cells produce, transmit and perceive ultraweak electromagnetic radiation (also called ultraweak photon emission, low-level bioluminescence and bioelectromagnetism). The controversy was instigated in 1923 by Gurwitsch (336), who reported that dividing *Paramecia* emit weak UV rays (luminescence) that are capable of stimulating cell division in other *Paramecia*. His results were supported by Alpatov and Nastjukova (337), who showed that the low intensity output from a broadband xenon arc lamp (visible and UV rays) increases the rate of cell division of *Paramecia*, whereas high intensities reduce it. Hollaender and Claus (338,339), however, were unable to obtain a mitogenic effect in bacteria with either UV or visible light. Using sensitive detection techniques, Popp (340) and others have measured spontaneous emission of low-intensity electromagnetic radiation (visible and UV) from many types of plant and animal cells including mammalian cells. The significance of these emissions, typically 10–100 photons per second, is still under investigation.

CONCLUSIONS

The discovery of UV radiation and its effects on living organisms was a gradual process that involved contributions from chemists, physicists and biologists. When it became clear that UV radiation is a component of sunlight, there was much interest in whether it might be responsible for some of the effects of sunlight on living organisms. The cumulative evidence to date indicates that UV radiation has both beneficial and harmful effects depending upon the type of organism, wavelength region (UVA, UVB or UVC) and irradiation dose (intensity × duration).

The biological data so far are consistent with the following general statements. First, high doses of either UVC, UVB or UVA radiation are harmful to all living organisms in the following order: UVC > UVB > UVA. In the case of UVC and UVB, the cause is direct damage to nucleic acids and proteins that can lead to genetic mutation or cell death. The mechanism underlying UVA damage is less well understood, but it probably involves the generation of reactive oxygen molecules that can damage many different components of cells including nucleic acids and proteins. Second, low doses of UVA radiation can induce physiological responses in organisms probably by activating specific genes. The mechanism underlying gene activation is unclear, and it is uncertain whether low doses of UVC and UVB radiation can induce similar responses. Third, many of the physiological and pathological effects of UVA radiation can be obtained with violet-blue light. This is most likley due to a common photochemical transduction process involving flavinoids and carotenoids.

REFERENCES

1. Laurens, H. (1928) The physiological effects of radiation. *Physiol. Rev.* **8**, 1–91.
2. Duggar, B. M. (1936) Effects of radiation on bacteria. In *Biological Effects of Radiation* (Edited by B. M. Duggar), pp. 1119–1149. McGraw-Hill Co., New York.
3. Blum, H. F. (1932) Photodynamic action. *Physiol. Rev.* **12**, 23–55.
4. Blum, H. F. (1945) The physiological effects of sunlight on man. *Physiol. Rev.* **25**, 483–530.
5. Blum, H. F. (1959) *Carcinogenesis by Ultraviolet Light.* Princeton University Press, Princeton, NJ.
6. Hollaender, A. (1946) Effects of ultraviolet radiation. *Annu. Rev. Physiol.* **8**, 1–16.
7. Hollaender, A. (1955–1956) *Radiation Biology,* Vol. 1–3 (Edited by A. Hollaender). McGraw-Hill, New York.
8. Giese, A. C. (1947) Radiations and cell division. *Q. Rev. Biol.* **22**, 253–282.
9. Giese, A. C. (1950) Action of ultraviolet radiation on protoplasm. *Physiol. Rev.* **30**, 431–458.
10. Giese, A. C. (1964) Studies on ultraviolet radiation action upon animal cells. In *Photophysiology,* Vol. 2 (Edited by A. C. Giese), pp. 203–245. Academic Press, New York.
11. Jagger, J. (1967) *Introduction to Research in Ultraviolet Photobiology.* Prentice-Hall, Englewood Cliffs, NJ.
12. Jagger, J. (1983) Physiological effects of near-ultraviolet radiation on bacteria. *Photochem. Photobiol. Rev.* **7**, 1–75.
13. Setlow, R. B. and J. K. Setlow (1972) Effects of radiation on polynucleotides. *Annu. Rev. Biophys. Bioeng.* **1**, 293–346.
14. Urbach, F. and P. D. Forbes (1976) Cutaneous photobiology: past, present and future. *J. Investig. Dermatol.* **67**, 209–224.
15. Webb, R. B. (1977) Lethal and mutagenic effects of near-ultraviolet radiation. *Photochem. Photobiol. Rev.* **2**, 169–261.
16. Senger, H. (1982) The effect of blue light on plants and microorganisms. *Photochem. Photobiol.* **35**, 911–920.
17. Ananthaswamy, H. N. and W. E. Pierceall (1990) Molecular mechanisms of ultraviolet radiation carcinogensis. *Photochem. Photobiol.* **52**, 1119–1136.
18. IARC (International Agency for Research on Cancer) (1992) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Solar and Ultraviolet Radiation,* Vol. 55. World Health Organization, United Kingdom.
19. Black, H. S., F. R. de Gruijl, P. D. Forbes, J. E. Cleaver, H. N. Ananthaswamy, E. C. deFabo, S. E. Ullrich and R. M. Tyrell (1997) Photocarcinogenesis: an overview. *J. Photochem. Photobiol. B* **40**, 29–47.
20. Hanawalt, P. C. (2001) Controlling the efficiency of excision repair. *Mutat. Res.* **485**, 3–13.
21. Burne, D. (1992) *Light.* Dorling Kindersley, London.
22. Luckiesch, M. (1920) *Artificial Light, Its Influence on Civilization.* Century, New York.
23. Pincussion, L. (1930) *Photobiologie.* Thieme, Leipzig.
24. Houston, R. A. (1938) *A Treatise on Light,* 7th ed. (Edited by Longmans). Green. New York.
25. Mead, R. (1748) *A Treatise Concerning the Influence of the Sun and Moon Upon Human Bodies, and the Diseases Thereby Produced* (English translation by T. Stack). Brindley, London.
26. Raum, J. (1889) Der gegenwärtige Stand unserer Kenntnisse über den Einfluss des Lichtes auf Bacterien und auf den thierischen Organismus. *Z. Hyg. Infektionskr.* **6**, 312–368.
27. Freund, L. (1904) *Elements of General Radio-Therapy for Practitioners* (English translation by G. H. Lancashire). Rebman, New York.
28. Rollier, A. (1923) *Heliotherapy.* Oxford Medical Publishers, London.
29. Goodman, H. (1926) *The Basis of Light Therapy.* Medical Lay Press, New York.
30. Russell, E. H. and W. K. Russell (1927) *Ultraviolet Radiation and Actinotherapy.* William Wood, New York.
31. Giese, A. C. (1964) Historical introduction. In *Photophysiology,* Vol. 1 (Edited by A. C. Giese), pp. 1–18. Academic Press, New York.
32. Loebel, L. (1815) Wichtige Ansichten über die Berücksichtigung der Insolation in mehreren Uebelseynsformen, vorzüglich in der Amaurose und über die Realisirung der Idee eines Sonnenbades. *J. der pract. Heilkunde* **40**, 56–85.
33. Bonnet, A. (1845) *Traite des Maladies des Articulations.* Bailliere, Paris.
34. Martin, E. (1879) De l'emploi de la lumiere bleue conjuguee avec la lumiere blanche dans le traitement des maladies chroniques de la retine et du nerf optique des bains de lumiere et des verres bichromiques. *Gaz. Hopitaux.* **52**, 115.
35. Scharling, E. A. (1843) Versuche über die Quantität der, von einem Menschen in 24 Stunden ausgeathmeten, Kohlensäure. *Ann. Chem. Pharm.* **45**, 214–242.
36. von Pettenkofer, M. and K. Voit (1866) Über die Kohlensäureausscheidung und Sauerstoffaufnahme während des Wachens und Schlafens beim Menschen. *Ber. Münchner Akad.,* Nov. 10 issue.
37. Berthold, A. A. (1850) Beobachtung über das quantitative Verhältniss der Nagel- und Haarbildung beim Menschen. *Arch. Anat. Physiol. Wiss. Med.* January 3 issue, 158–166.
38. Fere, C. (1888) *Degenerescence et Criminalite; Essai Physiologique.* Bailliere, Paris.
39. Wehr, T. A. and N. E. Rosenthal (1989) Seasonality and affective illness. *Am. J. Psychiatry* **146**, 829–839.
40. Ponza, G. (1876) De l'influence de la lumiere coloree dans le traitement de la folie. *Ann. Med. Psychol., Ser. 5,* **15**, 20.
41. Hasselbalch, K. A. (1905) Die Wirkungen des chemischen Lichtbades auf Respiration und Blutdruck. *Skand. Arch. Physiol.* **17**, 431–472.
42. Siebeck, R. (1946) Gedenktage: Dr. Helmut Marx. *Dtsch. Med. Wochenschr.* **71**, 322.
43. Lewy, A. J., H. E. Kern, N. E. Rosenthal and T. A. Wehr (1982) Bright artificial light treatment of a manic-depressive patient with a seasonal mood cycle. *Am. J. Psychiatry* **139**, 1496–1498.
44. Picton, J. M. W. (1832) Traitement de la variole par l'exclusion de la lumiere. *Arch. Gen. Med.* **30**, 406–407.
45. Piorry, P. A. (1848) *Traite de Medecine Practique et de Pathologie Iatrique ou Medicale,* Vol. 7, p. 495. Bailliere, Paris.
46. Black, C. (1867) How to prevent pitting on the face by small-pox in persons unprotected by vaccination. *The Lancet* July 29 issue, 792–793.
47. Waters, J. H. (1871) Action of light in small-pox. *The Lancet* Feb. 4 issue, 151–152.
48. Barlow, W. H. (1871) On the exclusion of light in the treatment of small-pox. *The Lancet* July 1 issue, 9–10.

49. Chatiniére, M. (1898) Contagiosite de la Rougeole Sa Phothérapie. *Presse Med.* No. 75, Septembre 10 issue, 78–79.

50. Finsen, N. R. (1901) *Phototherapy* (English translation by J. H. Sequeira). Edward Arnold Press, London.

51. Anonymous (1872) Dr. Richardson's researches on the transmission of light through animal structures. *The Lancet* Oct. 26 issue, p. 617.

52. Gebhard, W. (1898) *Die Heilkraft des Lichtes*, p. 131. Grieben, Leipzig.

53. Darbois, P. (1901) *Traitement du lupus vulgaire.* Thesis, Paris.

54. Kime, J. W. and P. Hortatler (1900) Light as a remedial agent. *Med. Rec.* (NY) **58**, 572–574.

55. Huang, D., E. A. Swanson, C. P. Lin, J. S. Schuman, W. G. Stinson, W. Chang, M. R. Hee, T. Flotte, K. Gregory, C. A. Puliafito and J. G. Fujimoto (1991) Optical coherence tomography. *Science* **254**, 1178–1181.

56. Home, E. (1821) On the black rete mucosum of the Negro, being a defence against the scorching effect of the sun's rays. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* (part 1), 1–6.

57. Fizeau and Foucault (1843) Observations concernant l'action des rayons rouges sur les plaques dagueeriennes. *C. R. Hebd. Seances Acad. Sci.* **23**, 679–682.

58. Charcot, P. (1859) Erytheme produit par l'action de la lumiere electrique. *C. R. Seances Soc. Biol. Fil.* **5**, 63–65.

59. Maklakoff (1889) L'influence de la lumiere voltaique sur les teguments du corps humain (l'insolation electrique). *Arch. Ophtalmol.* **9**, 97–113.

60. Widmark, E. J. (1889) Über den Einfluss des Lichtes auf die Haut. *Hygiea* 3, 1–23.

61. Widmark, J. (1889) De l'influence de la lumiere sur la peau. *Biol. Fören. Forhandl. Verhandlungen Biolog. Vereins* **1**, 9–13 and 131–134.

62. Hammer, F. (1891) *Über den Einfluss des Lichtes auf die Haut.* Ferdinand Enke, Stuttgart.

63. Hausser, K. W. and W. Vahle (1927) Sonnenbrand und Sonnen-bräunung. In *Zellteilung und Strahlung,* Vol. 6 (Edited by T. Reiter and D. Gabor), pp. 101–120. Springer, Berlin.

64. Unna, P. (1885) Ueber das Pigment der menschlichen Haut. *Monatsschr. prakt. Dermatol.* **4**, 277–294.

65. Berliner, C. (1890) Ueber Hutchinsons Sommererprurigo und Sommereruption. *Monatsschr. prakt. Dermatol.* **11**, 449, 480.

66. Wolters, M. (1892) Beitrag zur Kenntniss der Sclerodermie. *Arch. Dermatol. Syphilol.* **24**, 695–738 and 943–981.

67. Unna, P. (1894) Carcinom der Seemanshaut. In *Lehrbuch der speciellen pathologischen,* Vol. 6 (Edited by J. Orth, H. Steinbrügge, P. G. Unna and R. Greeff), p. 719. August Hirschwald, Berlin.

68. Dubreuilh, W. (1896) Des Hyperkeratoses circonscriptes. *Ann. Dermatol. Syphiligr.* **7**, 1158–1204.

69. Veiel, T. (1887) Ueber einen Fall von Eczema solare. *Arch. Dermatol. Syphilol.* **19**, 1113–1116.

70. Anderson, T. M. (1898) Hydroa aestivale in two brothers complicated with the presence of haematoporphyrin in the urine. *Br. J. Dermatol.* **10**, 1–4.

71. Ehrmann, S. (1909) Weitere Untersuchungen über Lichtwirkung bei Hydroa aestivalis (Bazin), Summereruption (nach Hutchinson). *Arch. Dermatol. Syphilol.* **97**, 75–86.

72. Günther, H. (1912) Die Haematoporphyrie. *Dtsch. Arch. Klin. Med.* **105**, 89–146.

73. Meyer-Betz, F. (1913) Untersuchungen über die biologische (photo-dynamische) Wirkung des Hämatoporphyrins und anderer Derivate des Blut- und Gallenfarbstoffs. *Dtsch. Arch. Klin. Med.* **112**, 476–503.

74. Moeller, M. (1900) *Der Einfluss des Lichtes auf die Haut in gesunden und krankhaften Zustande.* E. Nägele, Stuttgart.

75. Hyde, J. N. (1906) On the influence of light in the production of cancer of the skin. *Am. J. Med. Sci.* **131**, 1–22.

76. Burge, W. E. (1916) The mode of action of ultra-violet radiation in injuring living cells with special reference to those constituting the eye. *Am. J. Physiol.* **39**, 335–344.

77. Verhoeff, F. H. and L. Bell (1916) The pathological effects of radiant energy upon the eye. *Proc. Am. Acad. Arts Sci.* **51**, 629–818.

78. van der Hoeve, J. (1920) Eye lesions produced by light rich in ultraviolet rays. Senile cataract, senile degeneration of macula. *Am. J. Ophthalmol.* **3**, 178–194.

79. Schanz, F. (1922) Phototherapy in eye diseases. *Munch. Med. Wochenschr.* **69**, 1341–1342.

80. Schanz, F. (1922) Die physikalischen Vorgänge bei der optischen Sensibilisation und beim Sehakt. *Munch. Med. Wochenschr.* **69**, 215–216.

81. Schouli, E. (1899) Die Lichttherapie (Phototherapie) bei Scarlatina. *Z. diät. phys. Ther.* **3**, 612.

82. Bie, V. (1901) Behandlung von Masern und Scharlach mit Ausschl. der sog. Chem. Lichtstrahlen. *Mitt. Finsens Med. Lysinst.* **2**, 146.

83. Rollier, A. (1923) *Heliotherapy.* Oxford Medical, London.

84. Hasselbach, K. A. and H. Jacobaus (1907) Ueber die Behandlung von Angina pectoris mit starken Kohlenbogenlichtbäden. *Berl. Klin. Wochenschr.* **44**, 1247–1252.

85. Huldschinsky, K. (1919) Heilung von Rachitis durch künstliche Höhensonne. *Dtsch. Med. Wochenschr.* **45**, 712–713.

86. Hess, A. F. (1924) Experiments on the action of light in relation to rickets. *Trans. Am. Pediatr. Soc.* **36**, 57.

87. Hess, A. F. (1923–1924) The role of ultraviolet rays in rickets. *Atl. Med. J.* **27**, 467–469.

88. Steenbock, H. (1924) The induction of growth promotive and calcifying properties in a ration by exposure to light. *Science* **60**, 224–225.

89. Dworetsky, A. (1902) Die Entwickelung und der gegenwärtige Stand der Lichttherapie in Russland. *Z. diät. phys. Ther.* **5**, 235–250.

90. Nicolas, F. (1922) A report of three cases of tuberculosis of the conjunctiva. *Arch. Ophthalmol.* **51**, 379–383.

91. Duke-Elder, W. S. (1926) The therapeutic action of ultra-violet light upon the eyes. *Br. Med. J.* **1**, 891–895.

92. Wright, J. W. (1923) Solarization in trachoma. *Am. J. Ophthalmol.* **6**, 279–280.

93. Ehrmann, S. (1901) Erfahrungen über die therapeutische Wirkung der Elektricität und der X-Strahlen. *Wien. med. Wochenschr.* **30**, 1418–1419.

94. Jüngling, O. (1916) Vergleichende Untersuchungen über dir Wirkung des Sonnenlichtes und des Lichtes der Quecksilber-Quarzlampe ("künstliche Höhensonne") auf die Haut. *Strahlentherapie* **7**, 413–438.

95. With, C. (1920) Studies on the effect of light on vitiligo. *Br. J. Dermatol.* **32**, 145–155.

96. Wickline, W. A. (1908) The effects of tropical climate on the white race. *Mil. Surgeon* **23**, 282–289.

97. Chamberlain, W. P. and E. B. Vedder (1911) A study of Arneth's nuclear classification of the neutrophiles in healthy and adult males, and the influence thereon of race, complexion and tropical residence. *Philipp. J. Sci.* **6**, 405–419.

98. Taylor, H. D. (1919) Effect of exposure to the sun on the circulating lymphocytes in man. *J. Exp. Med.* **29**, 41–51.

99. Aschenheim, E. (1913) Der Einfluss der Sonnenstrahlen auf die leukocytäre. Blutzusammensetzung. *Z. Kinderheilkd.* **9**, 87–98.

100. Edwards, W. F. (1824) *De l'influence des agens physiques sur la vie,* Vol. 16, pp. 12, 13, 396. Crochard, Paris.

101. Higginbothom, J. (1850) Influence of physical agents on the development of the tadpole of the Triton and the frog. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **140**, 431–436.

102. Beclard, J. (1858) Note relative a l'influence de la lumiere sur les animaux. *C. R. Hebd. Seances Acad. Sci.* **46**, 441–443.

103. Schnetzler, M. J.-B. (1874) De l'influence de la lumiere sur le developpement des larves des grenouilles. *Bibl. Univ. Arch. Sci. Phys. Nat.* **51**, 247–258.

104. Yung, E. (1878) De l'influence des differentes couleurs du spectre sur le developpement des animaux. *C. R. Hebd. Seances Acad. Sci.* **87**, 998–1000.

105. Schenk, S. (1880) Zur Lehre über den Einfluss der Farbe auf das Entwickelungsleben der Thiere. In *Mittheilungen aus dem Embryologischen Institute der K.K. Universitat in Wien,* Vol. 1, pp. 265–277. University of Wien, Wien.

106. Pöey, A. (1871) Influence de la lumiere violette sur la croissance de la vigne, des cochons et des taureaux. *C. R. Hebd. Seances Acad. Sci.* **73**, 1236–1238.

107. Hammond, W. A. (1874) Some points relevant to the sanitary influence of light. *The Saniarian.* **1**, 58–63.

108. Borissow, P. (1902) Zur Lehre von der Wirkung des Lichtes und der Dunkelheit auf den thierischen Organismus. *Z. diät. phys. Ther.* **5**, 337–338.

109. Degkwitz, R. (1924) Über Einflüsse der Ernährung und der Umwelt auf wach sende Tiere. *Z. Kinderheilkd.* **37**, 27–97.

110. Selmi, A. and G. Piacentini (1870) Dell influenza del raggi colorati sulla respiratione. *Rend. Ist. Lomb. Sci. Lett. Milan* **3**, 51–56.

111. Chassanowitz, J. (1872) Ueber den Einfluss des Lichtes auf die Kohlensäureausscheidung im thierischen Organismus. Inaugural-dissertation. Königsberg.

112. Von Platen, O. (1875) Ueber den Einfluss des Auges auf den thierischen Stoffwechsel. *Pfluegers Arch.* **11**, 272–290.

113. Pott, R. (1875) Vergleichende Untersuchungen über die Mengenverhältnisse der durch Respiration und Perspiration ausgescheidenen Kohlensäure bei verscheidenen Thierspecies in gleichen Zeiträumen, nebst einigen Versuchen über Kohlensäureausscheidung desselben Thieres unter verschiedenen physiologischen Bedingungen. *Habilitationsschrift*, Jena.

114. Van Pesch, F. J. (1879) Eenige verschijnselen bij de ademhaling van kleine kevers. *Mandblad Naturwet.* **9**, 116–120.

115. Fubini, S. (1881) Ueber den Einfluss des Lichtes auf die Kohlensäure-Ausscheidung bei den Batrachiern nach Wegnahme der Lungen. *Untersuchungen Nat. Menschen Thiere* **12**, 100–111.

116. Moleschott, J. and S. Fubini (1881) Ueber den Einfluss gemischten und farbigen Lichtes auf die Ausscheidung der Kohlensäure bei Thieren. *Untersuchungen Nat. Menschen Thiere* **12**, 266–428.

117. Moleschott, J. (1885) Ueber den Einfluss des Lichtes auf die Menge der vom Thierkörper ausgeschieden Kohlsäure. *Wien. Med. Wochenschr.* **35**, 1081, 1109, 1137.

118. Fubini, S. and F. Spallitta (1887) Influenza della luce monochromatica sulla espurgazione di acido carbonico. *Arch. Sci. Med. (Torino)* **11**, 315–333.

119. Lubbock, J. (1883) Observations on ants, bees and wasps—part X. With a description of a new genus of honey ant. *Zool. J. Linn. Soc.* **17**, 41–52.

120. Van Herwerden, M. A. (1914) Ueber die Perzeptionsfähigkeit des Daphnienauges für untraviolette Strahlen. *Biol. Zentbl.* **34**, 213–216.

121. Von Frisch, K. (1924) Sinnesphysiologie und "Sprache" der Bienen. *Naturwissenschaften* **12**, 981–987.

122. Lutz, F. E. (1924) Apparently non-selective characters and combinations of characters including a study of ultraviolet in relation to the flower-visiting habits of insects. *Ann. N. Y. Acad. Sci.* **29**, 181–283.

123. Schiemenz, F. (1924) Über den Farbensinn der Fische *Z. Vgl. Physiol.* **1**, 175–220.

124. Wolff, H. (1925) Das Farbenunterscheidungsvermögen der Ellritze. *Z. Vgl. Physiol.* **3**, 279–329.

125. Pearn, S. M., A. T. Bennett and I. C. Cuthill (2001) Ultraviolet vision, fluorescence and mate choice in a parrot, the budgerigar Melopsittacus undulatus. *Proc. R. Soc. Lond. B* **268**, 2273–2279.

126. Wehner, R. (1989) Neurobiology of polarization vision. *Trends Neurosci.* **12**, 353–359.

127. Hawryshyn, C. W. (2000) Ultraviolet polarization vision in fishes: possible mechanisms for coding e-vector. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **355**, 1187–1190.

128. Shoji, Y. (1922) Untersuchung uber die Absorption der ultravioletten Strahlen durch die Augenmedian. *Mitt. Med. Fak. Kais. Univ. Tokyo* **29**, 61–129.

129. Mayer, E. and M. Dworski (1924) Studies with ultraviolet light. I. The effect of quartz-mercury-vapor irradiations (Alpine quartz-light) on experimental tuberculosis of the cornea in rabbits. *Am. Rev. Tuberc.* **10**, 146–156.

130. Mayer, E. and M. Dworski (1924) Studies with ultraviolet light. II. The action of quartz-mercury-vapor irradiation on inhalation tuberculosis in primarily infected and sensitized guinea pigs. *Am. Rev. Tuberc.* **10**, 157–165.

131. Boll, F. (1877) *Sull'anatomia e Fisiologia della Retina.* pp. 1–24. Roma.

132. Boll, F. (1877) Zur Anatomie und Physiologie der Retina. *Centralbl. Med. Wiss.* **15**, 230–233.

133. Kühne, W. (1878) *On the photochemistry of the retina and on visual purple* (English translation by Michael Foster). McMillan, London.

134. Kühne, W. (1878) Ueber die Farbstoffe der Vogelretina. *Centralbl. Med. Wiss.* **16**, 1–2.

135. Hoyosa, Y. (1937) Veranderung der Absorption und der Farbe des Sehpurpurs durch Bestrahlung im sichtbaren und ultavioletten Spektralgebiet. *Jap. J. Med. Sci. III. Biophys.* **4**, 49–52.

136. Hunt, D. M., S. E. Wilkie, J. K. Bowmaker and S. Poopalasundaram (2001) Vision in the ultraviolet. *Cell. Mol. Life Sci.* **58**, 1583–1598.

137. Fubini, S. (1876) Ueber den Einfluss des Lichtes auf das Körpergewicht der Thiere. *Untersuchungen zur Naturlehre des Menschen und der Thiere* **11**, 488–503.

138. Bert, P. (1878) Influence de la lumiere sur les etres vivants. *L'Abeille Med.* **7**, 981–990.

139. Wedensky, N. (1879) Ueber die Wirkung des Lichtes auf die Erregbarkeit der Haut bei Fröschen. *Bull. Acad. Imperiale Sci. St. Petersbourg*, p. 349.

140. Wedensky, N. (1888) *Das Tagebuch der III. Versammlung der Gesellschaft rüssischer Aerzte.* December 31 issue, no. 2.

141. Graber, V. (1883) Fundamentalversuche über die Helligkeits- und Farbenempfindlichkeit augenloser und geblendeter Thiere. *Sitzungsber. Math-Nat. Kl. kaiser. Akad. Wiss.* **87**, 201–236.

142. Dubois, R. (1890) Sur la perception des radiations lumineuses par la peau, chez les protees aveugles des grottes de la Carniole. *C. R. Hebd. Seances Acad. Sci.* **110**, 358–361.

143. Loeb, J. (1893) Ueber künstliche Umwandlung positiv heliotropischer Thiere in negativ heliotropische und umgekehrt. *Pfluegers Arch.* **54**, 81–107.

144. Hesse, R. (1897) Untersuchungen über die Organe der Lichtempfindlichung bei neiderer Thieren: II. Die Augen der Plathelminthen, insoderheit der tricladen Tubellarien. *Z. Wiss. Zool.* **62**, 527–582.

145. Parker, G. H. and F. L. Burnett (1901) The reactions of Planarians, with and without eyes, to light. *Am. J. Physiol.* **4**, 373–385.

146. Arnold, F. (1844–1951) *Handbuch der Anatomie des Menschen, mit besonderer Rücksicht auf Physiologie und praktische Medicin,* Vol. II. Emmerling, Freiburg.

147. Reinhardt (1843) Det Kongelige danske Videnskabernen Selskabs. *Isis* (edited by L. Oken). **12**, 732–734.

148. Brown-Sequard, C. E. (1859) Recherches de experimentales sur l'influence excitatrice de la lumiere, du froid et du la chaleur sur l'iris, dans les cinq classes d'animaux vertebres. *J. Physiol. Homme Anim* **2**, 281–294, 451–460.

149. Steinach, E. (1892) Untersuchungen zur vergleichenden Physiologie der Iris. *Pfluegers Arch.* **52**, 495–525.

150. Marmé, W. and J. Moleschott (1857) Ueber den Einfluss des Lichtes auf die Reizbarkeit der Nerven. *Untersuchungen Nat. Menschen Thiere* **1**, 15–51.

151. Uskoff, N. (1879) Einfluss von farbingem Lichte auf das Protoplasm des Tierkörpers. *Centralbl. Med. Wiss.* **25**, 449–450.

152. Dreyer, G. and H. Jansen (1905) Über den Einfluss des Lichtes auf tierisches Gewebe. *Mitt. Finsens Med. Lysinst.* **9**, 180–191.

153. Campbell, A. and L. Hill (1924) The effects of light upon leucocytes and blood-vessels in the mesentery of the living animal. *Br. J. Exp. Pathol.* **5**, 317–327.

154. Adler, L. (1919) Über Lichtwirkungen auf überlebende glattmuskelige Organe. *Arch. Exp. Pathol. Pharmakol.* **85**, 152–177.

155. Giese, A. C. and E. J. Furshpan (1954) Ultraviolet excitation of a stretch receptor. *J. Cell. Comp. Physiol.* **44**, 191–201.

156. Pierce, S. and A. C. Giese (1957) Photoreversal of ultraviolet injury to frog and crab nerves. *J. Cell. Comp. Physiol.* **49**, 303–317.

157. Fork, R. L. (1971) Laser stimulation of nerve cells in aplysia. *Science* **171**, 907–908.

158. Hirase, H., V. Nikolenko, J. H. Goldberg and R. Yuste (2002) Multiphoton stimulation of neurons. *J. Neurobiol.* **51**, 7–247.

159. Brücke, E. (1852) Ueber die Zunge der Chamäleons. *Sitzungsber. Math-Nat. Kl. kaiser. Akad. Wiss.* **8**, 65–70.

160. Wittich, V. (1854) Die grüne Farbe der Haut unserer Frösche, ihre physiologischen und pathologischen Veränderungen. *Arch. Anat. Physiol. Wiss. Med.* 41–59.

161. DuBois-Reymond, E. (1858) Ueber lebend nach Berlin gelangte Zitterwelse aus West-Afrika. *Untersuchungen Nat. Menschen Thiere* **5**, 109–136.

162. Pouchet, M. G. (1874) Ueber die Wechselbeziehung zwischen der Netzhaut und der Hautfarbe einiger Thiere. *Medizinische Jährbucher* (Wien), 42–44.

163. Bert, P. (1875) Des changements de couleur du cameleon. *Gaz. Hebd. Med. Chir.* **12**, 731.

164. Hoppe-Seyler, F. (1881) *Physiologische Chemie,* p. 25. Hirschwald, Berlin.

165. Kondratieff (1880) Einige Versuche über den Verlauf der bei Thieren künstlich erzeugten Sepsis unter dem Einfluss verschiedenartiger Belichtung. Inaugural-Dissertation, St. Petersburg.

166. Polito, G. (1908) L'influenza dei raggi solari sul sangue. *Gazz. Int. Med. Chir.* **11**, 329–331.

167. Clark, J. H. (1921) The action of light on the leucocyte count. *Am. J. Hyg.* **1**, 39–62.

168. Murphy, J. B. and E. Strum (1919) The lymphocytes in natural and induced resistance to transplanted tumors in mice. *J. Exp. Med.* **29**, 25–40.

169. Levy, M. (1916) Über anatomische Veränderungen an der Milz der Mansnach Bestrahlung mit ultraviolett Licht. *Strahlentherapie* **7**, 602–609.

170. Levy, M. (1916) Der Einfluss ultravioletter Strahlen auf die inneren Organe der Maus. *Strahlentherapie* **9**, 618–623.

171. Gassul, R. (1920) Experimentelle Studien über die biologische Wirkung des Quecksilber-Quarzlichtes ("künstliche Hohensonne") auf die inneren Organe. *Strahlentherapie* **9**, 232–238.

172. Anonymous (1729) Observation botanique. *Histoire de l'Academie Royale des Sciences. Avec les Memoires de Mathematique et de Physique, pour la meme Annee*, p. 35–36. Panckoucke, Paris.

173. Bunning, E. (1960) Opening address: biological clocks. *Cold Spring Harbor Symp. Quant. Biol.* **25**, 1–9.

174. Kiesel, A. (1894) Untersuchungen zur Physiologie des facettierten Auges. *Sitzungsber. Math-Naturwiss. Kl. kaiser. Akad. Wiss.* **103**, 97–139.

175. Marcovitch, S. (1924) The migration of Aphididae and the appearance of sexual forms as affected by the relative length of the daily light exposure. *J. Agric. Res.* **27**, 513–522.

176. Bremer, H. (1926) Über die tageszeitliche Konstanz im Schlüpftermine der Imagines einiger Insekten. *Z. Wiss. Insektenbiol.* **21**, 209–216.

177. Beiling, L. (1929) Über das Zeitgedächtnis der Bienen. *Z. Vgl. Physiol.* **9**, 259–338.

178. Bisonette, T. H. (1932) Studies on the sexual cycle in birds. VI. Effects of white, green, and red lights of equal luminous intensity on the testis activity of the European starling (*Sturnus vulgaris*). *Physiol. Zool.* **5**, 92–123.

179. Rowan, W. (1926) On photoperiodism, reproductive periodicity, and the annual migration of birds and certain fishes. *Proc. Boston Soc. Nat. Hist.* **38**, 147–189.

180. Bunning, E. (1936) Die endogene Tagesrhythmik als Grundlage der photoperiodischen Reaktion. *Ber. Dtsch. Bot. Ges.* **54**, 590–607.

181. Aschoff, J. (1965) Circadian rhythms in man. *Science* **148**, 1427–1432.

182. Benschoff, H. M., G. C. Brainard, M. D. Rollag and G. R. Lynch (1987) Suppression of pineal melatonin in Peromyscus leucopus by different monochromatic wavelengths of visible and near-ultraviolet light (UV-A). *Brain Res.* **420**, 397–402.

183. Brainard, G. C., F. M. Barker, R. J. Hoffman, M. H. Stetson, J. P. Hanifin, P. L. Podolin and M. D. Rollag (1994) Ultraviolet regulation of neuroendocrine and circadian physiology in rodents. *Vision Res.* **34**, 1521–1533.

184. Amir, S. and B. Robinson (1995) Ultraviolet light entrains rodent suprachiasmatic nucleus pacemaker. *Neuroscience* **69**, 1005–1011.

185. Hattar, S., H.-W. Liao, M. Takao, and D. M. Berson and K.-W. Yau (2002) Melanopsin-containing retinal galglion cells: architecture, projections, and intrinsic photosensitivity. *Science* **295**, 1065–1070.

186. Berson, D. M., F. A. Dunn and M. Takao (2002) Phototransduction by retinal ganglion cells that set the circadian clock. *Science* **295**, 1070–1073.

187. Mishkin, R. and R. Ben-Ishai (1982) Induction of plasminogen activator by UV light in normal and xeroderma pigmentosum fibroblasts. *Proc. Natl. Acad. Sci. USA* **78**, 6236–6240.

188. Kupper, T. S., A. O. Chua, P. Flood, J. McGuire and U. Gubler (1987) Interleukin one gene expression in cultured human keratinocytes is augmented by ultraviolet radiation. *J. Clin. Investig.* **80**, 430–436.

189. Büscher, M., H. J. Rahmsdorf, M. Litfin, and M. Karin and P. Herrlich (1988) Activation of the c-fos gene by UV and phorbol ester: different signal transduction pathways converge to the same enhancer element. *Oncogene* **3**, 301–311.

190. Kartasova, T. and P. van de Putte (1988) Isolation, charcterization, and UV-stimulated expression of two families of genes encoding polypeptides of related structure in human epidermal keratinocytes. *Mol. Cell. Biol.* **8**, 2195–2203.

191. Fornace, A. J. (1992) Mammalian genes induced by radiation; activation of genes associated with growth control. *Annu. Rev. Genet.* **26**, 507–526.

192. Uchiumi, T., K. Kohno, H. Tanimura, K.-I. Matsuo, S. Sato, Y. Uchida and M. Kuwano (1993) Enhanced expression of the human multidrug resistance one gene in response to UV light irradiation. *Cell Growth Differ.* **4**, 147–157.

193. Liu, M., K. R. Dhanwada, D. F. Birt, S. Hecht and J. C. Pelling (1994) Increase in p53 protein half-life in mouse keratinocytes following UV-B irradiation. *Carcinogenesis* **15**, 1089–1092.

194. Tyrrell, R. M. (1996) Activation of mammalian gene expression by the UV component of sunlight--from models to reality. *Bioessays* **18**, 139–148.

195. Marshall, A. M. (1882) Die Ontogenie von Reniera filigrand O. Schm. *Z. Wiss. Zool.* **37**, 221–246.

196. Ultzmann, R. (1885) Ueber Potentia generandi und Potentia coeundi. *Wien. Klin.* **11**, 1–32.

197. Kripke, M. L. (1984) Immunologic unresponsiveness induced by UV radiation. *Immunol. Rev.* **80**, 87–102.

198. Halliday, G. M., R. Bestak, K. S. Yuen, L. L. Cavanagh and R. St. C. Barnetson (1998) UVA-induced immunosuppression. *Mutat. Res.* **422**, 139–145.

199. Altenburg, E. (1928) The limit of radiation frequency effective in producing mutations. *Am. Nat.* **62**, 540–545.

200. Findlay, G. M. (1928) Ultra-violet light and skin cancer. *The Lancet* Nov. 24 issue, 1070–1073.

201. Roffo, A. H. (1934) Cancer et soleil. *Bull. Assoc. Fr. Etud. Cancer* **23**, 590–616.

202. Funding, G., O. M. Henriques and E. Rekling (1936) Über Licht-kanzer. In *Internationaler Kongress für Lichtforschung* 3rd ed., pp. 166–168. International Congress on Light, Wiesbaden.

203. Latarjet, R. (1935) Influence de l'ozone atmospherique sur l'activite biologique du rayonnement solaire. *Rev. Opt. Theor. Instrum.* **14**, 398–411.

204. Blum, H. F., J. S. Kirby-Smith and H. G. Grady (1941) Quantitative induction of tumors in mice with ultraviolet radiation. *J. Natl. Cancer Inst.* **2**, 259–268.

205. Kirby-Smith, J. S., H. F. Blum and H. G. Grady (1941) Penetration of ultraviolet radiation into skin, as a factor in carcinogenesis. *J. Natl. Cancer Inst.* **2**, 403–412.

206. Bain, J. A. and H. P. Rusch (1943) Carcinogenesis and ultraviolet radiation of wavelength 2800–3400A. *Cancer Res.* **3**, 425–430.

207. Freeman, R. G. (1975) Data on the action spectrum for ultraviolet carcinogenesis. *J. Natl. Cancer Inst.* **55**, 1119–1121.

208. Zigman, S., E. Fowler and A. L. Kraus (1976) Black light induction of skin tumors in mice. *J. Investig. Dermatol.* **67**, 723–725.

209. Strickland, P. T. (1986) Photocarcinogenesis by near-ultraviolet (UVA) radiation in sencar mice. *J. Investig. Dermatol.* **87**, 272–275.

210. Setlow, R., E. Grist, K. Thompson and A. D. Woodhead (1993) Wavelengths effective in induction of malignant melanoma. *Proc. Natl. Acad. Sci. USA* **90**, 6666–6670.

211. De Gruijl, F. R. and J. C. Van der Leun (1994) Estimate of the wavelength dependency of ultraviolet carcinogenesis in humans and its relevance to the risk assessment of a stratospheric ozone depletion. *Health Phys.* **67**, 320–325.

212. Brash, D. E., J. A. Rudolph, J. A. Simon, A. Lin, G. J. McKenna, H. P. Baden, A. J. Halperin and J. Ponten (1991) A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc. Natl. Acad. Sci. USA* **88**, 10124–10128.

213. Ziegler, A., D. J. Leffell, S. Kunala, H. W. Sharma, M. Gailani, J. A. Simon, A. J. Halperin, H. P. Baden, P. E. Shapiro, A. E. Bale and D. E. Brash (1993) Mutation hotspots due to sunlight in the p53 gene of nonmelanoma skin cancers. *Proc. Natl. Acad. Sci. USA* **90**, 4216–4220.

214. Berg, R. J., H. J. Van Kranen, H. G. Rebel, A. De Vries, W. A. Van Vloten, C. F. Van Kreijl, J. Van Der Leun and F. R. De Gruijl (1996) Early p53 alterations in mouse skin carcinogenesis by UVB radiation: immunohistochemical detection of mutant p53 protein in clusters of preneoplastic epidermal cells. *Proc. Natl. Acad. Sci. USA* **93**, 274–278.

215. Moles, J.-P., C. Moyret, B. Guillot, P. Jeanteur, J.-J. Guilhou, C. Theillet and N. Basset-Seguin (1993) p53 gene mutations in human epithelial skin cancers. *Oncogene* **8**, 583–588.

216. Van Kranen, H. J., A. De Laat, J. Van De Ven, P. W. Wester, A. De Vries, R. J. W. Berg, and C. F. Van Kreijl and F. R. De Gruijl (1997) Low incidence of p53 mutations in UVA (365-nm)-induced skin tumors on hairless mice. *Cancer Res.* **57**, 1238–1240.

217. Lewis, M. R. and W. H. Lewis (1915) Mitochondria (and other cytoplasmic structures) in tissue cultures. *Am. J. Anat.* **17**, 339–401.

218. Macklin, C. C. (1916) Binucleate cells in tissue cultures. *Contrib. Embryol.* **13**, 69–106.

219. Churchland, J. W. and D. G. Russell (1914) The effect of genetian violet on protozoa and on growing adult tissue. *Proc. Soc. Exp. Biol. Med.* **11**, 120–124.

220. Kite, G. L. (1913) Studies on the physical properties of protoplasm. *Am. J. Physiol.* **32**, 146–164.

221. Withrow, R. B. and A. P. Withrow (1956) Generation, control, and measurement of visible and near-visible radiant energy. In *Radiation Biology,* Vol. 3 (Edited by A. Hollaender), pp. 125–258. McGraw-Hill, New York.

222. Goodrich, H. B. and J. A. Scott (1922) The effect of light on tissue cultures. *Anat. Rec.* **24**, 315–318.

223. Frederic, J. (1958) Recherches cytologiques sur le chondriome normal ou soumis a l'experimentation dans des cellules vivantes cultivees in vitro. *Arch. Biol.* **69**, 169–349.

224. Kemp, T. and J. Juul (1932) Influence of ultraviolet rays upon mitosis in tissue cultures. *Acta Pathol. Microbiol. Scand.* **9**, 222–235.

225. Mayer, E. and H. Schreiber (1934) Die Wellenlängenabhängigkeit der Ultraviolettwirkung auf Gewebekulturen ("Reinkulturen"). *Protoplasma* **21**, 34–61.

226. Carlson, J. G. and A. Hollaender (1944) Immediate effects of low doses of ultraviolet radiation of wavelength 2537A on mitosis in the grasshopper neuroblast. *J. Cell. Comp. Physiol.* **23**, 157–166.

227. Wang, R. J., J. D. Stoien and F. Landa (1974) Lethal effect of near-ultraviolet irradiation on mammalian cells in culture. *Nature* **247**, 43–45.

228. Parshad, R., K. K. Sanford, G. M. Jones and R. E. Tarone (1978) Fluorescent light-induced chromosome damage and its prevention in mouse cells in culture. *Proc. Natl. Acad. Sci. USA* **75**, 1830–1833.

229. Sanford, K. K., R. Parshad and R. Gantt (1986) Responses of human cells in culture to hydrogen peroxide and related free radicals generated by visible light: relationship to cancer susceptibility. In *Free Radicals, Aging, and Degenerative Diseases*, pp. 373–394. Liss, New York.

230. Peak, J. G. and M. J. Peak (1991) Comparison of initial yields of DNA-to-protein crosslinks and single-strand breaks induced in cultured human cells by far- and near-ultraviolet light, blue light and X-rays. *Mutat. Res.* **246**, 187–191.

231. Audait, J. (1931) Action des rayons ultra-violets sur l'excitabilite du nerf. *C. R. Seances Soc. Biol. Fil.* **107**, 931–934.

232. Hutton-Rudolph, M. (1943) Photochemische versuche an einzelnen Nervenfasern. *Helv. Physiol. Pharmacol. Acta* **1**, C15–C19.

233. Lüthy, H. and A. Von Muralt (1947) Ueber den ultraviolett Dichroismus der peripheren Nervefaser. *Schweiz. Med. Wochenschr.* **77**, 5–6.

234. Booth, J., A. Von Muralt and R. Stampfli (1950) The photochemical action of ultraviolet light on isolated single nerve fibers. *Helv. Physiol. Pharmacol. Acta* **8**, 110–127.

235. Boyarsky, L. L. (1952) Effect of ultraviolet on electrical properties of nerve. *Proc. Soc. Exp. Biol. Med.* **79**, 213–214.

236. Von Muralt, A. and R. Stämpfli (1953) Die photochemische Wirkung von Ultraviolettlicht auf den erregten Ranvierschen Knoten der einzelnen Nervenfaser. *Helv. Physiol. Pharmacol. Acta* **11**, 182–193.

237. Gasteiger, A. L. (1953) Effects of ultraviolet on electrical properties of invertebrate nerve. *Fed. Proc.* **12**, 48–49.

238. Lüttgau, H. C. (1956) Elektrophysiologische Analyse der Wirkung von UV-Lichte auf die isolierte markhaltige Nervenfaser. *Pfluegers Arch.* **262**, 244–255.

239. Chalazonitis, N. (1957) *Effects de la Lumiere sur l'Evolution des Potentiels Cellulaires et sur Quelques Vitesses d'Oxydoreduction dans les Neurones.* Bosc Freres, Lyons.

240. Ham, W. T., H. A. Mueller and D. H. Sliney (1976) Retinal sensitivity to damage from short wavelength light. *Nature* **260**, 153–154.

241. Reme, C., J. Reinboth, M. Clausen and F. Hafezi (1996) Light damage revisited: converging evidence, diverging views? *Arch. Clin. Exp. Ophthalmol.* **234**, 2–11.

242. Ackroyd, R., C. Kelty, N. Brown and M. Reed (2001) The history of photodetection and photodynamic therapy. *Photochem. Photobiol.* **74**, 656–669.

243. Dammann, C. (1883) *Gesundheitspflege der landwirthschaftlichen Haussäugethiere,* pp. 411–414. Parey, Berlin.

244. Wedding, M. (1887) Einfluss des Lichtes auf die Haut der Thiere. *Z. Ethnol.* (part 2) **19**, 67–69.

245. Raab, O. (1900) Über die Wirkung fluorescirender Stoffe auf Infusorien *Z. Zool.* **39**, 524–546.

246. Von Tappeiner, H. (1909) Die photodynamische Erscheinung (Sensibilisierung durch fluoreszierenden Stoffe). *Ergeb. Physiol.* **8**, 698–741.

247. Straub, W. (1904) Ueber chemische Vorgänge bei der Einwirkung von Licht auf fluoreszierende Substanzen (Eosin und Chinin) und die Bedeutung dieser Vorgänge für die Giftwirkung. *Munch. Med. Wochenschr.* **51**, 1093–1096.

248. Hausmann, W. (1910) Die Sensibilisierende Wirkung des Hämatopophyrins. *Biochem. Z.* **30**, 276–316.

249. Adler, L. (1919) Über Lichtwirkungen auf überlebende glattmuskelige Organe. *Arch. Exp. Pathol. Pharmakol.* **85**, 152–177.

250. Earle, W. R. (1928) Studies upon the effect of light on blood and tissue cells. I. The action of light on white blood cells *in vitro*. *J. Exp. Med.* **48**, 457–473.

251. Earle, W. R. (1928) Studies upon the effect of light on blood and tissue cells. III. The action of light on fibroblasts *in vitro*. *J. Exp. Med.* **48**, 683–693.

252. Büngeler, W. (1937) Über den Einfluss photosensibilisierender Substanzen auf die Entstehung von Hautgeschwülsten. *Z. Krebsforsch.* **46**, 130–167.

253. von Tappeiner, H. (1900) Ueber die Wirkung fluorescirender Stoffe auf Infusorien nach Versuchen von O. Raab. *Munch. Med. Wochenschr.* **47**, 5–7.

254. von Tappeiner, H. and A. Jesionek (1903) Therapeutische Versuche mit fluorescierenden Stoffen. *Munch. Med. Wochenschr.* **50**, 2042–2044.

255. Dougherty, T. J. (2002) An update on photodynamic therapy applications. *J. Clin. Laser Med. Surg.* **20**, 3–7.

256. Schmarda, L. K. (1845) Der Einfluss des Lichtes auf die Infusionsthierchen. *Med. Jahrbücher des k. k. Österreichischen Staates.* **54**, 257–270.

257. Lessona, F. (1875) *Dell' azione della luce gugli animali*. Turino.

258. Engelmann, T. W. (1879) Ueber Reizung contractilen Protoplasmas durch plötzliche Beleuchtung. *Pfluegers Arch.* **19**, 1–6 and 7–14.

259. Engelmann, T. W. (1879) Ueber die Bewegungen der Oscillarien und Diatomeen. *Pfluegers Arch.* **19**, 7–14.

260. Hockberger, P. E. (2000) The discovery of the damaging effect of sunlight on bacteria. *J. Photochem. Photobiol. B.* **58**, 185–191.

261. Koch, R. (1890) *Ueber bakteriologische Forschung*. Hirschwald, Berlin.

262. Tizzoni, G. and G. Cattani (1891) Ueber die Widerstandsfähigkeit der Tetanusbacillen gegen physikalische unde chemische Einwirkungen. *Arch. Exp. Pathol. Pharmakol.* **28**, 41–60.

263. Dandrieu, P. (1888) Influence de la lumiere dans la destruction des bacteries p. servir a l'etude du "tout a l'egout." *Ann. Hyg. Publ. Med. Legale* Ser. 3, **20**, 448–451.

264. Klebs, E. (1887) *Die Allgemeine Pathologie*, pp. 85, 97, 131. Fischer, Jena.

265. Wesbrook, F. F. (1896) Some of the effects of sunlight on tetanus cultures. *J. Pathol. Bacteriol.* **3**, 70–77.

266. Wesbrook, F. F. (1896) The growth of cholera (and other) bacilli in direct sunlight. *J. Pathol. Bacteriol.* **3**, 352–358.

267. Richardson, A. (1893) The action of light in preventing putrefactive decomposition and in inducing the formation of hydrogen peroxide in organic liquids. *Trans. Chem. Soc. Lond.* **63**, 1109–1130.

268. D'Arcy, R. F. and W. B. Hardy (1894) Note on the oxidizing powers of different regions of the spectrum in relation to the bactericidal action of light and air. *J. Physiol.* **17**, 390–393.

269. Bedford, T. H. (1927) The nature of the action of ultra-violet light on micro-organisms. *Br. J. Exp. Pathol.* **8**, 437–444.

270. Bie, V. (1900) Untersuchungen über die bakterientötende Wirkung der verschiedenen Abteilungen des Spektrums. *Mitt. Finsens Med. Lysinst.* **1**, 40–77.

271. Bie, V. (1904) Über die bakterische Wirkung ultravioletter Strahlen. *Mitt. Finsens Med. Lysinst.* **7**, 65–77.

272. Bie, V. (1905) Ist die Bactericide Wirkung des Lichtes ein Oxydationprozess? *Mitt. Finsens Med. Lysinst.* **9**, 5–74.
273. Strebel, H. (1901) Untersuchungen über die bakterizide Wirkung des Hochspannung-funkenenlichtes. *Dtsch. Med. Wochenschr.* **27**, 69–72.
274. Bang, S. (1901) Die Wirkungen des Lichtes auf Mikrooganismen. *Mitt. Finsens Med. Lysinst.* **2**, 1–107.
275. Bang, S. (1903) Über die Wirkungen des Lichtes auf Mikroben. II. Eine verbesserte Untersuchungs methode. *Mitt. Finsens Med. Lysinst.* **3**, 97–112.
276. Barnard, J. E. and H. Morgan (1903) Upon the bactericidal action of some ultraviolet radiations as produced by the continuous current arc. *Proc. R. Soc. Lond. B.* **72**, 126–128.
277. Thiele, H. and K. Wolf (1906) Über die Abtötung von Bakterien durch Licht. I. *Arch. Hyg. Bakteriol.* **57**, 29–55.
278. Thiele, H. and K. Wolf (1907) Über die Abtötung von Bakterien durch Licht. II. *Arch. Hyg. Bakteriol.* **60**, 29–39.
279. Cernovodeanu, P. and V. Henri (1910) Action des rayons ultraviolets sur les microorganisms et sur differents cellules. Etude micro-chimique. *C. R. Hebd. Seances Acad. Sci.* **150**, 52–54.
280. Cenovodeanu, P. and V. Henri (1910) Etude de l'action des rayons ultraviolets sur les microbes. *C. R. Hebd. Seances Acad. Sci.* **150**, 729–731.
281. Henri, V. and V. Moycho (1914) Action des rayons ultraviolets monochromatique sur les tissues. Mesure de l'energie de rayonnement correspondant au coup de soleil. *C. R. Hebd. Seances Acad. Sci.* **158**, 1509–1511.
282. Henri, Mme. V. and V. Henri (1914) Variation du pouvoir abiotique des rayons ultraviolets avec leur longueur d'onde. *C. R. Seances Soc. Biol. Fil.* **73**, 321–322.
283. Browning, C. H. and S. Russ (1917) The germicidal action of ultra-violet radiation, and its correlation with selective absorption. *Proc. R. Soc. Lond. B.* **90**, 33–38.
284. Bovie, W. T. and D. M. Hughes (1918) The effect of quartz ultraviolet light on the rate of division of Paramecium caudatum. *J. Med. Res.* **39**, 223–231.
285. Henri, V. (1919) *Etudes de Photochemie*. Gauthier Villars et Cie, Paris.
286. Burge, W. E. (1917) The action of ultra-violet radiation in killing living cells such as bacteria. *Am. J. Physiol.* **43**, 429–432.
287. Bayne-Jones, S. and J. S. Van Der Lingen (1923) The bactericidal action of ultra-violet light. *Bull. Johns Hopkins Hosp.* **34**, 11–16.
288. Coblentz, W. W. and H. R. Fulton (1924) A radiometric investigation of the germicidal action of ultra-violet radiation. *U.S. Bur. Stand. Sci. Pap.*, no. 495, **19**, 641–680.
289. Wykoff, R. W. (1930) The killing of certain bacteria by X-rays. *J. Exp. Med.* **52**, 435–446.
290. Wykoff, R. W. (1932) The killing of certain bacteria by ultraviolet light. *J. Gen. Physiol.* **15**, 351–361.
291. Gates, F. L. (1929) A study of the bactericidal action of ultraviolet light. I. The reaction to monochromatic light. *J. Gen. Physiol.* **13**, 231–248.
292. Gates, F. L. (1929) A study of the bactericidal action of ultraviolet light. II. The effect of various environmental factors and conditions. *J. Gen. Physiol.* **13**, 249–260.
293. Gates, F. L. (1930) A study of the bactericidal action of ultraviolet light. III. The absorption of ultra violet by bacteria. *J. Gen. Physiol.* **14**, 31–42.
294. Tatum, E. L. and G. W. Beadle (1945) Biochemical genetics of Neurospora. *Ann. MO Bot. Gard.* **32**, 125–129.
295. Hollaender, A. (1943) Effect of long ultraviolet and short visible radiation (3500 to 4900A) on *Escherichia coli*. *J. Bacteriol.* **46**, 531–541.
296. Jagger, J., W. C. Wise and R. S. Stafford (1964) Delay in growth and division induced by near ultraviolet radiation in *Escherichia coli* B and its role in photoprotection and liquid holding recovery. *Photo-chem. Photobiol.* **3**, 11–24.
297. Webb, R. B. and J. S. Bhorjee (1967) The effect of 3000–4000A light on the synthesis of b-galactosidase and bacteriophages by *Escherichia coli*. *Can. J. Microbiol.* **13**, 69–79.
298. D'Aoust, J. Y., W. G. Martin, J. Giroux and H. Schneider (1980) Protection from visible light damage to enzymes and transport in *Escherichia coli*. *Photochem. Photobiol.* **31**, 471–474.
299. Hartman, P. S. (1986) *In situ* hydrogen peroxide production may account for a portion of NUV (300–400 nm) inactivation of stationary phase *Escherichia coli*. *Photochem. Photobiol.* **43**, 87–89.
300. Galland, P. and H. Senger (1988) New trends in photobiology: The role of flavins as photoreceptors. *J. Photochem. Photobiol. B* **1**, 277–294.
301. Beukers, R. and W. Berends (1960) Isolation and identification of the irradiation product of thymine. *Biochim. Biophys. Acta* **41**, 550–551.
302. Setlow, R. B. (1966) Cyclobutane-type pyrimidine dimmers in polynucleotides. *Science* **153**, 379–386.
303. Hanawalt, P. C. and R. B. Setlow (1960) Effect of monochromatic UV on macromolecular synthesis in *E. coli*. *Biochim. Biophys. Acta* **41**, 283–294.
304. Setlow, R. B. and W. L. Carrier (1964) The disappearance of thymine dimmers from DNA: an error correcting mechanism. *Proc. Natl. Acad. Sci. USA* **51**, 226–231.
305. Pettijohn, D. and P. C. Hanawalt (1964) Evidence for repair-replication of ultraviolet damaged DNA in bacteria. *J. Mol. Biol.* **9**, 395–410.
306. Sancar, A. (1996) DNA excision repair. *Annu. Rev. Biochem.* **65**, 43–81.
307. Kelner, R. (1949) Effect of visible light on the recovery of Streptomyces griseus conidia from ultraviolet irradiation injury. *Proc. Natl. Acad. Sci. USA* **35**, 73–79.
308. Sancar, A. (1996) No 'end of history' for photolyase. *Science* **272**, 48–49.
309. Cleaver, J. E. (1968) Defective repair replication of DNA in xeroderma pigmentosum. *Nature* **218**, 652–656.
310. Cleaver, J. E. and K. H. Kraemer (1995) Xeroderma pigmentosum and Cockayne syndrome. In *The Metabolic and Molecular Bases of Inherited Disease,* 7th ed. (Edited by C. R. Scriver, A. L. Beaudet, W. S. Sly and D. Valle), pp. 4393–4419. McGraw-Hill, New York.
311. Pfiefer, G. P., R. Drouin, A. D. Riggs and G. P. Holmquist (1992) Binding of transcription factors creates hotspots for UV photo-products. *Mol. Cell. Biol.* **12**, 1798–1804.
312. Pfeifer, G. P. (1997) Formation and processing of UV photoproducts: effects of DNA sequence and chromatin environment. *Photochem. Photobiol.* **65**, 270–283.
313. Engelmann, T. W. (1883) Ueber Licht- und Farbenperception niederster Organismen. *Pfluegers Arch.* **29**, 387–400.
314. Engelmann, T. W. (1888) I. Ueber Bacteriopurpurin und seine physiologische Bedeutung. *Pfluegers Arch.* **42**, 183–186.
315. Loeb, J. (1888) Der Einfluss des Lichtes auf die Oxydationsvorgänge in thierischen Organismen. *Pfluegers Arch.* **42**, 393–407.
316. Mast, S. O. (1911) *Light and the Behavior of Organisms*. Wiley, New York.
317. Buder, J. (1915) Zur Kenntnis des *Thiospirillum jenense* und seiner Reaktionen auf Lichtreize. *Jahrbücher Wiss. Bot.* **56**, 529–584.
318. Brucker, W. (1954) Beiträge zur Kenntnis der Phototaxis grüner Schwärmzellen. I. Die Lichtempfindlichkeit von *Lepocinclis texta* und ihre Abhängigkeit von der Vorbelichtung und vom Kohlensäuregehalt des Mediums. *Arch. Protistenkd.* **99**, 294–327.
319. Clayton, R. K. (1964) Phototaxis in microorganisms. In *Photo-physiology,* Vol. 2 (Edited by A. C. Giese), pp. 51–77. Academic Press, New York.
320. Beijerinck, M. W. (1902) Photobacteria as a reactive in the investigation of the chlorophyll-function. *Proc. Acad. Sci. Amst.* **4**, 45–49.
321. Metzner, P. (1919) Über die Wirkung photodynamischer Stoffe auf Spirillum volutans und die Beziehungen der photodynamischen Erscheinung zur Phototaxis. *Biochem. Z.* **101**, 33–53.
322. Manten, A. (1948) Phototaxis in the purple bacterium *Rhodospirillum rubrum*, and the relation between phototaxis and photosynthesis. *Antonie Leeuwenhoek* **14**, 65–86.
323. Schlegel, H. G. (1956) Vergleichende Untersuchungen über die Lichtempfindlichkeit einiger Purpurbakterien. *Arch. Protistenkd.* **101**, 69–97.
324. Clayton, R. K. (1959) Phototaxis of purple bacteria. In *Handbuch der Pflanzenphysiologie* Part 1, Vol. 17 (Edited by W. Rushland), pp. 371–387. Springer, Berlin.
325. Zalokar, M. (1955) Biosynthesis of carotenoids in Neurospora: action spectrum of photoactivation. *Arch. Biochem. Biophys.* **56**, 318–325.

326. Curry, G. M. and H. E. Gruen (1959) Action spectra for the positive and negative phototropism of Phycomyces sporangiophores. *Proc. Natl. Acad. Sci. USA* **45**, 797–804.
327. Delbrück, M. and W. Shropshire (1960) Action and transmission spectra of Phycomyces. *Plant Physiol.* **35**, 194–203.
328. Sargent, M. L. and W. R. Briggs (1967) The effects of light on a circadian rhythm of conidiation in Neurospora. *Plant Physiol.* **42**, 1504–1510.
329. Diehn, B. (1969) Action spectra of the phototactic responses in Euglena. *Biochim. Biophys. Acta* **177**, 136–143.
330. Bialcyzyk, J. (1979) An action spectrum for light avoidance by Physarum nudum plasmodia. *Photochem. Photobiol.* **30**, 301–303.
331. Selbach, M. and H. W. Kuhlmann (1999) Structure, fluorescent properties and proposed function in phototaxis of the stigma apparatus in the ciliate Chlamydodon mnemosyne. *J. Exp. Biol.* **202**, 919–922.
332. Castle, E. S. (1935) Photic excitation and phototropism in single plant cells. *Cold Spring Harbor Symp. Quant. Biol.* **3**, 224–229.
333. Bünning, E. (1937) Phototropismus und carotinoide. I. Phototropische Wirksamkeit von Strahlen versciedener Wellenlange und Strahlum-gasabsorption im Pigment bei Pilobolus. *Planta* **26**, 710–736.
334. Galston, A. W. (1950) Riboflavin, light, and the growth of plants. *Science* **111**, 619–624.
335. Galland, P. (1992) Forty years of blue-light research and no anniversary. *Photochem. Photobiol.* **56**, 847–853.
336. Gurwitsch, A. G., S. Grabje and S. Salkind (1923) Die Natur des spezifischen Erregers der Zellteilung. *Arch. Entwicklungsmech. Org.* **100**, 11–40.
337. Alpatov, W. W. and O. K. Nastjukova (1933) The influence of different quantities of ultra-violet radiation on the division rate in Paramecium. *Protoplasma* **18**, 281–285.
338. Hollaender, A. and W. Claus (1937) An experimental study of the problem of mitogenic radiation. *Bull. Natl. Res. Council* **100**, 3–96.
339. Hollaender, A. (1939) Present status of mitogenic radiation. *Radiology* **32**, 404–410.
340. Popp, F.-A. (1988) Biophoton emission. *Experientia* **44**, 543–544.