Ultraviolet radiation therapy and UVR dose models

David Robert Grimes[a)]
School of Physical Sciences, Dublin City University, Glasnevin, Dublin 9, Ireland and Cancer Research UK/MRC Oxford Institute for Radiation Oncology, Gray Laboratory, University of Oxford, Old Road Campus Research Building, Oxford OX3 7DQ, United Kingdom

(Received 30 May 2014; revised 29 October 2014; accepted for publication 30 November 2014; published 30 December 2014)

Ultraviolet radiation (UVR) has been an effective treatment for a number of chronic skin disorders, and its ability to alleviate these conditions has been well documented. Although nonionizing, exposure to ultraviolet (UV) radiation is still damaging to deoxyribonucleic acid integrity, and has a number of unpleasant side effects ranging from erythema (sunburn) to carcinogenesis. As the conditions treated with this therapy tend to be chronic, exposures are repeated and can be high, increasing the lifetime probability of an adverse event or mutagenic effect. Despite the potential detrimental effects, quantitative ultraviolet dosimetry for phototherapy is an underdeveloped area and better dosimetry would allow clinicians to maximize biological effect whilst minimizing the repercussions of overexposure. This review gives a history and insight into the current state of UVR phototherapy, including an overview of biological effects of UVR, a discussion of UVR production, illness treated by this modality, cabin design and the clinical implementation of phototherapy, as well as clinical dose estimation techniques. Several dose models for ultraviolet phototherapy are also examined, and the need for an accurate computational dose estimation method in ultraviolet phototherapy is discussed.
 [http://dx.doi.org/10.1118/1.4903963]

Key words: ultraviolet radiation, dosimetry, dose models

1. INTRODUCTION

The fact that exposure to sunlight can alleviate certain skin ailments has been known since antiquity; it is from Greek we derive the word heliotherapy and indeed ancient Greeks practiced a form of this, as did numerous others ancient cultures, including the Assyrians, Egyptians, Romans, and Inca. This practice was not limited to hot climates; early German settlers[1] and presumably other cultures also worshiped the health beneficial properties of the sun. Scientific investigation into the subject, and the rigor that entails began in the 19th century with understanding of the solar spectrum. The ultraviolet (UV) portion of the solar spectrum was discovered by Johann Ritter in 1801.[2] Toward the end of the 19th century, Niels Finsen proved experimentally that sunburn was caused by ultraviolet radiation (UVR) and not radiant heat as such a name might suggest. The work of Finsen effectively laid the foundations for modern ultraviolet phototherapy as he painstakingly researched the application of UVR to biological processes. As a reward for his efforts, Finsen was awarded the Nobel prize in Medicine and Physiology in 1903 in recognition of his contribution to *"the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science*."

The early 20th century saw the formation of the Light league by the author and physician Caleb Saleeby.[3] Saleeby and his supporters were evangelical about their beliefs, and stated their motive to be "*..the education of the public to the appreciation of sunlight as a means of health; teaching the nation that sunlight is nature universal disinfectant, as well as a stimulant and tonic*." Saleeby based this passion for natural light on some highly questionable testimony, including that of a Dr. Rollier, who claimed he had successfully cured ailments ranging from bedsores to spinal tuberculosis to warwounds with sunlight alone. In a review on the subject, Diffey[4] aptly notes the contrast between the views of Saleeby and the opinion of the dermatologists at the VIIth International congress of Photobiology in Rome, 1976, who were of the opinion that even moderate exposure to sunlight could be potentially very harmful. Perhaps this historical background is the very epitome of phototherapy: beneficial at correct dosage, and potentially detrimental when taken to excess.

While light therapy can encompass huge swathes of the electromagnetic spectrum, we are concerned primarily in this work with ultraviolet radiation, used to treat a variety of skin conditions. For dermatological applications, UVR treatments tend to be either narrowband UVB treatments centered around 311 nm or broadband UVA treatments in conjunction with a skin photosensitizing agent or Psoralen, which readily absorbs UVA. The latter treatment is commonly referred to as a PUVA treatment.[5]

2. ULTRAVIOLET RADIATION

The UVR portion of the electromagnetic spectrum lies between 100 and 400 nm, between the visible and x-ray part of the spectrum as illustrated in Fig. 1. The term UV arises as this wavelength band begins just beyond visible violet light. The UV band is usually divided into three further subdivision, UVA, UVB, and UVC based on their respective biological effects. The most commonly encountered classification is that

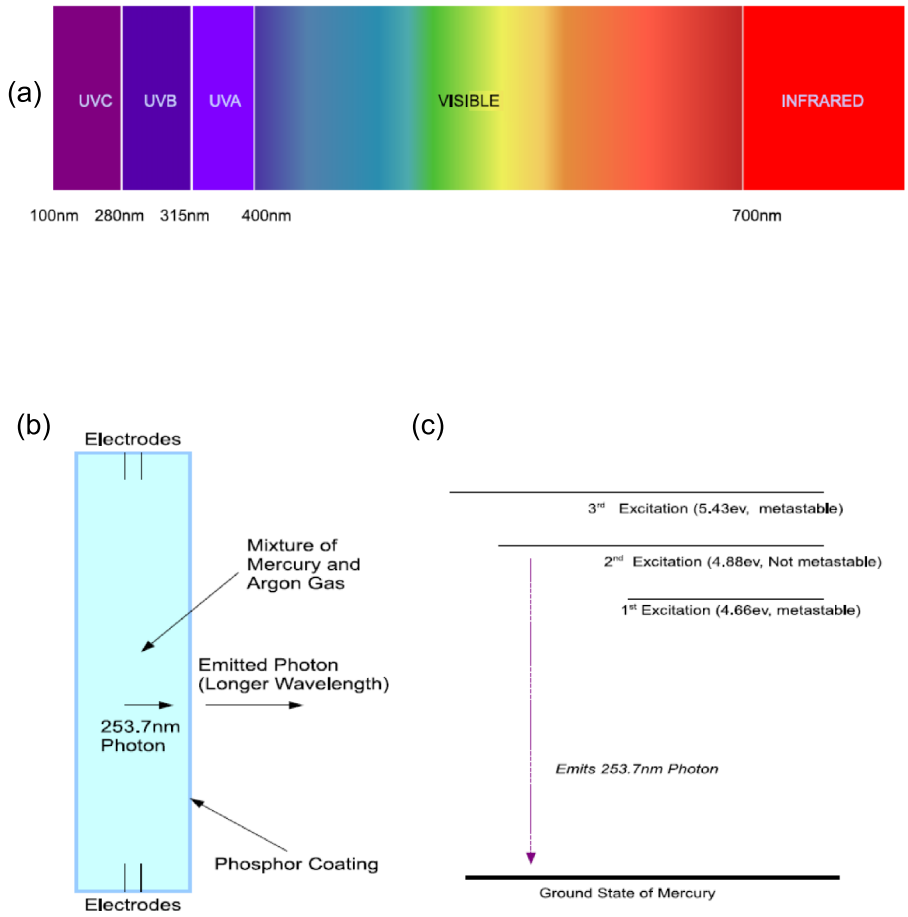

FIG. 1. (a) UVR portion of the electromagnetic spectrum, (b) UVR tube, and (c) energy states of mercury gas.

defined by the International Commission on Radiation (CIE)[6] shown in Table I.

While this is perhaps the most common classification, variations exist on the boundaries between these bands—occasionally 320 nm is taken as the boundary between UVA and UVB while 290 nm is defined the boundary between UVB and UVC.[7] The sun is the primary source of UVR incident upon the Earth's surface. While the sun emits large amounts of all UVR, the Earth's atmosphere is remarkably efficient at attenuating the more biologically harmful bands by absorption; wavelengths of less than 290 nm are effectively removed by the atmosphere and as a result are not present on the Earth's surface. Of the sun's radiation that reaches Earth, only 5% is in the UVR range. Rayleigh scattering by particles of oxygen and nitrogen has a significant effect on reducing UVR with wavelengths longer then 310 nm.[8] Of the UVR that reaches the Earth's surface, 96.65% is UVA and 3.35% is UVB.[9]

TABLE I. CIE ultraviolet classification.

Classification	Wavelength band (nm)
Ultraviolet A (UVA)	400–315
Ultraviolet B (UVB)	315–280
Ultraviolet C (UVC)	280–100

2.A. UVR production and spectra

There are numerous ways to produce artificial UVR, including gas discharge lights, arc lamps, and metal halide lamps. In the context of ultraviolet phototherapy, however, the UVR source used is a fluorescent lamp. A fluorescent tube operates on the same principle as a gas discharge lamp—the lamp consists of a tube containing a low pressure gas or gas mixture which is ionized by running a current through it. These excited atoms fall back to their ground state, emitting a photon. The wavelength of this emitted photon is dependent on the gas mixture used. In addition to this, the tube itself is often coated with a phosphor so that when the emitted photon is incident upon the tube walls, it stimulates the emission of a photon of a different wavelength through the mechanism of fluorescence. UVR lamps use a mixture of mercury vapor and inert argon gas. Electrons are emitted from the electrodes at either end of the tube either by thermionic emission, high-field emission, or a mixture of both methods. These electrons are accelerated by the applied electric field where they encounter the argon atoms and excite them. The first ionization stage of Argon is metastable (11.56 eV), and the Argon helps to

establish an arc by forming a Penning mixture with Mercury; this has the net effect of making mercury easier to excite to the desired level.[10] Mercury has an ionization level of 10.39 eV and an excited state at 4.88 eV that is not metastable, so the excited atoms revert immediately to their ground state and radiate a photon in the UVC range of wavelength 253.7 nm as in Fig. 1. These photons then impinge on the phosphor coat of the tube and fluoresce and emit a photon of a wavelength dependent on the phosphor used. For a visible fluorescent lamp, this output will be over a broadband with an average wavelength of 555 nm. For a narrowband tube such as the TL/01 used in phototherapy, the output will be narrowband at 311 nm. The mechanism remains the same in both cases, but the type of phosphor used determines the output wavelength. Mercury is used as the active gas for three main reasons: first, it produces a single ultraviolet line and has a high probability of reaching the emitting nonmetastable state. Second, due to the room temperature vapor pressure it mercury the lamp does not have to be heated excessively. Finally, for high luminous output it is required that the source have a high quantum ratio. This quantity is defined as

$$\mathrm{QR} = \frac{E_{\mathrm{UV}}}{E_0} = \frac{\lambda_0}{\lambda_{\mathrm{UV}}}, \tag{1}$$

where E_0 and E_{UV} are the respective energies of the output and ultraviolet photons and λ_0 and λ_{UV}, their respective wavelengths. So for a tube producing visible light at 555 nm, the QR is 0.46 and for a narrowband UV tube at 311 nm, the QR is very high at 0.8158.[10] Using inert gases such as argon in the mixture helps to establish the arc as they ionize at lower tube voltages than other gases, increasing the likelihood of further excitation. The excitation of inert gas also leads to the Penning effect, making the process more efficient. Finally, the mercury arc must be contained, and without the inert gas pressure the mercury atoms and ions would move toward the tube wall, making the resultant combinations excessive and inefficient. The presence of the inert gas in the form of argon counteracts this.[7,10]

Gas discharge lamps are examples of negative resistance phenomena, which essentially means that as current increases, lamp voltage decreases. This must be controlled with in order to limit current. The most simple solution is to use a resistor but this leads to large power loss and reduction in efficiency. Consequently, resistive ballasting is thus used only when a lamp is being operated under conditions of direct current. For all other situations, reactive or electronic ballasting is employed to regulate the current running into the lamp.[10]

2.A.1. Source spectra

The output spectra of a particular lamp will depend upon the gas mixture and phosphor used. For different therapeutic applications, different spectra may be used and as a result there are many readily available commercial lamps with varying outputs at various wavelengths available. While UV lamps are often divided into UVA and UVB lamps, this does not always characterize the lamps themselves; some may have output in both the UVA and UVB or may be relatively broadband across the spectrum[7] so it is more correct to analyze UVR lamps in terms of their spectral power distribution. Outputs of some common UVR lamps are shown in Fig. 2.

2.A.2. Source stability and output

Individual fluorescent lights reach full output within 1 min of being powered in Ref. 7. However, factors such as temperature of the cabin can have an influence when many lamps are being operated together, as is usually the case in a clinical setting. In such cases, it can take up to 15 min for the lamps to stabilize, depending on the degree of forced cooling provided by the unit. Maximum UVR output is achieved when the lamps are run in free air with ambient temperatures of 25 °C–30 °C. If cooling is not adequate and temperature increases above 30° the output decreases for older model tubes[7] but some newer tubes have an optimal temperature of 40 °C as shown in Fig. 2. Tube output also decreases with active lifetime; fluorescent lamps typically have a "running in" period where the radiation output rate falls steeply in comparison to the tube's later life. This period is typically 100 h. The useful lifetime of a tube is approximately 500–1000 h, after which tubes tend to fall to about 70%–80% of their output at the end of the running in period. At such a time, the tubes are typically replaced.

3. BIOLOGICAL EFFECTS OF UVR

Despite the fact that ultraviolet radiation is nonionizing, it is nevertheless quite damaging to the molecular integrity of DNA through both direct and indirect interactions.[11,12] To combat this, the human body has adapted the defense of melanin pigmentation[13] to counteract the negative repercussions of ultraviolet exposure. These repercussions run the gambit from trivial to severe; the signature effect of UVR upon the skin is erythema, more commonly known as sunburn. This is familiar and causes painful blistering effects on skin which are familiar to many from overexposure to the sun. Acute ocular exposure to UVR can cause photokeratisis or snow blindness, and chronic overexposure can result in increased incidence of cataracts.[14] Light in the UV wavelength band can damage collagen, decreasing skin elasticity, and promoting advanced aging and wrinkling.[4,15] While these effects of UVR exposure are considerably unpleasant, the primary concern with this spectrum of radiation is the potential for carcinogenesis. Exposure to high amounts of ultraviolet radiation has long been a risk factor in developing skin cancers.[16] In order of seriousness, cancers commonly associated with overexposure to UVR are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma.[7]

It is important to note that the term "dose" in photobiology differs from the radiobiological definition of dose; the photobiological dose is analogous to energy fluence in radiotherapy (energy per unit area) rather than absorbed dose. The problem of determining the energy absorbed by critical targets in the skin remains open and unsolved.[20] It is also important to note that the penetration depth of UVR

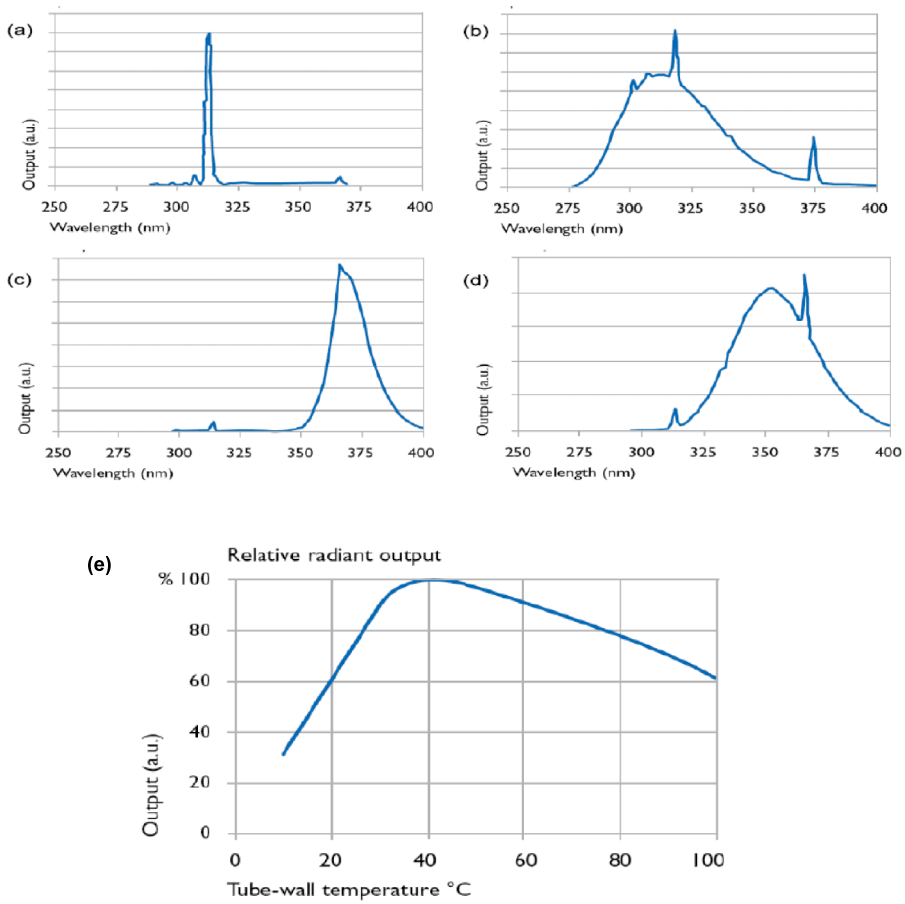

FIG. 2. Spectral outputs from some common Phillips UV lamps (a) narrowband TL/01, (b) TL/12, (c) TL/10, (d) TL/209, and (e) radiant output versus temperature for Phillips UV lamps.

tends to be very shallow; at 311 nm, penetration is only 20–40 μm.[17,18] Radiometric terminology can vary greatly between various branches of optics, and in this work we shall use the convention laid down by Sliney,[14] where irradiance is defined as the power per unit area, and denoted E. The irradiance at a skin or detector surface is angle dependent[19] so surface orientation of a target site is an important factor to consider when estimating or measuring irradiance in practice. The most commonly encountered radiometric calculation in phototherapy relates prescribed dose D_p to irradiance through

$$t_e = \frac{D_P}{E}, \tag{2}$$

where t_e is the treatment exposure time. If irradiance is known at a target site, then any desired dose can be delivered by simply modifying the exposure time. For this reason, irradiance is of fundamental importance in phototherapy and is the quantity that clinicians and physicists are most concerned with.[18,20]

3.A. The effect of UVR on DNA and melanin

Melanin and DNA are extremely efficient and well adapted photoprotective agents. This is due to them having an extremely efficient internal conversion, converting the vast majority of incident UV photons to harmless amounts of heat. Melanin and DNA in skin can convert the vast majority of incident UV to small amounts of heat which dissipate harmlessly as the ultrafast conversion process of DNA means that the excited lifetime is in the femtosecond (10^{-15}) regime, and thus the excited molecule does not have enough time to react with other molecules. If the excited state was much longer, then it would lead to the generation of harmful free radical and reactive species like the hydroxyl radical or singlet oxygen which would damage DNA.[12] The quantum yield (percentage of molecules quickly dissipating the photon to heat) of both DNA and eumelanin, the form of melanin most common in humans is over 99.9% for both molecules.[21] While the photoprotection provided by these agents is extremely efficient, there are two distinct cases where it can break down and DNA can be damaged.

3.A.1. Direct DNA damage

While DNA can convert the vast majority of incoming photons rapidly into harmless heat energy, there are a small percentage of photons that will get through this evolved defense. When this occurs, an incoming UVB photon is completely absorbed, forcing thymine base pairs in DNA to bond to each other which would not naturally occur. In the case of UVR, this most often results in thymine forming bonds with itself, called a thymine–thymine dimer.[22] These

erroneous pairs form lesions in the structure of the DNA, which may be repaired by the mechanism of nucleotide excision repair, but unrepaired dimers can be mutagenic.[23] This mutagenic DNA can lead to the skin cancer melanoma.[24] This form of cancer is localized to the site of exposure. Direct DNA damage also provokes an increase in melanin production to counteract the damage, such as a long lasting tan. Overexposure leads to sunburn.[11] These effects can be considered a painful warning sign of direct DNA damage, but it is worth noting that this mechanism of DNA damage only accounts for 8% of melanomas, the rest being attributable to indirect DNA damage.[25]

3.A.2. Indirect DNA damage

Indirect DNA damage occurs when a UV photon is incident upon a chromophore that cannot quickly reduce the excited molecule to harmless heat and thus has a correspondingly long lifetime, around 10^3–10^6 times than that of melanin.[26] Because of this long excited state, reactions with other molecules can occur. Two processes which can occur are the generation of free radicals and reactive oxygen species, both of which are mutagenic and detrimental to DNA integrity through the mechanism of oxidative stress.[12] Indirect DNA damage accounts for 92% of melanomas including the most serious cases of malignant melanoma[25] and unlike direct DNA damage, there is no pain warning. The melanoma can manifest in unexposed sites as free radicals can travel throughout the body. Indirect DNA damage has raised concerns that some of the chemicals in certain sunscreens could contribute to free radical production and hence cellular damage.[27–29] An example reaction is illustrated in Fig. 3.

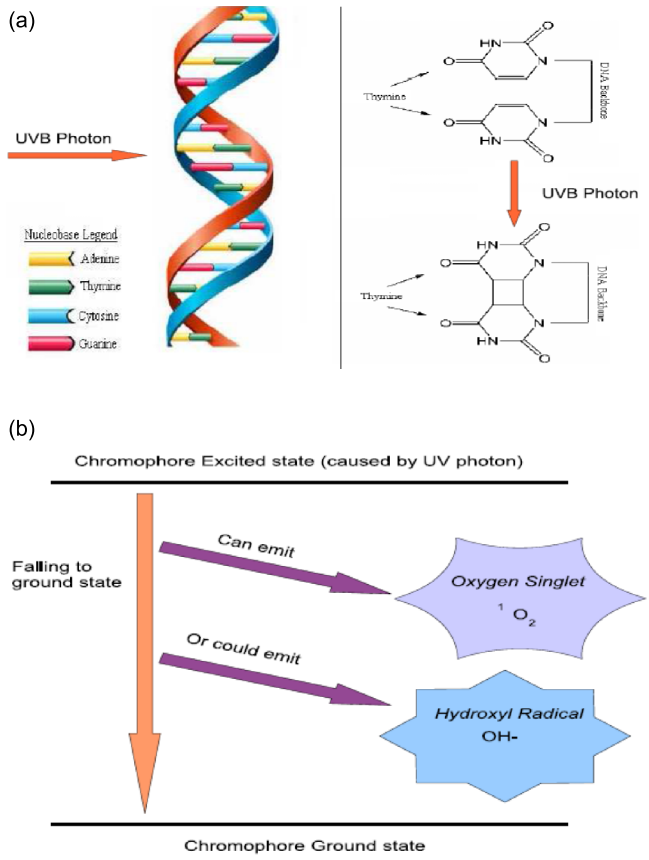

FIG. 3. (a) Direct deoxyribonucleic acid (DNA) damage caused by a UVB photon and (b) indirect DNA damage.

3.B. Erythema, melanogenesis, and immune system modulation

The acute and long term effects of exposure to ultraviolet radiation on human biological tissue are well documented.[4] The effect of this exposure is dependent upon both the exposure wavelength and the duration of that exposure. UVC or germicidal band photons are not used in phototherapy, and even in nature are effectively attenuated to nothing by atmospheric absorption[30] so the biological effects of UVC are not considered in UVR therapy. Erythema is a common consequence of exposure to UVR. It is the reddening of the skin induced by hyperemia (increase in blood flow) of the capillaries in lower skin layers.[31] In the case of relatively long-wave UVA, erythemal effects appear without any latency whereas erythema due to UVB tends to have a delayed appearance.[32] Erythema is often referred to by its colloquial term of sunburn, and is an unwanted side effect of treatment with an improper dose. In more extreme cases, there can be extensive blistering and peeling of epidermal layers.[7] UVB radiation is 100–1000 times more likely to induce an erythemal effect than UVA, this is clear from the CIE relative action spectrum shown in Fig. 4. UVB exposure also causes the production of vitamin D in skin,[33] specifically vitamin D_3. UVB can also modulate the immune system, depressing dendritic activity and thus inhibiting or otherwise altering immune system responses.[34] It is this property of UVR that may explain in part its beneficial effect on autoimmune disorders. Finally, UVR exposure triggers melanogenesis or darkening of the skin, commonly referred to as tanning.

3.C. Skin aging

Deeply penetrating UVA tends to cause collagen damage. Photoaged skin is characterized by loss of elasticity, wrinkles, uneven pigmentation, brown spots, and a leathery appearance whereas chronologically aged skin without over exposure to UVR is smooth and free of blemishes, though some natural loss of tone and elasticity occurs.[15]

3.D. Human eyes

Effects on the eye from overexposure to UVR include photokeratisis (snow blindness) from acute exposure and cataracts from chronic exposure.[14] Conjunctivitis can also occur due to UVR exposure, an inflammation of the eyelid membranes characterized by various degrees of photophobia (light aversion), blepharospasm (eyelid muscle spasm), lacrimation (tear shedding), and erythema of eyelid skin.[7] Unlike the epidermis, the human eye does not photoadapt and consequently has less of a protection mechanism.

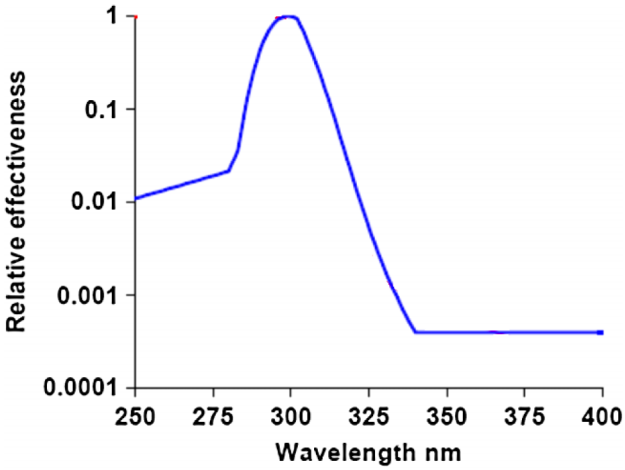

FIG. 4. CIE erythemal action spectrum (Ref. 35).

3.E. Epidermal response and photoadaptation

The amount of melanin and other chromophores present in the epidermis will influence strongly the amount of reaction that will take place. Skin with more pigment will appear darker, and skin color can be used to estimate the reaction to UVR. The Fitzpatrick phototyping scale[36] was developed to help classify skin types based on their appearance and reaction to UVR for predominantly white skin. This scale was later extended to include dark and even black skin.[13] This is outlined in Table II and often used by phototherapists to estimate starting dose. The minimal erythemal dose (MED) is the minimum dose required to observe an erythemal effect.

Photoadaptation is a trait of skin to respond to UVR irradiation by changing in such a way that future equivalent doses of such radiation have a diminished response.[37] While these processes are not entirely understood, but they have implications for UVR phototherapy in so much as a constant dose seems less than optimum for treatment response. Fitzpatrick scale gives an indication of the tolerance of the skin to UVR, and this is useful in determining a starting dose. However, it has been shown that doses close to the erythemal dose are most effective[38] so in practice the dose has to be increased in subsequent sessions. A general rule of thumb used is the 70/20 rule: begin at 70% of MED and increase by 20% each successive treatment. This seems to work well for all skin types, as evidence suggests that regardless of skin type, patients adapt approximately equally per physical unit of UVR.[39] In essence, human skin adapts to increasing amounts of UVR by increasing production of melanin and other chromophores. This process is called melanogensis and it triggers tanning in human skin.

3.F. Carcinogenesis

As the skin absorbs most UVR and this can result in DNA damage, there has been a well documented correlation of certain UVR therapies and skin cancers, particularly PUVA treatments.[40,41] In order of seriousness, UVR treatments have been implicated in basal cell carcinoma, squamous cell carcinoma, and malignant melanoma.[7] Current research indicates that UVB treatments are much less likely to be carcinogenic[42] than conventional UVA therapies. This may be because indirect DNA damage and the oxygen species it can create are more damaging than direct DNA damage caused by UVB. Indirect DNA damage is synonymous with UVA exposure[43] and the risk of cancer and carcinogensis must be accounted for in any therapy involving UVR.

4. UVR TREATMENTS

While UVR can be damaging to DNA integrity and has a host of potentially severe side effects, it is singularly effective at treating a range of chronic skin conditions. UVR treatments are typically given in one of the two ways: Ultraviolet A with a skin sensitizing psolaren (PUVA) or narrowband Ultraviolet B (NB-UVB) centered at 311 nm.

4.A. PUVA and narrowband UVB

The choice of PUVA versus NB-UVB comes down to a variety of factors. First, some diseases respond better to one type, and the medical reality of the patient condition then may decide the modality. There are other factors to be considered, however—even for ailments that respond better to PUVA, many patients can have toxic reactions to the psoralen which renders it ineffective. Also, pregnant women and those on blood thinners or certain medications cannot use the photosensitizing agent, and thus UVB is often used, even if it is slightly less effective for the disease in question. NB-UVB treatments do not have the side effects associated with PUVA treatments, such as unpredictable phototoxic reactions, vomiting, and nausea. NB-UVB therapy also has zero drug costs and shorter treatment duration[44] for patients

TABLE II. Fitzpatrick phototype scale—skin-type response to varying ultraviolet fluence.

Type	UVR response	Skin color	UVA MED (mJ/cm^2)	UVB MED (mJ/cm^2)
I	Burns easily/never tans	Ivory white	20–35	15–30
II	Burns easily/tans little	White	30–45	25–40
III	Burns moderately/often tans	White	40–55	30–50
IV	Burns minimally/tans easily	Olive	50–80	40–60
V	Burns rarely/tans profusely	Brown	70–100	60–90
VI	Never burns/tans profusely	Black	100	90–150

with vitiligo. For many conditions, NB-UVB has a better outcome than the older PUVA treatments. Importantly, the carcinogenic potential of both modalities must be considered; there is a body of evidence to suggest that long term PUVA treatments lead to higher carcinogenicity, specifically increased rates of SCC.[40] The same study concluded that NB-UVB treatments do not significantly increase the risk of developing SCC or BCC. A more recent study[41] confirms that while there is increased risk of cancers with PUVA treatments, NB-UVB treatments do not seem to increase the risk. For this reason, along with the relative ease of treatments, many clinicians opt to use NB-UVB treatments if possible. The question of why PUVA treatments seem to increase incidence of cancers is still being examined, but research suggests that UVA can cause mutagenesis in mammalian cells.[42,45]

4.B. Diseases treated with UVR

There are a wide range of skin disorders for which ultraviolet phototherapy is the primary means of treatment. The most common of these is psoriasis, a common chronic noninfectious disease of the skin which presents as raised patches on the skin known as psoriatic plaques. These plaques are caused by hyperprolific production of keratinocytes in the basal layer of the epidermis, resulting in regions with an overabundance of skin cells. Psoriasis is highly idiosyncratic and has a variety of different manifestations. While the exact causes of psoriasis are still under investigation, there is considerable evidence that psoriasis is an autoimmune disease.[46–48] Hence, T-cells from the immune system react with epidermal cells to stimulate abnormally high production of keratinocytes. There is also strong evidence that various types of interleukin (an immune signal protein) can stimulate overproduction of these cells and the inflammation associated with psoriasis.[49,50] There is also a strong genetic component, related again to immune issues.[51] As UVR modulates the immune system, it can reduce the number of dendritic immune cells and may explain why it is such an effective treatment.[51,52] UVR also reduces the activity of these immune cells.[53]

UVR phototherapy is highly beneficial for patients suffering from this disease, and both PUVA and NB-UVB treatments have been widely used to induce remission.[5] In clinical trials, PUVA has been show to be slightly more effective at causing remission of psoriasis versus NB-UVB (Refs. 54–56) though with potentially a much higher risk of carcinogenesis. NB-UVB used thrice weekly was found to be statistically no different in effectiveness or remission length than PUVA used twice weekly for chronic plaque psoriasis.[57] As a general rule, clinics will only use PUVA if NB-UVB has failed as aside from the higher cancer risk, the use of psolaren can make the patient hypersensitive to light and can be phototoxic in some cases. As a result, NB-UVB has fast become the dominant form of phototherapy in modern treatments. For chronic and stubborn eczema, UVR treatments can provide some clearance and reduction in severity.[58,59] Both PUVA and NB-UVB are effective, and equally effective at reducing conditions like chronic hand eczema which is resistant to other forms of treatment.[60]

Vitiligo, the depigmentation of the skin caused by the death of melanocytes, can also be treated with UVR. The reason why this occurs is not entirely clear, but autoimmune reactions are implicated. PUVA and NB-UVB have both been used successfully in repigmentation; a study by Bhatnagar[61] found NB-UVB treatments to be more effective than PUVA for this condition, being successful in 67.57% of cases versus 54.2% of cases for PUVA where traditionally treatment resistant sites such as hands and feet were not considered. It should be noted that patients with this condition have a much greater susceptibility to erythemal effects due to the decreased level of photoprotection. UVR is also an effective treatment for polymorphic light eruption (PMLE), a condition where skin becomes hypersensitive to UVR in sunlight, reacting with hive-like skin irritations. It seems counterintuitive and perhaps contradictory that a condition triggered by UVR exposure may also be treated with the very factor that triggers the reaction but indeed both PUVA and NB-UVB therapies have been proven to be effective treatment in stubborn cases. Whether this is due to some photoadaptive mechanism or the immunomodulatory nature of UVR is not clear, but despite curious mechanism of action, the effectiveness of the treatment is well established not in doubt.[62] In recent years, ultraviolet therapies have also shown promise for a range of other skin disorders, including acquired perforating dermatosis (APD),[37] Lichen Planus,[63,64] and Mycosis fungoides.[65] For all these treatments, the ideal scenario would be where dose is sufficient to yield maximum therapetic effect but sufficiently low that detrimental effects are minimized.

4.C. Cabin design

Phototherapy cabins are free standing structures, designed to provide approximately equal irradiance to all body sites during treatment. This is an important consideration, as skin disorders typically affect a large area of epidermis. There are a multitude of different designs available from numerous manufacturers. In general, cabins consist of multiple fluorescent lamps with their associated ballasts mounted in front of mirrors, where a patient stands at the cabin center. Cabins tend to be electrically cooled to keep the lamps at optimum operating temperature and there is usually a grill or UVR transparent plastic safety sheet between the patient and the lamps to reduce the potential of the patient coming into contact with the tubes or ballasts. Various models of Waldmann cabin are most frequently encountered in phototherapy centers across Europe, and other manufacturers include Dixwell, National Biological, and Daavlin. There is much variation in size, number of tubes, and reflector placement but the design should be such that the UVR cabin directs as much UVR as possible upon the patient epidermis. Some common cabin designs are shown in Fig. 5.

4.C.1. Reflector design and properties

Reflectors are usually mounted behind or around the UVR lamps to direct more light onto the patient epidermis. Like photocabins themselves, there is much variation in how these

FIG. 5. (A) Waldmann UV-5040, (B) National Biological Houva III, and (C) Waldmann UV-1000.

mirrors are designed and where they are placed. While early reflectors consisted of a single sheet reflector behind the tubes, modern cabins tend to shape a reflective sheet around the tube to better forward direct the incident UVR. This situation is illustrated in Fig. 6. The reflective sheets used as mirrors tend to be aluminum, as this has a reflectivity in the wavelength band of interest (300–400 nm) of about 92%.[66] In practice, they are coated with an anodic layer to protect the aluminum, as aluminum tends to oxidize and corrode unless it is protected. This has the net effect of decreasing the reflectivity significantly.

Anodization is the process of increasing the naturally forming oxide layer on a metal to increase its resistance to damage and corrosion. Anodic layers are nonconductive and increase surface hardness. In addition to anodization, aluminum alloys are often used in combination with anodization.[67] This provides protection, but has repercussions for the reflective properties of the material; some typical coatings for UVR reflectors are shown in Table III.[68] In general, the higher the purity of the aluminum used, the greater the specular reflectivity[69,70] and anodizing metal causes a large drop in reflectance.[71]

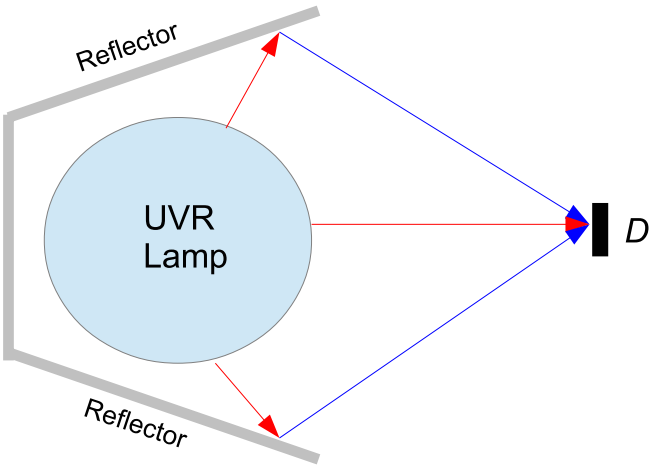

FIG. 6. A typical folded sheet reflector—A detector at D measures both a direct irradiance from the lamp and reflected irradiance from the shaped mirrors.

5. DOSE ESTIMATION TECHNIQUES

For treatments without a photosensitizing agent, the MED is ascertained for a patient. For a treatment such as PUVA with a phototoxic agent, the minimum phototoxic dose (MPD) must be found. The method for yielding these quantities is essentially the same. The most common method involved uses a thin plastic template with eight small windows; the template is positioned over an area of skin relatively unaccustomed to UV light, such as buttocks or back. The remainder of the body is protected. A sequence of exposures are performed on each slit, with each successive one in the ratio of $\sqrt{2}$ to the previous exposure.[72] In UVB treatments, erythema peaks between 8 and 24 h after initial exposure, and the template sites can be examined to find the lowest dose of UVB that yields an erythemal effect. This is the MED for the patient. UVA exposure peaks tend to be between 48 and 72 h after exposure and the MPD can be determined then by a similar visual inspection. Treatment usually begins as a ratio of the MED or MPD, typically 50%–70%. The patient is then started on this dose and it is incremented over several weeks until a marked improvement of the condition is observed by the physician or clinician.[72] There are other similar methods for ascertaining the starting dose; another method involves a phototesting template with a number of foil apertures. These apertures are all differing sizes and thereby attenuate the incident UVR by varying amounts, thus causing skin exposure of varying irradiance at different hole sites. The MED/MPD is then inspected visually again. It should be noted that the starting dose method relies on visual inspection and can be somewhat subjective. Once this starting dose is estimated, the exposure time required in the cabin is estimated. For this to be calculated, some knowledge of the skin dose due to the cabin must be ascertained. The skin testing method can only then give information about the

TABLE III. Anodic layers and their respective reflectivity (Ref. 18).

Anodic layer	Reflectivity for UVB
Coilzak	0.3
Alzak	0.6
Anodized 316G2	0.85

skin response to that particular test source and so the problem remains of comparing two sources with an objective method. The dose delivered to a patient inside a UVR cabin is of paramount importance, and we shall discuss two clinically used methods for estimating the cabin dose.

5.A. Scottish ultraviolet dosimetry (ScUVido) protocol

The Scottish photochemotherapy audit board identified this as a serious problem and recommended steps so that UVR therapy sources could be correctly compared and contrasted over the lifetime of a unit and even between units and phototherapy centers. The guidelines laid down improved PUVA treatment doses and were updated in 2001 (Ref. 73) for NB-UVB sources. The premise of the ScUViDo is to provide a standard for UV irradiance in treatment centers. The UVR meter used must be calibrated against the source which it is designed to work with; in the case of a UVA meter, a bank of UVA tubes and for a UVB meter, a bank of TL/01 tubes. The cosine response error of the meter should be low with an f_2 error of less than 10%. The calibration of all meters used must be traceable to the National Physical Laboratory, and the accuracy should be ±10%. Meter calibration should be performed annually and any anomalies corrected.

ScUViDo utilizes the concept of designated patient irradiance (DPI), which is the average irradiance on a patient of average height and build standing in a phototherapy cabin at chest, waist, and knee height. An investigating physicist in appropriate UVR protection gear stands in the cabin and adopting the position of a patient in treatment makes a series of measurements at various positions as shown in Fig. 7. All lamps in the cabin are warmed up 5 min prior to measurements being made, and the investigating physicist uses a hand held UV meter appropriate for the wavelength band of the lamps. Measurements are taken on the 12 sites and recorded. This gives the mean DPI at each body site without requiring a recourse to a known body correction factor. It is important to ensure that clothing does not obstruct any emitting sources, as this can lead to self-shielding problems. The color of the clinicians clothing can lead to variations of approximately 5%.[73] There is also an indirect method for obtaining the DPI by placing a retort stand with a clamped meter in place and multiplying by a correction factor for the particular cabin in question.

The major advantage of ScUViDo is that it allows comparison of treatments between different centers and units. It also indicates when lamps need to be replaced, typically when DPI has changed by 10%. Despite the practicality of this approach, clinicians and patients can have wildly differing body types and will shield different regions, resulting in large differences.

5.B. Automated detector

The ScUVido protocol is useful for providing localized calibration and facilitates comparison of irradiance between different phototherapy centers, as well as indicating when

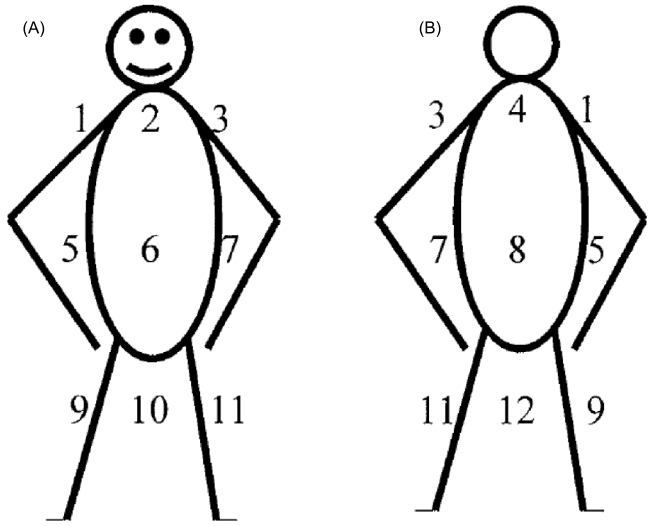

FIG. 7. DPI measurement sites (A) anterior and (B) posterior. Adapted from Ref. 73.

irradiance has dropped due to lamp failure, aging, or some other degradation. It is inexpensive to implement and as a consequence is used not only in Scotland but across many European phototherapy centers. Another method to examine and calibrate UVR cabins involves the use of an automated detection system as outlined by Currie *et al.*,[74] which comprises of two detectors facing opposite directions from each other; one is a wide-angle UVR photodiode detector with a raised polytetrafluorethylene (PTFE) diffuser and the other is another UVR sensitive photodiode housed at the end of a 200 mm tube with slots at either end measuring 10×1 mm to provide collimation. The entire mount rotates on a stepper motor which records the irradiance at 800 points in a full rotation for both the wide-angle and collimated detector. The data are send to a laptop computer which can display this information as a linear or polar plot. There are major advantages to such a system; first, it does not require an operator so self-shielding by the investigator is not a problem. Second, the collimated detector allows the user to see specifically which individual tubes are failing or have diminished output. Finally, it offers greater repeatability than the ScUViDo method and less uncertainly as readings are automated and human error is a less of a factor. As many hundreds of readings are made in a full rotation, specific dose incident upon the detector at various heights can be ascertained. The downside is that the system is quite costly and so far it has not been widely adopted despite its advantages. It also does not factor self-shielding into the analysis, meaning results would need to be considered and interpreted with this in consideration. The setup is shown in Fig. 8.

6. DOSE MODELS

While dosimetry methods exist for UVR therapy, there is a shortage of adequate dose models for quantifying the radiation incident upon the epidermis. Perhaps because UVR is nonionizing, it has been viewed as much less of

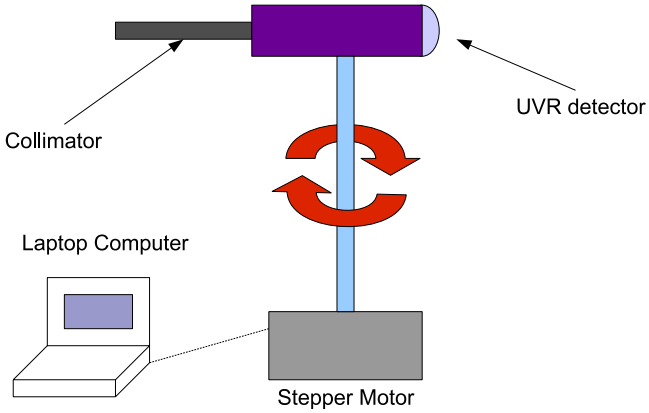

FIG. 8. Automated detector system. Arrows denote rotation direction.

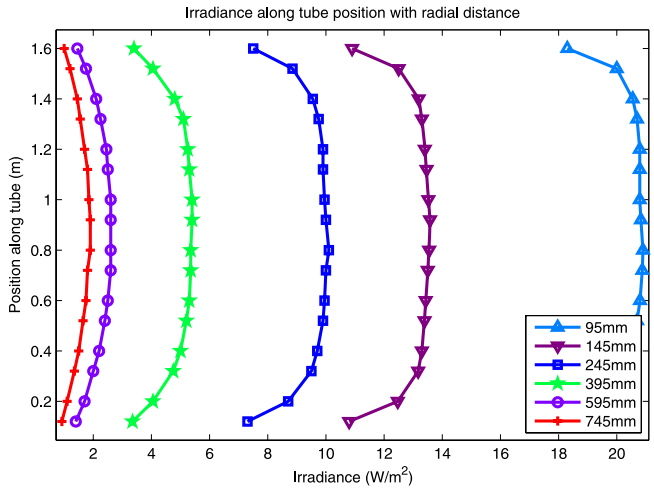

FIG. 9. Variation of irradiance along length of UV-100 W tube (Ref. 18). If the dose tubes were perfect radial emitters, the data sets would all record the same value along the length. This is not seen in practice.

a risk than other more energetic therapies and as such a less pressing concern. It bears consideration, however, that exposure to UVR has a number of unpleasant side effects and is potentially carcinogenic. The ailments treated with UVR tend to be lifelong chronic disorders, and patients may be exposed regularly their entire life, increasing the risk of an adverse event or even eventual oncogenesis. Thus, better dose quantification would not only improve treatments, it would be of great use in estimating the lifetime dose that a patient receives. An accurate dose model would also allow for better treatment plans and the targeting of particularly resistant areas.

6.A. Early radial models

Prior to 1970, radial emitter models were used exclusively in approximating photochemical reactors.[67] While these are not exactly UVR lamps, the analysis is similar. A radial emitter model assumes all photons emitted from a source are perpendicular to the surface of the source. This is of course not fully realistic; as is illustrated in Fig. 9, radiation emitted from the tube is not isotropic along the length. Despite the obvious inaccuracy, this method can give remarkably good results under certain conditions as the nonperpendicular elements can essentially cancel each other out.[75] The form for the radial emitter is inherently simple; a distance r from the emitter, the irradiance would be proportional to that measured on the surface of a cylinder of that radius. This can be expressed as

$$E = S_L/2\pi r, \tag{3}$$

where S_L is the power per unit length in units of W/m. The radial model can give accuracy of within 10% where the distance from lamp to detector is small but fails at predicting the irradiance from small surface elements.[68,75] It is unable to account for the angle at which photons strike the detector or skin site,[67] rendering it of limited use in UVR dosimetry.

6.B. Specular and diffuse emitter models

Specular and diffuse models of irradiance have been examined in context of photochemical reactors[75] and can be readily applied to phototherapy. The basic emitting profile of these two models is shown in Fig. 10. Figure 10(a) illustrates specular emission whilst Fig. 10(b) depicts diffuse emission. The specular model makes the assumption that each small element of the lamp acts as a point source and emits uniformly into a solid angle of 4π. In this case, the total radiation flux from the segment of length dx is equal to the sum of the radiation crossing the sphere of unit-length radius whose origin is at the center of dx, which can be manipulated to yield the radiant intensity per unit source length

$$\frac{dI}{dx} = S_L/4\pi. \tag{4}$$

The diffuse model approximates each element to a Lambertian radiator, which means cosine dependence on the intensity from an element. After manipulation, this yields a radiant intensity per unit element of

$$\frac{dI}{dx} = S_L/\pi^2. \tag{5}$$

These identities quantify the radiant intensity from an infinitesimal source element. While not directly applicable to phototherapy, they can be adapted to estimate the intensity of emitted radiation from a source and both models represent an improvement over the radial model.[76] For a fluorescent tube, the radiation is likely to diffuse and thus this assumption would likely give better results. For the purposes of UVR dosimetry, however, the model is simply not validated or adequate.

6.C. Simple barrier model

Prior to the late 1990s, there was no model that specifically considered UVR from a medical physics or patient dosimetry perspective. It was not until the work of Langmack[77] that the first substantial attempt to consider UVR dose models was published. In this work, a simple model was put forward that considers direct contributions from line source tubes and indirect contributions from reflections of tubes upon a

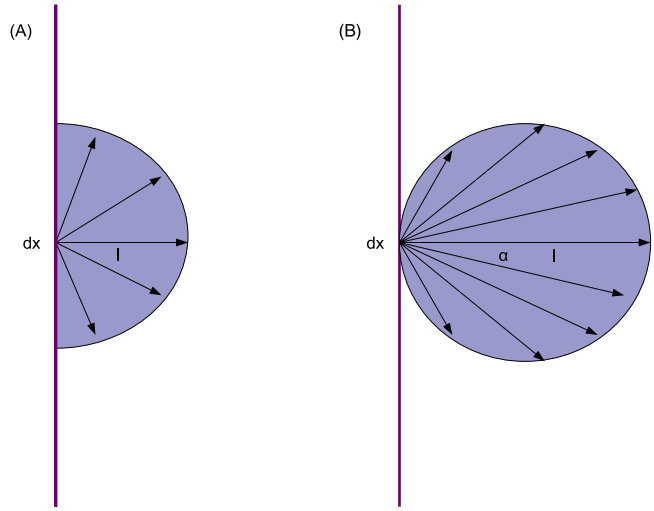

FIG. 10. (A) Specular emitter and (B) diffuse emitter.

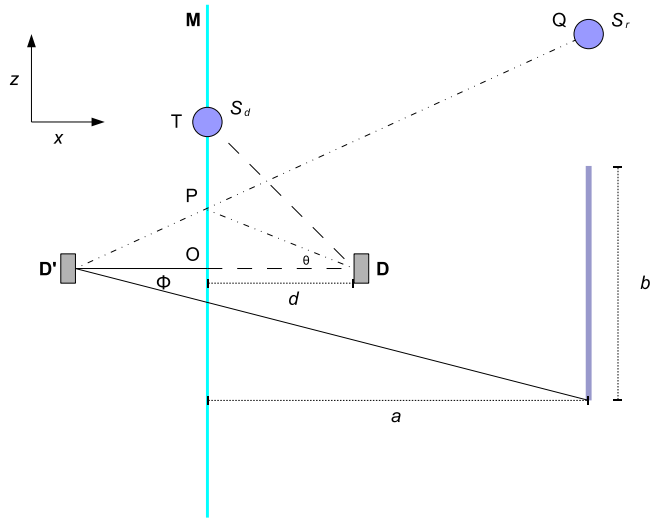

FIG. 11. Geometry of barrier model. Adapted from Ref. 77.

mirrored surface. A person in the cabin acts as a barrier of width b. Their presence can block some of the reflections and lower the recorded irradiance. The geometry of this model is shown in Fig. 11.

In this model, O is the origin of a coordinate system $(X–Z)$. M is a mirrored wall and D is a detector a distance d away from this wall so that the image of that detector, D', is also a distance of d away from the M. A barrier of width b (presenting a patient) is placed a distance a from M. There are two light sources: one on M denoted S_d and one beyond the barrier denoted S_r. S_d makes an angle of $\theta(S_d)$ with the D ($\angle TDO$) and the reflection of S_r makes an angle $\theta(S_r)$ ($\angle ODP$) with D. There are then two possible ways for D to see a light source. If $\theta < 90°$, then the tube is directly visible. If the tube is not on M, it can be viewed by reflection in M. Certain tubes will satisfy both these conditions, giving them two components to detector reading. A person of width b acts as a barrier; this means reflected light with angles less than ϕ will be blocked from the detector. The correction factor is then the ratio of reading with barrier to reading without it. The detector reading when viewing an indirect or direct source i is $I(S_i)$. In this model, the irradiance falls off to $1/l$ where l is the path length from the tube center to the detector. After rearrangement, the irradiance from a number of primary sources can be expressed as

$$I_d \propto \sum \frac{d}{z^2(S_i)+d^2}. \tag{6}$$

This model provides a simple approximation of the effect of self-shielding a patient could produce. The irradiance in this model falls off to $1/r$, when r is the radial distance from the source, similar to the cylindrical approximation. Langmack also outlined a simple extension considering the contribution from reflectors, given by

$$I_r \propto \sum \frac{x(S_r)+d}{[x(S_r)+d]^2+z^2(S_r)}. \tag{7}$$

Thus, total irradiance for a finite number of direct and reflected sources without a barrier present (denoted by $\bar{b}$) is approximated by

$$I_t(\bar{b}) = I_d + I_r(\bar{b}). \tag{8}$$

The barrier model then allows estimation of the effects of both self-shielding and reflection, providing an insight into how these factors influence received dose. The underlying model is radial, and it does not consider 3D factors, or realistic geometries. While useful in illustrating issues of self-shield, it is not in itself a dosimetry model as it does not provide quantification of the dose incident upon patient epidermis.

6.D. Detector-irradiance model

The detector-irradiance model[78] was designed specifically to test the angular responses of radiometers for UVR phototherapy rather than to act as a generalized dosimetry model. Despite this, it can yield good accuracy in many cases. This model considers the irradiance on a vertical surface O (a surface of skin or a radiometer) from a line source tube broken into elements of length Δl_α. The geometry of this situation is depicted in Fig. 12. From this, one can compute the irradiance from this finite length $\Delta I_{R\alpha}$ and summate all the discrete irradiances, giving an estimate of expected irradiance. At a height of l_α above or below the reference point at O with a mean angle of incidence α, the irradiance can be expressed as

$$\Delta I_{R\alpha} = \frac{S_L \cos\alpha \Delta l_\alpha}{a^2+b^2+l_\alpha^2} = \frac{S_L a \Delta l_\alpha}{(a^2+b^2+l_\alpha^2)^{3/2}}. \tag{9}$$

So the irradiance for each lamp over a discrete range of angles α can be expressed as

$$I_R = \sum \frac{S_L a \Delta l_\alpha}{(a^2+b^2+l_\alpha^2)^{3/2}}. \tag{10}$$

It is important to note that α refers to the angle with the vertical and the values of α used in this model are discrete; they were 0°–2.5°, sixteen 5° ranges from 2.5° to 82.5° and three ranges to cover angles from 82.5° to 90°. This means in practice that the number of elements being summed will change at varying displacements. For example, a 1.74 m lamp 200 mm from

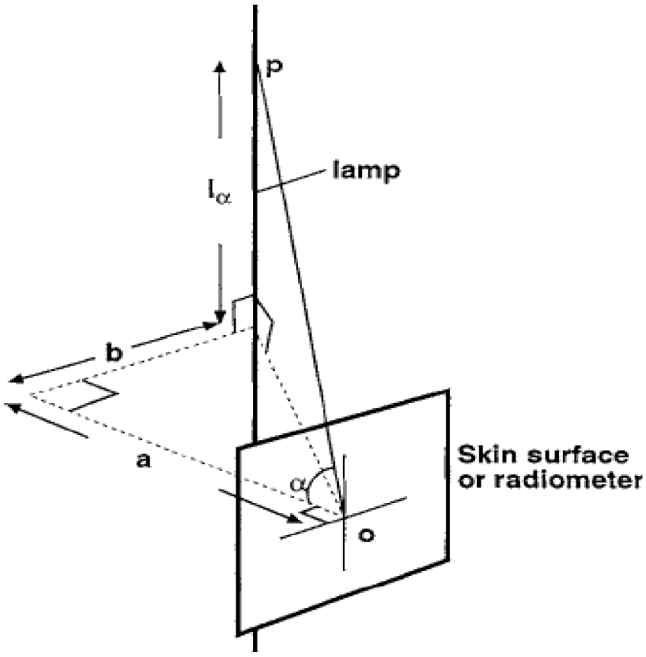

FIG. 12. Geometry of Martin–Pye Model. Reproduced with permission from Martin and Pye, Phys. Med. Biol. **45**, 2713–2729 (2000). Copyright 2000 by IOP Publishing.

the detector would be divided into 32 elements with angles between 0° and 77°. If the displacement was instead 555 mm, there would be 24 elements summed for angles between 0° and 57.5°. This model was developed to test the angular response of radiometers and diffusers rather than construct a comprehensive dose model but it does have some merit for this purpose. As the model was not specifically developed for dose modeling, it does not contain any correction terms for reflection contribution. In this model, irradiance falls off with an inverse square relationship ($1/r^2$) with distance from the lamp source.

6.E. Comprehensive dose model

While both the barrier and detector irradiance model have implications for the implementation of phototherapy, they do not amount to a computational dose model for patients undergoing radiotherapy. As all UVR is incident and absorbed superficially by the skin, the orientation of the skin surface is of paramount importance if accurate dosimetry is to be achieved. A first principles model of UVR dose that factors in skin orientation was published in 2010,[19] which treats the UVR tube as a line source continuum of point sources. Figure 13(a) shows the vector convention used in such a formulation for a skin surface and Fig. 13(b) illustrated radiation incident upon a skin surface from a point source and the normal angle relative to the skin surface. The UVR tube is treated as a diffuse irradiator and it can be shown through manipulation of radiometric identities that the resultant expression has both cosine dependence and obeys an inverse square law. Irradiance (E) can thus be expressed as a vector integral given by

$$E = \frac{S_L}{\pi^2}\int \frac{\cos\theta}{r^2}\mathrm{d}l = \frac{S_L}{\pi^2}\int \frac{\vec{n}\cdot\vec{r}}{|n||r|^3}\mathrm{d}l, \tag{11}$$

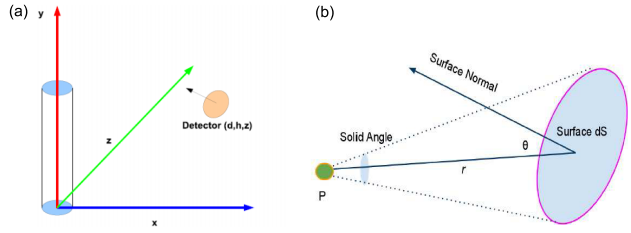

FIG. 13. (a) Vector convention used in comprehensive dose model and (b) point source irradiation incident upon a skin or detector site.

where S_L is the power per unit length of the UVR tube. Defining the surface normal at the skin or detector site as $\vec{n} = (A\vec{x} + B\vec{y} + C\vec{z})$, then for a tube of length L, the irradiance at a given point at a point (d, h, z) is given by

$$E = \frac{-S_R}{|n|v}\left[\frac{(Ad+Cz)(L-h)-Bv}{\sqrt{v+(L-h)^2}} + \frac{(Ad+cz)(h)+Bv}{\sqrt{v+h^2}}\right], \tag{12}$$

where $v = d^2 + z^2$ and $S_R = S_L/\pi^2$. This analysis yields the general case for a detector or epidermal surface at any orientation relative to the source. This equation can produce negative values of E when the absolute angle between the $\vec{n}$ and $\vec{r}$ vectors is greater than $\pi/2$ so care must be taken to ensure that simulated irradiance is forced to zero when a negative value occurs. This arises because cosine is negative between $\pi/2$ and $3\pi/2$. However, at these angles, the radiation is not incident upon the surface and thus it can be set to zero in any simulation. The general equation derived can handle any orientation, rendering it very useful in dealing with varying directions. Interestingly, when the detector is focused on the tube with no incline $n = -d\vec{x}$ and the previous equation reduces to

$$E = \frac{S_R}{d}\left[\frac{L-h}{\sqrt{d^2+(L-h)^2}} + \frac{h}{\sqrt{d^2+h^2}}\right] \tag{13}$$

which is the analytical analog to the numerical summation equation derived by Martin and Pye for a tube. This model is powerful in that it allows fully analytical quantification of dose from a lamp regardless of relative angle and orientation of that surface. The reduced constant S_R must be determined for specific lamps being tested. This was found to range from 0.96–0.99.[18,19,68] The model was tested using hand-held dedicated photodiode UVR irradiance meters by International Light (*International Light Technologies, MA*) and the automated rotating detector to provide variation of the detector orientation relative to a test lamp,[74] yielding agreement of within 1% between model and measured values. A comparison of model and measured data is shown in Fig. 14 and Table IV. The major benefit of this model is that it is highly accurate and easily implemented for any lamp source in UVR.

In principle, the analytical dose model can quantify dose regardless of orientation, but in the form derived in Eq. (14), the effects of reflection are not considered. In order to quantify the reflected irradiance, this model can also be extended by allowing an image of the tube to be formed in each of the mirrors surrounding the tube. If these mirrors have reflectivity

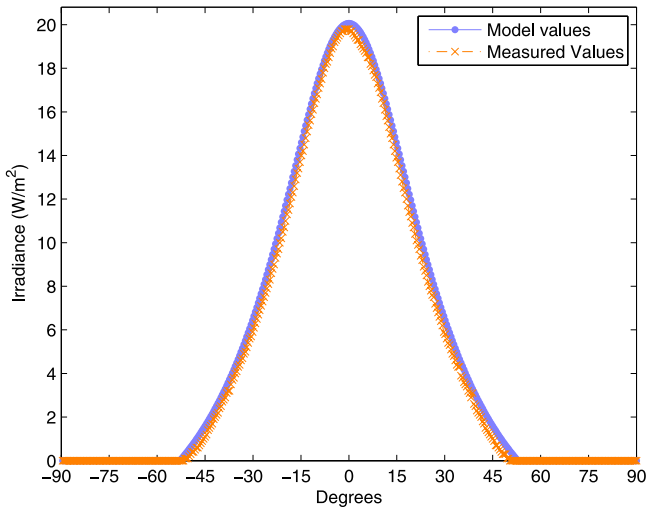

FIG. 14. Model/measurement data for rotating detector 248.5 mm from tube.

R_f and no longer stand at the origin but instead at some new point, then we may write $v_o = d_o^2 + z_o^2$ and the original equation can be expanded in terms of reflection to

$$E = \frac{S_R R_f}{|n| v_o}\left[\frac{(Ad + Cz)(L-h) - Bv_o}{\sqrt{v_o + (L-h)^2}} + \frac{(Ad + cz)(h) + Bv_o}{\sqrt{v_o + h^2}}\right]. \quad (14)$$

This broadly describes the technique for extending the model to cover reflections, but care must be taken to properly calculate the zones of reflection and other complicating factors. As the reflections "originate" from various mirror points, these must be calculated prior to simulation. A full mathematical treatment is handled in Grimes *et al.* 2011.[68] In reality, the tube is not a perfect line source but instead has a physical extent. This is typically around 37 mm (Ref. 19) and some of the radiation from the mirror is "shielded" by the tube itself in or close to this region. This is difficult to quantify analytically, and an ad hoc approximation for tube clipping has been introduced in the analysis to factor in clipping effects due to the physical extent of the tube obstructing reflected UVR. The reflection model was experimentally verified using a similar setup as before but with the mirrors in place in a UV-1000 unit and the zones of reflection calculated. The coefficient of determination of this model is high ($R^2 > 0.99$)[68] but there is some slight overestimation in zones where tube clipping is substantial, likely due to the imperfect attenuation approximation function. The analytical model handles both direct and reflected irradiance well once the orientation of the detector or skin surface is known. This means to construct a shielding model using this as a basis, the patient geometry would have to be known. If this can be well estimated, in theory this model could then quantify the irradiance on any surface of the patient.

TABLE IV. Goodness of fit for full rotations at various distances.

Distance from tube (mm)	R^2 fit
248.5	0.9971
368.5	0.9943
478.5	0.9904
576.5	0.9904

7. TOWARD FULL CABIN DOSIMETRY

The models outlined in this review have significant promise, but to qualify as a true dosimetric tool, they must be able to predict dose in an entire cabin. This is not a trivial exercise; UVR cabins can consist of up to 48 tubes in various geometry and mirror arrangement. More difficult still is that patient dimensions vary hugely, rendering the analysis even more complex. Despite this, some preliminary work has been done with this aim.[79] In principle, the comprehensive dose model with reflection extension should be able to quantify the dose at any point inside a cabin. This has been experimentally investigated using a Waldmann UV-1000 cabin, as this is readily separable into two halves. Even with the dubious attenuation function, fits were above $R^2 = 0.9927$ for all distances tested. As in the reflective case, the model still slightly overestimates the dose incident at certain angles, likely due to the imperfect and ad hoc attenuation function in the reflection extension.

7.A. Implications for cabin design

The results of this model have implications for cabin design and patient dose; the reflection extension of the analytical model predicts that the mirror angle around the tubes becomes increasingly important. While tighter angles allow more tubes to be packed in close together, they narrow the range that reflections can contribute in, potentially reducing over all irradiance and homogeneity. This leads to the perhaps counterintuitive finding that more tubes in a cabin may in fact lead to a diminishing returns situation with lower average output per tube.[79] This has been measured in practice, and the general trend seems apparent that cabins with more tubes have a lower average output. The effects of cabin geometry on predicted dose have been well simulated using the analytical model,[80] and examples of this are shown in Fig. 15. In this figure, there are regions where the reflection cutoff zones exhibit almost interference like effects, and even regions where the irradiance is greater from an 8 tube bank than a 10 tube bank. While changing the design of UVR cabins is not something a clinician can realistically be expected to undertake, it is important to be aware that simply packing more tubes into a region can in fact reduce homogeneity and dose rather than improve it.

8. DISCUSSION AND CONCLUDING REMARKS

UVR treatments have shown extraordinary effectiveness in treating a wide range of chronic skin conditions, but the question of maximizing beneficial biological effect whilst minising detrimental exposure is one that has still not be

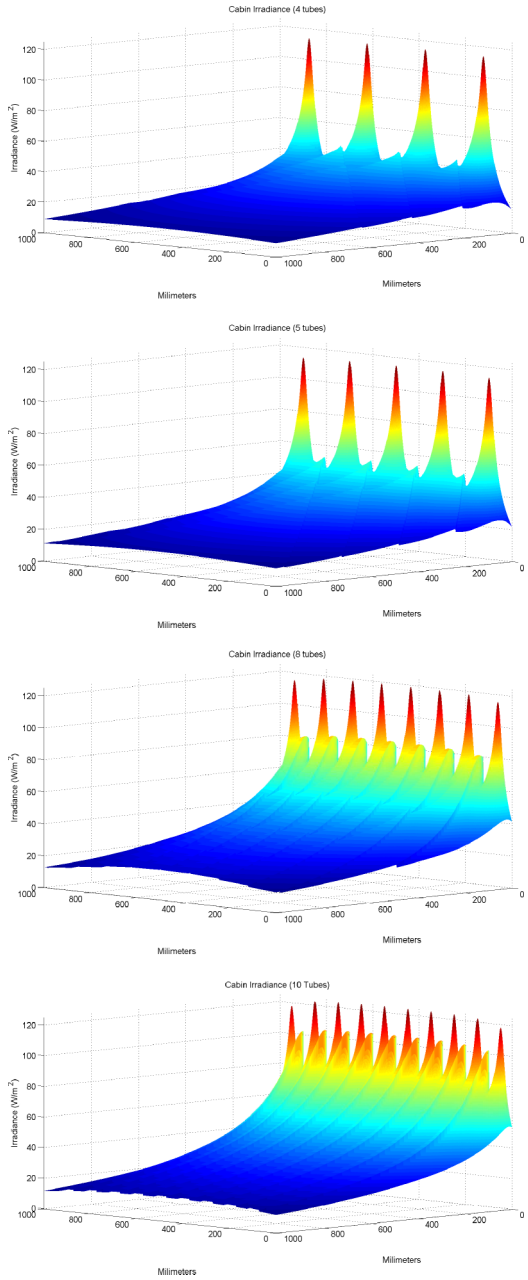

FIG. 15. Estimated irradiance profiles over a 1 m^2 area from banks of 4, 5, 8 and 10 tubes and reflectors (Ref. 80).

adequately answered. Because the conditions UVR treats are chronic, this means a potential lifetime of exposure and currently there is no reproducible way to quantify this. The ScUVido protocol is extremely pragmatic and serves as a vital calibration but is not designed to act as a dose model, and in essence provides a measure of the reproducibility for a particular cabin and operator combination.

Unlike most other photon treatments, UVR is deposited entirely on the skin. This complicates matters significantly, as the complex orientation of human epidermis greatly affects dose and renders accurate UVR dosimetry far from trivial. The models discussed in this review have applicability for different applications; the barrier model is useful for estimating potential effects of patient self-shielding, and has application is roughly estimating factors influencing reflection. It is limited by its 2D geometry and not readily extendible into realistic 3D modeling. The detector model is useful for gauging the Lambertian response of a particular photodetector, and was designed solely for this purpose. It can also provide a good estimate of dose for situations where the detector is normal to the tube surface. In a clinical situation, this could be a rapid test to investigate if a detector is giving the expected response. In terms of a fully computational dosimetry solution, the comprehensive model was designed for this purpose and delivers very accurate dose estimations at any orientation or distance. The reflection extension also yields good results, and an improved attenuation function for mirror clipping would improve this further. While this model has accuracy within 1%, it can be difficult to implement and if approximation is acceptable another method may suffice.

Yet despite these advances, patient-centric UVR dosimetry still eludes us, and is likely to do for the foreseeable future. While we can quantify irradiance well for known geometries, the inescapable fact is that patients have complex geometries that are currently unaccounted for, and difficult to quantify. Indeed, while we can very accurately estimate dose incident upon a known surface, surface information is simply not available on a patient-specific basis. More complex again would be to factor self-shielding into such an analysis. This makes an accurate dosimetric model exceptionally difficult to implement, posing the question of how this might be achieved—in principle, it may be possible to do this with a ray-tracing program calibrated to the cabin and the patient, but given the complex geometries of UVR cabins and self-shielding issues, it would be a formidable task and likely computationally intensive.

Cabin design is another factor worthy of more investigation. In particular, there is good evidence that tighter

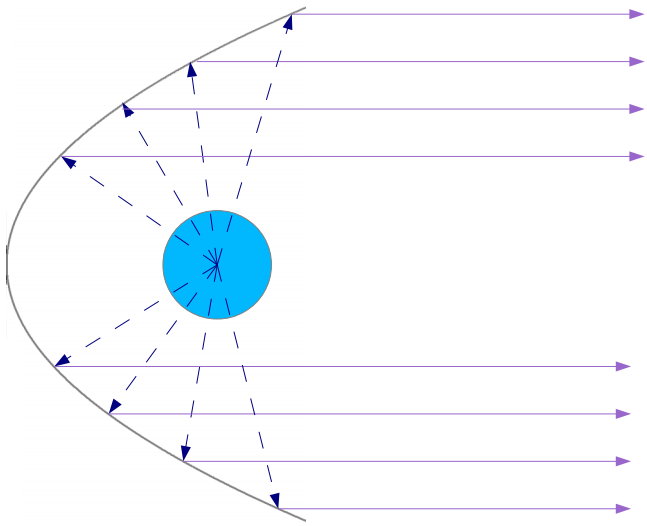

FIG. 16. A hypothetical parabolic type reflector with each tube at its focus. Simulation indicates (Ref. 80) such designs would result in a more homogeneous distribution of radiation and avoid the diminishing returns problem but no such designs are currently in common use.

mirror angles reduce average dose, and may serve to create inhomogeneous regions of lower than expected dose. While many modern cabins cram in as many UVR tubes as they can fit in the limited space available, this may result in tighter mirror angles and hence decreased uniformity and efficiency. To increase dose uniformity, cabin manufacturers might be well advised to experiment with more effective mirror design, and be aware that simply forcing more tubes into a UVR cabin may be far from the ideal solution. One possibility that might improve dose uniformity are parabolic mirrors, as illustrated in Fig. 16; this would in principle have the net effect of homogenizing output from a reflector array. This is of course not a factor a clinician can readily influence, but it is important to be aware of it, and for future cabin designs to consider such issues. Cabin geometry itself has a substantial effect on dose uniformity, and ideally cabins should be constructed in geometries with high levels of symmetry if dose is to be kept uniform throughout the cabin.

UVR offers relief for a growing number of skin conditions and substantially improves the quality of life for those afflicted, but overexposure has detrimental effects. Due to the potentially negative effects of UVR and the lifelong nature of many of the ailments it is used to treat, there is urgent need for improved dosimetry and quantification of dose delivery to patients. This might be achieved either through better dose models, improved computational modeling, refined cabin design, or a combination of all these elements. While much valuable work has been done on phototherapy over the last two decades, there is still much more to do from a medical physics perspective if functional UVR dosimetry is to be achieved in a clinical setting.

ACKNOWLEDGMENTS

Heartfelt thanks to Dr. Colin Martin and Graeme Phanco of Royal Gartnavel Hospital for their vital input. Thanks also to Professor Neil O'Hare of St James's Hospital and Dr. Chris Robbins of Grallator for their UVR related assistance. The author would also like to extend his gratitude to Professor Harry Moseley of Dundee university for his help and advice.

[a]Electronic mail: davidrobert.grimes@oncology.ox.ac.uk

[1]F. Ellinger, "Medical radiation biology," Cancer **11**, 872 (1958).
[2]J. Frercksa, H. Weberb, and G. Wiesenfeldt, "Reception and discovery: The nature of Johann Wilhelm Ritter invisible rays," Stud. Hist. Philos. Sci. Part A **40**, 143–156 (2009).
[3]C. W. Saleeby, *Sunlight and Health* (Nisbet and Company Limited, London, 1923).
[4]B. L. Diffey, "Ultraviolet radiation physics and the skin," Phys. Med. Biol. **25**, 405–426 (1980).
[5]C. Green, B. L. Diffey, and J. L. M. Hawk, "Ultraviolet radiation in the treatment of skin disease," Phys. Med. Biol. **37**, 1–20 (1992).
[6]Commission Internationale de l'Eclairage, International Lighting Vocabulary, 1970.
[7]B. Diffey and G. Hart, *Ultraviolet and Blue-light Phototherapy: Principles, Sources, Dosimetry and Safety* (Institute of Physics and Engineering in Medicine, York, 1997).
[8]H. Moseley *et al.*, *Non-ionising Radiation: Microwaves, Ultraviolet and Laser Radiation* (Adam Hilger Bristol, Philadelphia, 1988).
[9]B. L. Diffey, "What is light?," Photodermatol., Photoimmunol. Photomed. **18**, 68–74 (2002).
[10]J. B. Murdoch, *Illumination Engineering: From Edison's Lamp to the Laser* (Macmillan, New York, NY, 1985).
[11]J. A. Parrish, K. F. Jaenicke, and R. R. Anderson, "Erythema and melanogenesis action spectra of normal human skin *," Photochem. Photobiol. **36**, 187–191 (1982).
[12]D. T. Ribeiro, C. Madzak, A. Sarasin, P. Di Mascio, H. Sies, and C. F. M. Menck, "Singlet oxygen induced dna damage and mutagenicity in a single-stranded sv40-based shuttle vector," Photochem. Photobiol. **55**, 39–45 (1992).
[13]T. B. Fitzpatrick, "The validity and practicality of sun-reactive skin types i through vi," Arch. Dermatol. **124**, 869–871 (1988).
[14]D. H. Sliney, "Ultraviolet radiation effects upon the eye: Problems of dosimetry," Radiat. Prot. Dosim. **72**, 197–206 (1997).
[15]G. J. Fisher, Z. Q. Wang, S. C. Datta, J. Varani, S. Kang, and J. J. Voorhees, "Pathophysiology of premature skin aging induced by ultraviolet light," N. Engl. J. Med. **337**, 1419–1429 (1997).
[16]F. R. de Gruijl, "Skin cancer and solar {UV} radiation," Eur. J. Cancer **35**, 2003–2009 (1999).
[17]M. Meinhardt, R. Krebs, A. Anders, U. Heinrich, and H. Tronnier, "Wavelength-dependent penetration depths of ultraviolet radiation in human skin," J. Biomed. Opt. **13**, 044030 (2008).
[18]D. R. Grimes, "Development of a computational dose model for use in ultraviolet phototherapy," Ph.D. thesis, Dublin City University, 2010.
[19]D. R. Grimes, C. Robbins, and N. J. OHare, "Dose modeling in ultraviolet phototherapy," Med. Phys. **37**, 5251–5257 (2010).
[20]B. L. Diffey, "Sources and measurement of ultraviolet radiation," Methods **28**, 4–13 (2002).
[21]P. Meredith and J. Riesz, "Radiative relaxation quantum yields for synthetic eumelanin," Photochem. Photobiol. **79**, 211–216 (2004).
[22]D. S. Goodsell, "The molecular perspective: Ultraviolet light and pyrimidine dimers," Oncologist **6**, 298–299 (2001).
[23]S. E. Whitmore, C. S. Potten, C. A. Chadwick, P. T. Strickland, and W. L. Morison, "Effect of photoreactivating light on uv radiation-induced alterations in human skin," Photodermatol., Photoimmunol. Photomed. **17**, 213–217 (2001).
[24]A. A. Vink and L. Roza, "Biological consequences of cyclobutane pyrimidine dimers," J. Photochem. Photobiol., B **65**, 101–104 (2001).
[25]H. Davies *et al.*, "Mutations of the braf gene in human cancer," Nature **417**, 949–954 (2002).
[26]A. Cantrell, D. J. McGarvey, and T. G. Truscott, "Sun protection in man," Compr. Ser. Photosci. **3**, 495–519 (2001).
[27]C. N. Mosley, L. Wang, S. Gilley, S. Wang, and H. Yu, "Light-induced cytotoxicity and genotoxicity of a sunscreen agent, 2-phenylbenzimidazole in salmonella typhimurium ta 102 and hacat keratinocytes," Int. J. Environ. Res. Public Health **4**, 126–131 (2007).
[28]C. Xu, A. Green, A. Parisi, and P. G. Parsons, "Photosensitization of the sunscreen octyl p-dimethylaminobenzoate by UVA in human melanocytes but not in keratinocytes," Photochem. Photobiol. **73**(6), 600–604 (2001).
[29]T. Armeni, E. Damiani, M. Battino, L. Greci, and G. Principato, "Lack of in vitro protection by a common sunscreen ingredient on uva-induced cytotoxicity in keratinocytes," Toxicology **203**, 165–178 (2004).
[30]D. M. Gates, "Spectral distribution of solar radiation at the earth's surface," Science **151**, 523–529 (1966).
[31]S. Rothman, "Physiology and biochemistry of the skin," in *Britain Medical Journal* (The University Press, London, 1954). p. 399; see http://agris.fao.org/agris-search/search.do?recordID=US201300609726.
[32]K. H. Kaidbey and A. M. Kligman, "The acute effects of long-wave ultraviolet radiation on human skin," J. Invest. Dermatol. **72** (1979).
[33]J. S. Adams, T. L. Clemens, J. A. Parrish, and M. F. Holick, "Vitamin-d synthesis and metabolism after ultraviolet irradiation of normal and vitamin-d-deficient subjects," N. Engl. J. Med. **306**, 722–725 (1982).
[34]Y. Matsumura and H. N. Ananthaswamy, "Toxic effects of ultraviolet radiation on the skin," Toxicol. Appl. Pharmacol. **195**, 298–308 (2004).
[35]CIE, *Reference Action Spectrum and Standard Eerythema Dose* (Commission Internationale de Iéclairage, Vienna, 1998), pp. 19–20.
[36]T. B. Fitzpatrick, "Soleil et peau," J. Med. Esthet. **2**, 33–4 (1975).
[37]S. Ohe, K. Danno, H. Sasaki, T. Isei, H. Okamoto, and T. Horio, "Treatment of acquired perforating dermatosis with narrowband ultraviolet b," J. Am. Acad. Dermatol. **50**, 892–894 (2004).
[38]A. Hofer *et al.*, "Comparison of phototherapy with near vs far erythemogenic doses of narrow-band ultraviolet b in patients with psoriasis," Br. J. Dermatol. **138**, 96–100 (1998).

[39]R. A. Palmer, S. Aquilina, P. J. Milligan, S. L. Walker, J. L. M. Hawk, and A. R. Young, "Photoadaptation during narrowband ultraviolet-b therapy is independent of skin type: A study of 352 patients," J. Invest. Dermatol. **126**, 1256–1263 (2006).
[40]R. S. Stern and N. Laird, "The carcinogenic risk of treatments for severe psoriasis," Cancer **73**, 2759–2764 (1994).
[41]M. Weischer, A. Blum, F. Eberhard, M. Röcken, and M. Berneburg, "No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband uvb phototherapy: A first retrospective study," Acta Derm.-Venereol. **84**, 370–374 (2004).
[42]H. M. Studniberg and P. Weller, "Puva, uvb, psoriasis, and nonmelanoma skin cancer," J. Am. Acad. Dermatol. **29**, 1013–1022 (1993).
[43]P. C. Dedon, J. P. Plastaras, C. A. Rouzer, and L. J. Marnett, "Indirect mutagenesis by oxidative dna damage: Formation of the pyrimidopurinone adduct of deoxyguanosine by base propenal," Proc. Natl Acad. Sci. U. S. A. **95**, 11113–11116 (1998).
[44]M. D. Njoo, J. D. Bos, and W. Westerhof, "Treatment of generalized vitiligo in children with narrow-band (tl-01) uvb radiation therapy," J. Am. Acad. Dermatol. **42**, 245–253 (2000).
[45]C. A. Jones, E. Huberman, M. L. Cunningham, and M. J. Peak, "Mutagenesis and cytotoxicity in human epithelial cells by far-and near-ultraviolet radiations: Action spectra," Radiat. Res. **110**, 244–254 (1987).
[46]H. Valdimarsson, B. S. Baker, I. Jónsdóttir, A. Powles, and L. Fry, "Psoriasis: A t-cell-mediated autoimmune disease induced by streptococcal superantigens?," Immunol. Today **16**, 145–149 (1995).
[47]B. S. Baker, A. F. Swain, L. Fry, and H. Valdimarsson, "Epidermal t lymphocytes and hla-dr expression in psoriasis," Br. J. Dermatol. **110**, 555–564 (1984).
[48]B. S. Baker and L. Fry, "The immunology of psoriasis," Br. J. Dermatol. **126**, 1–9 (1992).
[49]R. M. Grossman, J. Krueger, D. Yourish, A. Granelli-Piperno, D. P. Murphy, L. T. May, T. S. Kupper, P. B. Sehgal, and A. B. Gottlieb, "Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes," Proc. Natl Acad. Sci. U. S. A. **86**, 6367–6371 (1989).
[50]Y. Zheng, D. M. Danilenko, P. Valdez, I. Kasman, J. Eastham-Anderson, J. Wu, and W. Ouyang, "Interleukin-22, a th17 cytokine, mediates il-23-induced dermal inflammation and acanthosis," Nature **445**, 648–651 (2007).
[51]F. O. Nestle, D. H. Kaplan, and J. Barker, "Psoriasis," N. Engl. J. Med. **361**, 496–509 (2009).
[52]M. Ozawa, K. Ferenczi, T. Kikuchi, I. Cardinale, L. M. Austin, T. R. Coven, L. H. Burack, and J. G. Krueger, "312-nanometer ultraviolet b light (narrow-band uvb) induces apoptosis of t cells within psoriatic lesions," J. Exp. Med. **189**, 711–718 (1999).
[53]D. A. Schmitt and S. E. Ullrich, "Exposure to ultraviolet radiation causes dendritic cells/macrophages to secrete immune-suppressive il-12p40 homodimers," J. Immunol. **165**, 3162–3167 (2000).
[54]P. M. Gordon, B. L. Diffey, J. N. S. Matthews, and P. M. Farr, "A randomized comparison of narrow-band tl-01 phototherapy and puva photochemotherapy for psoriasis," J. Am. Acad. Dermatol. **41**, 728–732 (1999).
[55]S. S. Yones, R. A. Palmer, T. T. Garibaldinos, and J. L. M. Hawk, "Randomized double-blind trial of the treatment of chronic plaque psoriasis: Efficacy of psoralen–uv-a therapy vs narrowband uv-b therapy," Arch. Dermatol. **142**, 836–842 (2006).
[56]E. Sezer, A. H. Erbil, Z. Kurumlu, H. B. Taştan, and I. Etikan, "Comparison of the efficacy of local narrowband ultraviolet b (nb-uvb) phototherapy versus psoralen plus ultraviolet a (puva) paint for palmoplantar psoriasis," J. Dermatol. **34**, 435–440 (2007).
[57]T. Markham, S. Rogers, and P. Collins, "Narrowband uv-b (tl-01) phototherapy vs oral 8-methoxypsoralen psoralen–uv-a for the treatment of chronic plaque psoriasis," Arch. Dermatol. **139**, 325–328 (2003).
[58]M. Grundmann-Kollmann, S. Behrens, M. Podda, R. U. Peter, R. Kaufmann, and M. Kerscher, "Phototherapy for atopic eczema with narrow-band uvb," J. Am. Acad. Dermatol. **40**, 995–997 (1999).
[59]N. J. Reynolds, V. Franklin, J. C. Gray, B. L. Diffey, and P. M. Farr, "Narrow-band ultraviolet b and broad-band ultraviolet a phototherapy in adult atopic eczema: A randomised controlled trial," Lancet **357**, 2012–2016 (2001).
[60]E. Sezer and I. Etikan, "Local narrowband uvb phototherapy vs local puva in the treatment of chronic hand eczema," Photodermatol., Photoimmunol. Photomed. **23**, 10–14 (2007).
[61]A. Bhatnagar, A. J. Kanwar, D. Parsad, and D. De, "Comparison of systemic puva and nb-uvb in the treatment of vitiligo: An open prospective study," J. Eur. Acad. Dermatol. Venereol. **21**, 638–642 (2007).
[62]H. Hönigsmann, "Polymorphous light eruption," Photodermatol., Photoimmunol. Photomed. **24**, 155–161 (2008).
[63]F. Pavlotsky, N. Nathansohn, G. Kriger, D. Shpiro, and H. Trau, "Ultraviolet-b treatment for cutaneous lichen planus: Our experience with 50 patients," Photodermatol., Photoimmunol. Photomed. **24**, 83–86 (2008).
[64]A. Wackernagel, F. J. Legat, A. Hofer, F. Quehenberger, H. Kerl, and P. Wolf, "Psoralen plus uva vs. uvb-311 nm for the treatment of lichen planus," Photodermatol., Photoimmunol. Photomed. **23**, 15–19 (2007).
[65]P. V. M. M. Diederen, H. van Weelden, C. J. G. Sanders, J. Toonstra, and W. A. van Vloten, "Narrowband uvb and psoralen-uva in the treatment of early-stage mycosis fungoides: A retrospective study," J. Am. Acad. Dermatol. **48**, 215–219 (2003).
[66]J. Bartl and M. Baranek, "Emissivity of aluminium and its importance for radiometric measurement," Meas. Phys. Quantities **43**, 31–36 (2004).
[67]R. Phillips, *Sources and Applications of Ultraviolet Radiation* (Academic, London, UK, 1983), Vol. 1, p. 434 (16pp.).
[68]D. R. Grimes, C. Robbins, C. J. Martin, G. Phanco, and N. J. OHare, "Reflection modeling in ultraviolet phototherapy," Med. Phys. **38**, 4312–4320 (2011).
[69]S. Wernick, R. Pinner, and P. G. Sheasby, *Surface Treatment and Finishing of Aluminium and its Alloys* (Draper, Teddington, 1956).
[70]B. Chalkley, "The chemical and electrochemical polishing of aluminum," in *Paper from "4th Symposium on Electroplating," Kiadja, Budapest, Hungary*, 1973, pp. 193–205(+ 6 plates).
[71]C. M. Jackson and R. W. Thomas, "The specular reflectivity of bright anodized aluminium," Trans. Inst. Met. Finish. **57**, 105–109 (1979).
[72]D. K. Taylor *et al.*, "Guidelines for dosimetry and calibration in ultraviolet radiation therapy: A report of a british photodermatology group workshop," Br. J. Dermatol. **146**, 755–763 (2002).
[73]H. Moseley, "Scottish uv dosimetry guideline, scuvido," Photodermatol., Photoimmunol. Photomed. **17**, 230–233 (2001).
[74]G. D. Currie, A. L. Evans, D. Smith, C. J. Martin, S. McCalman, and D. Bilsland, "An automated dosimetry system for testing whole-body ultraviolet phototherapy cabinets," Phys. Med. Biol. **46**, 333–346 (2001).
[75]T. Akehata and T. Shirai, "Effect of light-source characteristics on the performance of circular annular photochemical reactor," J. Chem. Eng. Jpn. **5**, 385–391 (1972).
[76]H. Funayama, K. Ogiwara, T. Sugawara, and H. Ohashi, "Light intensity profiles in photoreactors applied by a low-pressure mercury lamp," Kagaku Kogaku Ronbunshu **3**, 354–358 (1977).
[77]K. A. Langmack, "An insight into the contributions of self-shielding and lamp reflectors to patient exposure in phototherapy units," Phys. Med. Biol. **43**, 207–214 (1998).
[78]C. J. Martin and S. D. Pye, "A study of the directional response of ultraviolet radiometers: Ii. Implications for ultraviolet phototherapy derived from computer simulations," Phys. Med. Biol. **45**, 2713–2729 (2000).
[79]D. R. Grimes, C. J. Martin, and G. Phanco, "Investigations of cabin design in uv phototherapy," Med. Phys. **39**, 3019–3025 (2012).
[80]D. R. Grimes, "A computational simulation of reflector and tube effects in ultraviolet phototherapy," Phys. Med. Biol. **57**, 6661–6670 (2012).