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Towards a broader use of phototesting

- in research, clinical practice and
skin cancer prevention



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Cover illustration: Front page image: Sun and Man. Redrawing of prehistoric rock carving. Back page image: The Inca sun god Viracocha.

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To My Family,

and

to the memory of my father,
once happily unaware of the
deleterious powers of the sun.

*“There is nothing new under the sun,
but there are lots of old things we don’t know”.*

– AMBROSE BIERCE

Abstract

In western societies, skin cancer incidence has increased dramatically over recent decades, due predominantly to increased sun exposure habits. Ultraviolet (UV) light exposure and individual light sensitivity of the skin constitute two important factors affecting the risk for skin cancer development. Individuals with a heightened propensity to get sunburnt have a higher risk for skin malignancies, and need to protect themselves more systematically from the sun. Individual UV-light sensitivity can be determined either by self-estimation of tendency to burn and tan, as in the *Fitzpatrick's classification*, or by use of a *phototest*. Although phototesting constitutes a considerably more objective method, it is only sparsely used, chiefly due to financial and resource related factors, and is mainly limited to investigation of *photodermatoses* or dose-management in *phototherapy*.

The general aim of this thesis was to develop and improve aspects of the phototest procedure in order to broaden the utilisation of phototesting within the fields of research, clinical practice and skin cancer prevention. As a first step, a new phototesting technique, using a *divergent, centrifugally attenuating, UVB beam* was evaluated. The principle of the method is to provoke a circular UVB-erythema in the skin, the diameter of which is related to the administered dose and thus the *Minimal Erythema Dose* (MED). In a test group of healthy subjects, naked eye reading by a trained observer resulted in a more exact estimation of UVB-sensitivity, compared to traditional phototesting. However, since the diffuse border of the provoked erythema was challenging for the untrained observer to read, the need for an objective, bio-engineering technique for test reading was clear. In this thesis, *Laser Doppler perfusion imaging* (LDPI) has been used. This data also enabled an objective description of dose-response for the reaction, an outcome not possible in traditional testing. The divergent beam method was also shown to be useful as a model for evaluation of the effect of topically applied substances.

In order to broaden the utilisation of phototests in general, a test procedure built on patient performed self-reading of skin tests (a traditional phototest and an irritant patch test) was evaluated. The reliability of these self-readings was shown to be substantial when compared to the control readings of a trained observer.

Using the self-reporting procedure, phototesting was evaluated as a tool in primary prevention of skin cancer. The study focussed on sun habits and sun protection behaviour, and also on investigating the impact of different forms of presentation of the preventive information. Results showed significantly higher impact for a personally mediated preventive message than by letter-form. For individuals with heightened UV-sensitivity, the performance of a phototest led to a greater tendency to adopt sun protection behaviour than for subjects with a lower UV-sensitivity, suggesting that phototesting is a useful way to improve the outcome in terms of preventive behaviours for this group of susceptible, at-risk individuals.

Divergent beam phototesting, patient-performed self-reading, and the application of phototesting in skin cancer prevention emerge as three novel, previously little investigated, aspects of phototesting, for which promising results could be demonstrated.

List of original Papers

This thesis is based on the following original papers, which will be referred to in the text by their Roman numerals:

- I:** Ilias M, Wårdell K, Falk M, Anderson C. Phototesting based on a divergent beam – a study on normal subjects. *Photodermatology Photoimmunology and Photomedicine* 2001(4): 17: 189-196.

- II:** Falk M, Ilias M, Anderson C. Inter-observer variability in reading of phototest reactions with sharply or diffusely delineated borders. *Submitted manuscript*.

- III:** Falk M, Ilias M, Wårdell K, Anderson C. Phototesting with a divergent UVB beam in the investigation of anti-inflammatory effects of topically applied substances. *Photodermatology Photoimmunology and Photomedicine*. 2003: 19(4): 195-202.

- IV:** Falk M, Anderson C. Can patients read their own UVB minimal erythema dose and irritant skin tests? *Submitted manuscript*.

- V:** Falk M, Anderson C. Prevention of skin cancer in primary health care – an evaluation of three different prevention effort levels and the applicability of a phototest. *Submitted manuscript*.

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Abbreviations

A	Area
A.U.	Arbitrary Unit
B.C.	Before Christ
C.I.	Confidence Interval
DNA	DeoxyriboNucleic Acid
I	Irradiance
LDPI	Laser Doppler Perfusion Imaging
MED	Minimal Erythema Dose
P	Radiometric flux
PLE	Polymorphic Light Eruption
PUVA	Psoralene + Ultraviolet A
SD	Standard Deviation
SLS	Sodium Lauryl Sulphate
SPF	Sun Protection Factor
UV	Ultraviolet
UVA	Ultraviolet A (315-400 nm)
UVB	Ultraviolet B (280-315 nm)
UVC	Ultraviolet C (100-280 nm)
UVR	Ultraviolet Radiation

1. Introduction

1.1. Man and the sun – an historical perspective

Man has been fascinated by the sun since ancient times. This fascination can be traced back as far as to early cave carvings from 15.000 – 20.000 years B.C. Findings indicating a more sophisticated interest in and knowledge about the sun and its properties appear between 2.000 – 3.000 years B.C. One of the more famous examples of this is *Stonehenge* in Wiltshire, England, which was erected somewhere between 1.500 – 2.800 B.C, and for which the placement of the stones reflects different aspects of the sun's location and movement in the sky. The ancient Egyptians also had a substantial knowledge of the sun, and began using the solar, 365 day-a-year calendar as early as 3.000 B.C, i.e. more than 5.000 years ago. In a majority of religious mythologies from all corners of the world and through all ages, the sun plays a central role, and has often even been considered a deity – e.g. in Egyptian mythology as the sun god Re, in Aztec mythology as Tonatiuh, and in Greek mythology as Apollo Helios. The sun represented life-force, rich harvests and well-being, but was also an expression of great power and relentlessness. Aztec, Incan and other mythologies of sun-worship even involved human sacrifice to placate the sun god [1, 2].



Fig 1. Sun and man. Illustration from a pre-historic rock-carving found in Valcamonica in the Italian alps.

Modern “sun-worship” in western societies is more about getting tanned than practice of religion, but it wasn't until the 20:th century that sun bathing actually became popular. During the 19:th century and earlier, a pale skin denoted high socio-economic status and the fact that you did not need to work, like peasants, outdoors on the fields to make your living [3, 4]. During the early 20:th century came the first indication of an association between sun exposure and skin cancer, when William Dubreuilh noted a higher frequency of skin tumours among farmers compared to urban citizens. This connection has since been confirmed in

repeated studies, and has during recent decades been the subject of growing attention as skin cancer incidence has escalated [5].

1.2. Radiation from the sun

Solar radiation outside the earth's atmosphere consists not only of visible light, but also of infrared and ultraviolet radiation, all three being expressions of different wavelengths of electromagnetic radiation. Electromagnetic radiation can be described as an emission of discrete packets of energy, each packet being called a photon. Electromagnetic energy is related to its wavelength, so that shorter wavelengths have higher energy and higher potential for biological effect [6-7].

The infrared fraction of sun light, which has the longest wavelength, constitutes about half of the total solar radiation reaching the surface of the earth, while the ultraviolet fraction, which has the shortest wavelengths, only constitutes a minor part [6-9].

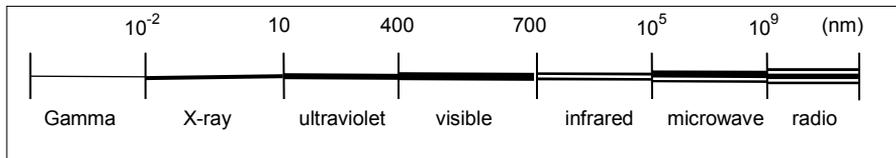


Fig 2. *The electromagnetic radiation spectrum and its wavelengths* [6, 7].

Ultraviolet light is by convention subdivided into the three wavebands; UVA, UVB and UVC. UVA (315-400 nm) is the part of UV-light closest to visible light, while UVC (100-280 nm) borders on x-ray radiation. UVB constitutes the remaining wavelengths in between (280-315 nm). The main source of UV-light reaching the surface of the earth is of course the sun, although other stars contribute to a very minor part [6-8].

When reaching the earth's atmosphere the UV-radiation content of solar radiation is either reflected, absorbed or further transmitted to reach the surface of the earth. Due to absorption by the stratospheric ozone layer, no UV-radiation below 290 nm reaches the surface of the earth, i.e. all UVC light and also a fraction of the UVB band is removed. The ozone layer also markedly diminishes the remaining UVB wavelengths [6-9].

For dosimetry purposes UV-radiation is commonly measured as Irradiance, which is an expression of the intensity of radiation reaching a surface, and is calculated by the equation: I (irradiance) = P (radiometric flux) / A (Area unit), (mW/cm^2). Radiation dose is gained by multiplying irradiance by exposure time (mJ/cm^2), i.e. radiation energy per area unit [6-8].

The biological effects of UV-light are dependant on dose, but also on the inherent effectiveness of the UV-radiation. This varies with the UV wavelength, being highest in the UVC spectrum and lowest in the UVA spectrum closest to visible light. This has been calculated for erythema, the chief and most easily observed effect of UVR, to give a relative erythema effectiveness [7, 10] (see Fig 3). Fortunately for humans and other life forms on earth, the solar UV-radiation with highest bio-effectiveness is to a great extent absorbed by the atmosphere. The remaining UV-radiation capable of causing erythema is referred to as the erythema effective energy [7] (see Fig 3).

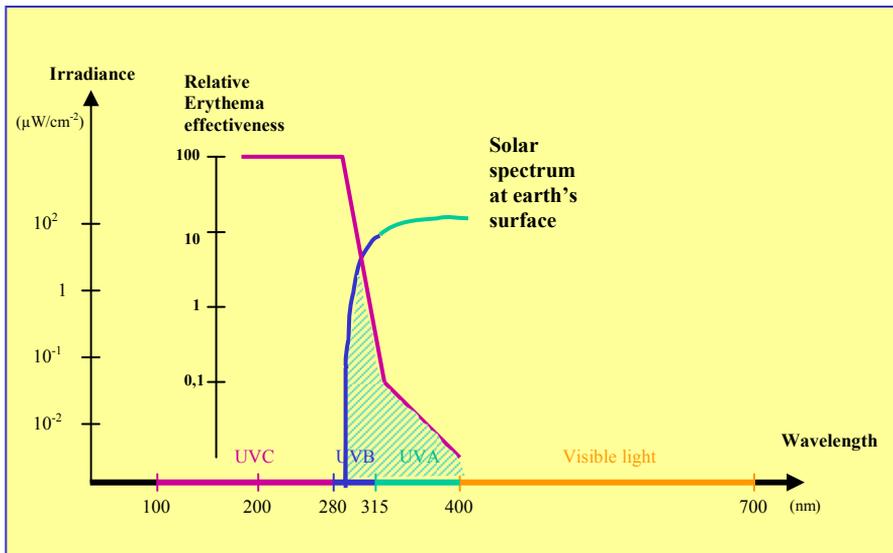


Fig 3. The UV-radiation spectrum, its relative erythema effectiveness, and proportion of the different wavelengths reaching the earth's surface (solar spectrum). The erythema effective energy is within the hatched area [7].

An important factor influencing the intensity of UV-radiation is the radiation angle, i.e. the height of the sun in the sky. A more acute angle at the point of reaching the earth's surface is associated with markedly reduced intensity compared to when the sun is in zenith, as an effect of prolonged distance travelled through the atmosphere and to spread of the radiation over a larger

target area. Once having reached the earth's surface, radiation intensity at a specific point can be increased by reflection from the environment, most effectively by snow, but also by sand, water surfaces and similar. Reflected UV radiation can thus result in UV-effects on skin even when in the shade out of direct sunlight [6-8].

1.3. UV-light and the skin

Biological effects of sunlight are caused by the UV component. The skin's structure, particularly the stratum corneum has important barrier functions in regard to protection from harmful effects of UV-radiation. About 5% of UVR is reflected at the skin's surface, the remaining part being transmitted through the upper epidermis, to be scattered and absorbed by the different skin components such as melanin and urocanic acid [6]. Transmission of UV light is wavelength-dependant, and varies as seen in Fig 4, with the shortest wavelengths having little penetration [7, 11].

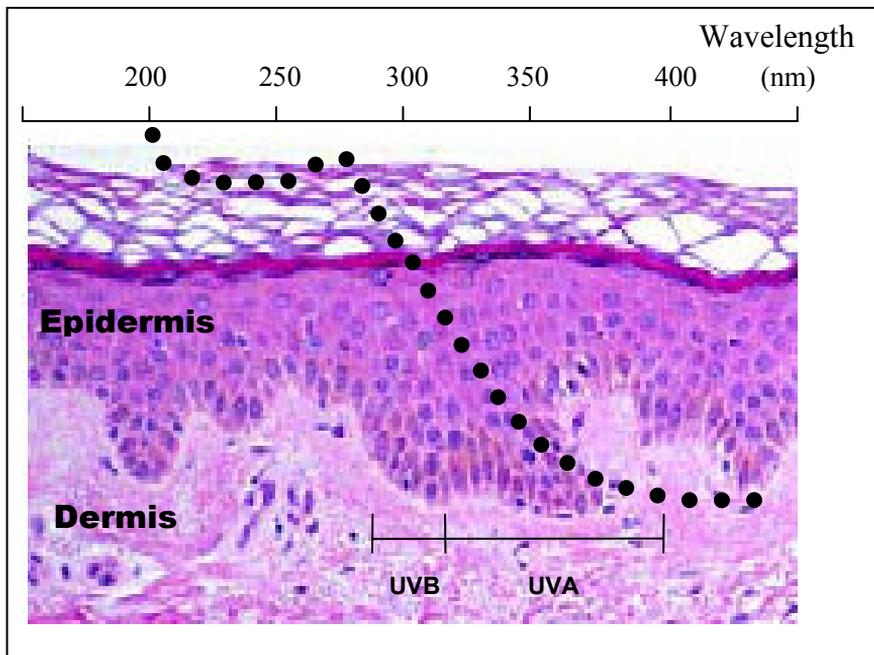


Fig 4. Schematic illustration of the 50% UV-radiation transmission depth for the skin at different wavelengths [7, 11].

The effects of UV light exposure on the skin can be divided into early and late effects, but has also other effects which cannot be so readily expressed as early or late.

Early effects: An immediate effect of UV radiation is the generation of cellular, DNA-mediated damage both in the epidermis and dermis, leading to the induction of an inflammatory process by the release of inflammatory mediators such as *cytokines, interleukins, histamine, prostaglandins* and others. These mediators in turn induce the infiltration of white blood cells to the area, and to vascular dilatation. The clinical effects of these processes manifest as erythema (redness), pain, and in severe cases even tissue swelling (oedema) [6, 10, 12, 13].

Within hours after UV-exposure photo-oxidation of existing skin pigment *melanin* and redistribution of *melanocytic melanosomes* (“*immediate pigment darkening*”) is induced, followed by increased melanin production from *melanocytes* (*melanogenesis* or “*delayed tanning*”), with the purpose to increase the protection of the skin from further UV-radiation. By increased skin pigmentation UV-sensitivity can, in Caucasians, be reduced up to fourfold [6]. Furthermore, induction of *skin hyperplasia* by increased cell mitosis leads to thickening of the skin, particularly the *stratum corneum* layer of the epidermis, which also contributes to increased UV protection [6, 7, 13].

Late effects: The most serious long-term effect of skin UV-exposure is its role in skin cancer development, including all of the three common cancer forms *basal cell carcinoma, squamous cell carcinoma* and *malignant melanoma*. Photocarcinogenesis is thought to be mediated by cellular DNA-damage, failure of cell repair and by cell mutations affecting the cell-cycle regulating protein *p53* [6, 13, 14, 15].

Another late UV-exposure effect is *photo ageing*, which means that continuous long-term UV-exposure leads to loss of skin elasticity, increased wrinkles, and irregular pigmentation, and other manifestations also seen in *chronological aging* [13].

Other effects: UV radiation also plays an important role in the vitamin D synthesis, by converting 7-dehydrocholesterol into vitamin D₃, and has well-documented effects on skin immunological function [6, 12, 13], a phenomenon used for therapeutic purpose (phototherapy) in skin diseases such as eczema and psoriasis [16, 17] but also of relevance in the consideration of sunscreen effectiveness [18].

Recently, the role of “innate immunity” in disease pathogenesis has been a subject of focus [19]. The concept of innate immunity involves different levels of

inherent defence mechanisms in an organism – sweat, surface bacteria, the stratum corneum, the viable epidermis mast cells and immune cells, and many other components which can be involved in phylogenetically preserved responses to microbial molecules and a range of cell damage danger signals. The capability to react to UVB can be considered to be a part of this inherent defence system [20], and has been shown to be associated with stimulation of a cytosolic multiprotein complex known as the *inflammasome* [21, 22], resulting in the production of cytokines, especially IL-1 β . Variability in this response is based on genetic polymorphism and can have direct and indirect consequences for an individual [23].

Phenotypic aspects of sun sensitivity: The degree of skin pigmentation is central for its sensitivity to UV-light. The description of the phenotypic basis for sun sensitivity was classically described by Fitzpatrick in his classification of skin type according to the reaction to sun light [24]:

Skin type I: always burns, never tans

Skin type II: always burns, sometimes tans

Skin type III: sometimes burns, always tans

Skin type IV: rarely burns, always tans,

Skin type V: ethnic groups with moderately pigmented brown skin

Skin type VI: ethnic groups with markedly pigmented dark or black skin

The classification uses delineation of ethnicity and variable tendency to burn or tan to achieve a skin type. Thus, ethnic groups with fair, poor-pigmented skin, common for example in Scandinavia and Britain, have a markedly higher risk for skin cellular damage due to UV-radiation, and consequently a higher risk of developing skin cancer, than people of darker skin pigmentation. This is true for all skin cancer types, for which skin UV-sensitivity has been found to be an independent risk factor [25].

Use of genetic markers to classify skin in regard to sun sensitivity has concentrated on melanin [26], but may also be associated with other aspects of reactivity to sunlight e.g. the recently described genotypic polymorphism in regard to the *inflammasome* [21, 23].

Other constitutional factors associated with a higher skin cancer risk are light hair colour, freckles and blue eyes [27]. The number of pigmented nevi has also been shown to be important for melanoma development [25, 27, 28]. An inherited increased risk for malignant melanoma is seen in individuals with two or more first-grade family members affected, and in individuals with the hereditary *dysplastic nevus syndrome* [29]. The presence of dysplastic nevi *per se* is also associated with an increased melanoma risk [28].

UV-radiation and disease: UVR undoubtedly causes the major part of skin malignancy. In western societies, due to increased sun exposure habits, the incidence of all forms of skin cancer have increased dramatically during recent decades. In Sweden for example, the annual incidence of malignant melanoma between 1970 and 2005 has risen from 683 to 2319 cases per year, which corresponds to a change in annual incidence from 8.5 to 25.7 cases per 100 000 inhabitants [30] (see Fig 5).

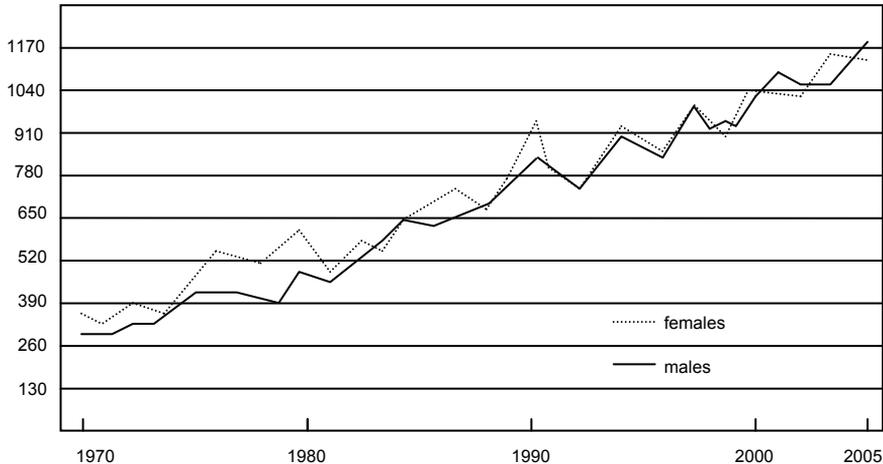


Fig 5. Annual incidence of malignant melanoma in Sweden between 1970 – 2005 [30].

There are a number of dermatoses associated with abnormal UV-sensitivity: In some individuals UV-radiation can lead to unexpected (pathological) skin reactions, termed photodermatoses. These include both a reactivity to abnormally low UV-doses and a spectrum of pathological aberrant effects (signs or symptoms) after UV-exposure. Many of the photodermatoses have a low incidence, but the most common form, *polymorphic light eruption (PLE)*, may occur in up to about 20% of populations in temperate regions with a pronounced seasonal cycle. It manifests itself as an itchy, erythematous, eczema-like rash, sometimes with papules and/or vesicles, occurring in the early spring and summer with improvement later in the season. Other examples of photodermatoses are *actinic prurigo*, *solar urticaria*, *chronic actinic dermatitis* and *hydroa vacciniforme* [6, 31-34].

Besides the essential photodermatoses, several other skin diseases may be regularly or sporadically aggravated by UV-exposure. *Atopic dermatitis* and *psoriasis* are two common dermatoses in which UV-sensitivity can be seen. Most

cases, however, react favourably to sunlight, indeed these dermatoses are common indications for phototherapy. *Rosacea*, *dermatomyositis*, *lupus erythematosus* and *pemphigus* are other examples of skin diseases that may be aggravated by UV-exposure [6, 7].

In *photoallergic* and *phototoxic* skin reactions, UV-light together with environmental, industrial or pharmacological agents coming into contact with the skin lead to an eczematous reaction which can be quite dramatic. The mechanism can be of “toxic”/irritant (an inherent reaction mechanism not requiring previous exposure) or allergic (occurring first after initial sensitisation) mechanisms [6, 7].

Phototherapy is an important therapeutic mainstay in dermatology. The main disease treated is psoriasis but atopic eczema, other eczema forms, and pruritic diseases in general are also common reasons for phototherapy which can be conducted with broad band UVB, narrow band UVB, UVA alone or in conjunction with UVB or less often by PUVA (oral or topical) [16, 17].

1.4. Phototesting

Individual skin sensitivity to UV-light can be determined by phototesting using incremental set of doses of artificial light applied to the skin. This is in clinical situations used routinely for the investigation of suspected photodermatoses, photoallergic/phototoxic sensitivities or other abnormal skin UV-sensitivity [31-35], but also as a tool for steering UV-dose in phototherapy [36]. In phototherapy, both starting dose and rate of dose increase can be influenced by the outcome of phototesting. Additionally phototesting can be used for evaluation of the efficacy of sunscreens [37].

The principle of phototesting is to provoke the skin with a series of increasing doses of UV-light of a chosen wavelength interval, either broad-band (e.g. “UVA” or “UVB”) or narrow-band, in order to determine the *Minimal Erythema Dose (MED)* of the individual, which is defined as the lowest UV-dose capable of causing skin erythema [38, 39]. Testing is preferably done on unaffected skin exposed to as little sunlight as possible. Common provocation sites are the upper back or the inner aspect of the arms. Light can also be used to provoke a reaction e.g. in a photopatch test when the suspected agent and light are administered together, or in *polymorphic light eruption*, where the ideal site is a previously affected skin area [31].

Traditional phototesting: The most common form of phototesting used in clinical practice is based on the estimation of MED by provocation of separate,

increasing, doses of UV light on multiple (commonly 4-6), closely located skin fields. Test reading is performed after a predetermined time interval (e.g. 24 h), with the lowest provoking UV-dose able to elicit skin erythema in the test field being considered to be the MED [38, 39].

Provocation is performed with broad band or monochromatic UV-light of chosen wavelengths, and provocation time is adjusted to the bio-effectiveness of the chosen UV-spectrum. Consequently, provocation within UVA demands a longer provocation time than UVB [32, 38].

Independent of chosen wavelength, the variation of UV-dose in the provoked fields can either be achieved by altering the provocation time, or the irradiance of the UV-field, since UV-dose is dependant of these two components (Dose = irradiance x time unit). Whilst time is the factor usually used, a metal foil attenuator of various dimensions can also be used to alter the irradiance [36].

UV-light sources for phototesting: Artificial UV-light used for phototesting can be produced classically either by *arc lamps* or *fluorescent lamps*.

In arc lamps, *xenon* gas or *mercury* vapour is ionized by electrodes to emit radiant energy. Depending on the pressure within the lamp, variation of electromagnetic wavelength can be achieved. Xenon lamps emit a broad spectrum of both visible and UV-light. Mercury lamps of low pressure are dominated by a peak of radiant energy at 254 nm (i.e. UVC). With increasing pressure, peaks of longer wavelengths take over (313, 334 and 365 nm, i.e. UVB and UVA). Medium or high pressure mercury lamps are mostly used for UVB-testing. For both xenon and mercury lamps, optical filters can be used to cut off undesired wavelengths, and to produce “solar simulation”, as originally described for the “Berger solar simulator” [40].

Fluorescent lamps also contain mercury at low pressure, though contained in a long tube supplied with an electrode in each end. As electric current passes through the tube, radiation of mainly 254 nm is emitted. Coating the inside of the tube with phosphor absorbs the radiation and reemits it at longer wavelengths. The UV-spectrum can be altered by adjusting the composition of the coating [7].

In the investigation of photodermatoses, the purpose of phototesting is not only to discover an abnormal photosensitivity, but also to determine the action spectrum for the reproduction of the disease morphology [31]. Thus, test reading puts high demands on the observer not only to be experienced in the detection of erythema but also to be familiar with the morphology of the different photosensitivity disorders. For this reason, test reading is normally performed by a dermatologist. Reading criteria may vary, but the importance is that the investigating clinic has a consensus among its own observers, usually achieved by training and quality control. An example is the definition of a reaction – an

erythema with a well defined border, or the weakest distinguishable erythema [39]. In addition, the erythematous reactions are also usually scored according to the degree of redness and to the presence of oedema or blisters [31-35].

A weakness of traditional phototesting, is that it only classifies MED into limited steps according to the number of UV-provocation fields used. The divergent beam phototest technique was developed for the purpose of getting a more refined determination of the MED as well as the possibility of dose-response data above the MED. Recent findings about mechanisms in the production of erythema and its individual variability make detailed testing capability no less interesting.

1.5. Sun habits and sun protection behaviour

Historically, sun habits in the western world have varied depending on social, economic and occupational conditions, fashion and trends. For a long time, a pale skin was an indication of high economic standard and social status, and it was not until the early 20:th century that a tanned skin became increasingly desirable [3, 4].

In modern western societies, sun exposure habits vary depending on geographic location in relation to solar intensity. In countries of high annual UV-radiation levels, and especially when the inhabitants have fair, UV-sensitive skin, e.g. in Australia, the importance of sun protection has been promoted for decades and accepted as a natural price to be paid for the inevitably high year-round UV-exposure. In countries with short summer seasons, such as in northern Europe, there is still a tendency to seek the sun, both during summer and during vacations on sunny resorts, and to intentionally tan as much as possible during the relatively short sun-season. This leads to two in principle different UV-exposure scenarios; in sunny countries a considerably higher total, cumulative UV-exposure during life, and in countries with short summer seasons a larger number of occasions with painful redness due to UV-exposure on poorly pigmented skin. This is believed to be of significance for the development of the main skin cancer forms. There are epidemiological studies showing that frequent, intermittent UV-exposure, especially during early childhood, is an important factor for development of cutaneous malignant melanoma, that total cumulative UV-exposure is more associated with the development of squamous cell carcinoma, and that a combination of both is relevant in the development of basal cell carcinoma [25, 41]. Thus behaviour in regard to sun exposure is highly relevant.

Sunbathing (or “intentional tanning”): There are some individual factors affecting the tendency to sunbathe frequently. The most important of these is gender, females being more frequent intentional tanners than men [42-44]. Age is another affecting factor, several studies showing sunbathing to be most frequent during the second and third decades of life, with a peak somewhere between 17-25 years of age [42-44]. Educational level and socio-economic status, as well as awareness and perception of solar radiation risks, have been proposed as factors affecting sunbathing frequency, but results in performed studies are not entirely consistent in this respect [42, 43, 46-49]. A negative association, or no association at all between heightened awareness and sun exposure has been reported in a few studies [45, 49], but several other studies suggest that knowledge and awareness can actually be associated with increased UV-exposure [43, 47, 48]. People with a sun-sensitive skin type, according to Fitzpatrick’s classification (see chapter 1.3) have in general a tendency to sunbathe less frequently than people with a lower UV-sensitivity [42, 43].

Outdoor activities associated with UV-exposure: Even without intentional tanning, UV-exposure during other outdoor (sun-exposed) activities, and especially during the middle of the day, may be high. Although women appear to sunbathe more frequently, some studies indicate that men tend to stay out in the sun longer anyway, being more often occupied with other outdoor activities of a social or sporting nature [50, 51].

Many occupations are associated with out-door work. An increased risk for malignant melanomas on the head and neck, and in the eye, as well as increased risk for non melanoma skin cancer on other body sites, have been demonstrated e.g. for farmers and building site workers [52, 53].

Use of sun-beds: The therapeutic use of UV light has been made more practical by the development of fluorescent tube based light delivery. The technology was introduced commercially to the general population as “sun-beds” to produce a tan in the early 1970’s. Early sun-beds for cosmetic purposes, though aiming at UVA, produced significant amounts of UVB and even UVC radiation, but since the eighties they have been restricted to mainly UVA and a smaller amount of UVB [54]. Sun-bed use has been, and in some countries still is, a common phenomenon. As for outdoor sunbathing, it is used most frequently in individuals around 20 years of age [55, 56].

The connection between sun-beds and skin cancer risk has been debated, and the results of the relatively few studies performed show incongruous results. Several studies, however, indicate an increased skin cancer risk [57-61]. A more proven skin cancer connection has been shown for medical sun-bed use in

patients with psoriasis receiving UVA therapy in combination with *psoralen* (PUVA) [62, 63].

Sun protection behaviour: The most effective way to protect oneself from the sun is of course to avoid the sun. If avoiding the sun isn't possible, sun exposure can be reduced by modifying behaviour in various ways. In studies on sun protection behaviour, the following terms are commonly used:

Staying in the shade – reduces UV-exposure markedly, but may vary depending on reflectance from the surrounding environment.

Staying out of the sun during the peak hours of strongest sun light – in northern Europe UV-intensity is highest between 11 a.m. and 3 p.m. which is therefore the time to avoid (“between eleven and three go under a tree”).

Using protective clothes – either with long or short sleeves/legs. Close-weave material with long sleeves/legs gives the best protection. Sun hat or cap is especially important with absent or thinned scalp hair. A broad brim has protective effects both on the face and the eyes.

Using dark glasses to protect the eyes – long-term UV-exposure is associated with increased incidence of retinal malignant melanoma, but also other conditions such as *cataract*, *pterygium*, and *macula degeneration* [64–66].

Using sunscreens. The SPF (Sun Protection Factor) describes the UVB dose-related protection effect, i.e. how many multiples of the time required to produce erythema (MED) on unprotected skin can be spent in the sun before burning [37]. Although sunscreens can be an important way to reduce sun exposure, several studies have shown what is often described as *the sunscreen paradox*, i.e. a positive association between sunscreen use and time spent in the sun [67, 68]. In this case, sunscreens are used as a way to enable a longer stay in the sun, a consequence of which is a greater UVA dose than would have been achieved without UVB sunscreen protection. In fact much more attention is now given to simultaneous UVA protection in sunscreens. UVA protection is harder to achieve in a product formulation but in the light of recent knowledge important [37, 69, 70].

1.6. Prevention of skin cancer

Primary prevention: Due to the strong correlation between UV-exposure and skin cancer incidence, primary prevention focuses chiefly on affecting sun habits, aiming at enhanced sun protective behaviour and reduced sun exposure. Around the world, this has been attempted by the use of extensive nation-wide media campaigns, by efforts focussing on specific populations or risk groups, or by secondary prevention programmes within the frameworks of health care services.

Since attitudes, beliefs and knowledge seem to be related to behaviour [45, 71-72], some authors have focused on investigating the effectiveness of measures on attitudes and awareness towards sun exposure, rather than the actual behaviour [73, 74]. On the other hand, as mentioned in the previous chapter, there are other studies which have not been able to prove any certain relationship at all [49], or even a negative relationship, between heightened awareness of UV-exposure risks and sun protective behaviour [43, 47, 48].

A common approach has been to focus intervention on specific target-groups. A recurring example of such a target-group is “beachgoers”, for whom successful target-group intervention has been demonstrated [75-77]. Since sun-exposure in early life is known to be of importance for skin cancer development later in life, at least in the case of malignant melanoma [25, 41], children and their parents have become another common target-group in skin cancer prevention, and in several cases this has been shown to be successful. As an example, Dietrich et al could demonstrate a significantly increased use of sunscreens by 2-11 year old children in school and kindergarten after an aimed sun protection campaign (“Sun-safe”) [78]. Buller et al noted a significant difference in attitudes after a directed intervention program towards school children in grades 4-6 (although there was no concurrent change in sun protection behaviour) [79].

Reviews on skin cancer prevention have been performed in Europe, Australia and the USA, and although in many cases there was insufficient evidence that the investigated intervention had demonstrable effect, at least a few studies have been able to demonstrate a marked effect on sun protection behaviour [80-82].

Secondary prevention: Secondary prevention of skin cancer emphasizes self-inspection of nevi, tumour-screening strategies and early detection of malignant skin tumours. The former is associated with improved prognosis and has thus been an important focus of efforts. In Sweden the “The Open House campaign for skin examinations” led to an increased diagnosis of skin cancer in early stages [83]. In Switzerland Heinzerling et al could show promising results during a campaign containing a questionnaire in combination with skin inspection by a dermatologist [84]. Similar outcomes have been demonstrated elsewhere [85, 86].

Individuals with a hereditary predisposition for skin cancer, individuals with multiple dysplastic nevi or patients treated for more than one primary melanoma constitute a specific high risk group, for which secondary prevention is probably of special importance, and for which secondary prevention programmes have been shown to be successful [87, 88].

The role of Primary Health Care in skin cancer prevention: In a study on children and their parents, Weinstein et al investigated the source of information they considered to have given most information about sun exposure and sun protection behaviour, and found these to be television and magazines. At the same time, many expressed a wish to get more information from dermatologists and general practitioners [74].

In primary health care, prevention in various forms comprises a considerable part of the daily work load. Both primary and secondary prevention within a multiplicity of medical fields and groups of diseases is handled covering both preventive treatments and information and education directed at life style change. The ready flow of patients in combination with close patient contact make primary health care a suitable base for preventive work, with the added advantage of the possibility for adequate follow-up. A patient's individual consultation with a doctor or with other health care professionals constitutes a unique occasion not only for delivering a preventive message, but also to adjust the message in accordance with the personality, individual risk factors and receptive communication abilities of the patient. The primary health care environment *per se* probably further contributes to this, since the general practitioner commonly has a comprehensive knowledge about the patient's holistic sickness panorama as well as the relevant social background.

1.7. Theoretical models of health behaviour and behaviour change

In the design of prevention campaigns or targeted preventive efforts, it is of interest to understand the psychological mechanisms and relationships in people's health behaviour and what affects their propensity to change it. Several models have been suggested and utilised in various prevention situations. Examples of more common models used to determine health-protective behaviour are the *Health Belief Model*, *Subjective Expected Utility Theory*, *The Theories of Reasoned action and Planned behaviour*, and *Protection Motivation Theory* [89, 90].

The *Health Belief Model* attempts to explain or determine the likelihood of performing a health protective behaviour, by mapping of four main components representing the perceived threats and net benefits: *perception of susceptibility* (one's perceived risk for getting a condition), *perception of severity* (one's consideration of the severity of the condition), *perception of benefits* (one's belief in the efficacy of the advised health protective actions), and *perception of barriers* (one's considerations of the psychological "cost" of following the advised health protective actions). According to the model, an individual will

adapt to a health protective behaviour depending on the level of perceived threat, and if the perceived net benefits outweigh the perceived barriers [89-91].

The *Subjective Expected Utility Theory* is based on the relationship between an individual's believed utility of a certain behaviour and the believed probability that this utility will actually be realized. The choice of behaviour taken varies from individual to individual depending on the personal utility of the behaviour and how strongly he or she believes it to be beneficial [89].

The *Theories of Reasoned action and Planned behaviour* are a combination of two explanatory behavioural models claiming that an individual's behavior is determined by his/her behavioral intention to perform it. This intention is itself determined by the person's attitudes and his subjective norms towards the behavior. The subjective norms are affected by normative beliefs and the person's motivation to comply with these, while attitudes depend on the person's belief of the outcome and consequence of the behaviour. Since not all actions appear to be under complete deliberate control, factors that affect the implementation of a behaviour, and the individual's own perception of these factors ("*control beliefs*"), are also thought to play a role. Together attitudes towards behaviour, subjective norms and control beliefs lead to an intention to behave, in a positive fashion [89, 90].

The *Protection Motivation Theory* has similarities to the *Health Belief Model*, and proposes that the intention to protect one self depends upon four factors: the perceived *severity* of a threatened condition, the perceived *probability* of the occurrence, the *efficacy* of the advised preventive behaviour, and the perceived *self-efficacy*, i.e. the level of confidence in one's ability to follow the advised preventive behaviour. The theory claims that a perceived health threat can lead either to an adaptive or a maladaptive behaviour, depending on the balance between these factors and on the individual's coping capacity. An adaptive response means that the individual takes adequate action that leads to health protection, while a maladaptive response includes both behaviours that lead to negative consequences as well as the absence of actions, which eventually may lead to negative consequences [89].

In studies on the effect of health promotion campaigns or interventions there is a need to measure, or grade, the change of behaviour. A common approach is to use some kind of graded scale related to level of health protection or risk behaviour, such as the Likert scale. This can be used to assess separate behavioural items, or integrated into a total score. An attempt in regard to sun exposure has been made for the latter in the *Sun Protection Behaviour Scale* [77]. Another common approach is to divide behaviour and behaviour change into

differentiated stages [92]. One of the most widely accepted models for this is the *Transtheoretical Model of Behaviour Change*, presented by Prochaska et al [93, 94], claiming that the individual is in one of five schematic stages of change, which can be identified by separate, associated statements. The model has been used extensively, in studies on sun exposure [75, 77, 95] as well as in other risk behaviour situations, not the least tobacco smoking [96, 97]. Since the method has in this thesis been utilised in *Paper V*, it will be more thoroughly described in Chapter 5.

2. Aims

The general aim of this thesis was:

- To develop aspects of the phototest procedure in order to broaden the utilisation of phototesting within the fields of research, clinical practice and skin cancer prevention.

The specific aims of this thesis were:

- To develop and evaluate the technical and clinical aspects of a single exposure divergent UVB beam phototest technique.
- To trial the divergent UVB beam phototest procedure as a model for evaluation and quantification of effects of topically applied substances.
- To investigate the capacity of subjects for self-reading and reporting of skin tests, represented in this thesis by a phototest and an irritant patch test.
- To investigate, in a primary health care setting, how differentiated levels of prevention initiatives, directed at skin cancer, can affect the propensity of the patient to change sun habits/sun protection behaviour, and whether the performance of a phototest with self-reading/reporting by patients/subjects could be used as a complementary tool in skin cancer prevention.

3. Divergent beam as a development in phototesting

3.1. Development and validation of the divergent beam methodology and technique (Paper I and II)

The general idea behind the divergent UV-beam phototesting technique is to achieve a more detailed estimation of MED on a continuous dose spectrum. Instead of using multiple, small provocation fields, as in traditional phototesting, the UV-beam is diverged over a single, somewhat larger skin area, by an optic lens placed at the end of the light guide. This produces a 45 mm in diameter UV-field for which the irradiance is highest in the centre, decreasing as it approaches the periphery. In this way, the MED will be correlated to the diameter of the provoked erythema (see Fig 6). The technical aspects of the method have previously been described by Ilias et al [98], and we now wanted to evaluate the method on a normal material of healthy subjects.

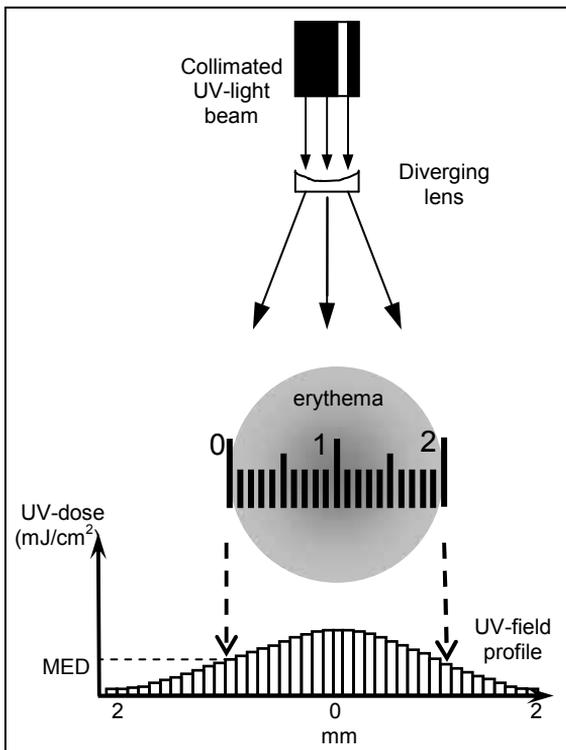


Fig 6. Principle of divergent beam phototest and the correlation between erythema diameter and Minimal Erythema Dose (MED).

The UV-light beam used in the studies was produced by a medium pressure mercury UV-lamp (HBO 200W/2), projected through the optical filters WG305 and UG5 (Schott Glass Technologies Inc, Durea, USA) to cut off all radiation under 280 nm, thus producing UV-light predominantly within the UVB spectrum, UVA also being present, though, for the used doses, biologically ineffective. The beam was transferred to the provocation area through a liquid light guide, and through the diverging lens (Melles Griot Inc, USA), producing an illumination area of 45 mm in diameter. Mapping of the irradiance field was done prior to provocation, and performed two-dimensionally, mm for mm, by a thermopile detector (Model 2M, Dexter Research Centre Inc, Michigan, USA), measuring the irradiance at each point.

The phototest was applied to 20 voluntary subjects, of which 11 subjects underwent double-provocation in order to study test reproducibility. Test reading was performed in two ways. The first way was to visually measure the diameter of the erythema using a transparent, mm-graded ruler. However, since the nature of the erythema border is inherently fading and un-sharp, the risk for inter- and intra-observer variability is obvious. For this reason, and in order to have a more

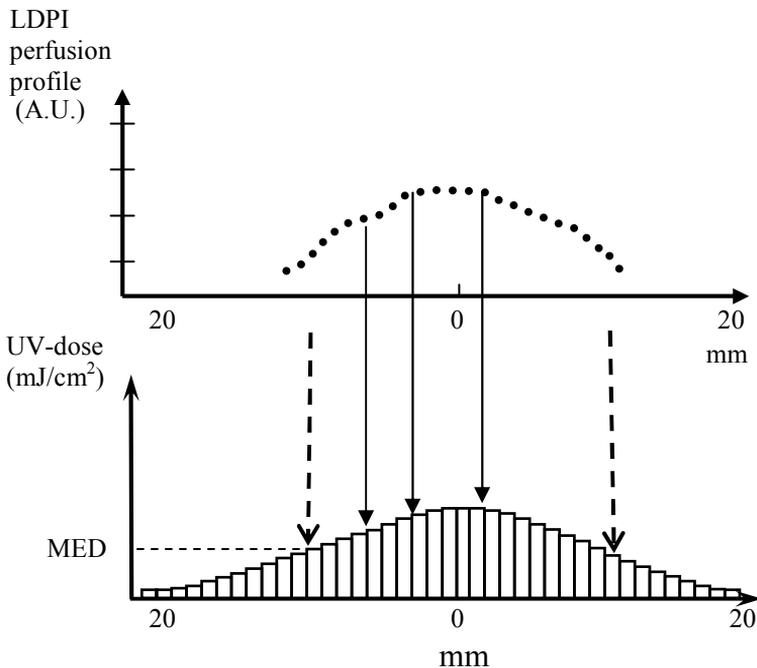


Fig 7. Principle of the relationship between erythema skin blood perfusion, measured by LDPI, and UV-dose, each LDPI-value corresponding to a separate dose-value.

detailed and objective, skin physiological assessment of erythema, test reading was also performed by LDPI (*Laser Doppler perfusion imaging*). LDPI (PIM 1.0, Lisca Stockholm, Sweden) is a non-invasive method which enables the quantitative estimation of superficial blood perfusion in tissues, by scanning a laser beam over the tissue area of interest, and measuring the backscattered light after interaction with moving red blood cells in superficial vessels [99]. Scanning over the UV-provoked skin was performed two-dimensionally, mm for mm, so that the measured blood flow values could be spatially associated to the mapping of the irradiance field (see Fig 7).

LDPI-measured diameters were extracted by thresholding. The mean perfusion value within an area of unaffected skin in each LDPI-image was used as a base perfusion value. All values above this value + 2 SD were considered as a part of the reaction, and reaction diameter was calculated from the mean value of two extracted diameters at right angles to each other (see Fig 8).

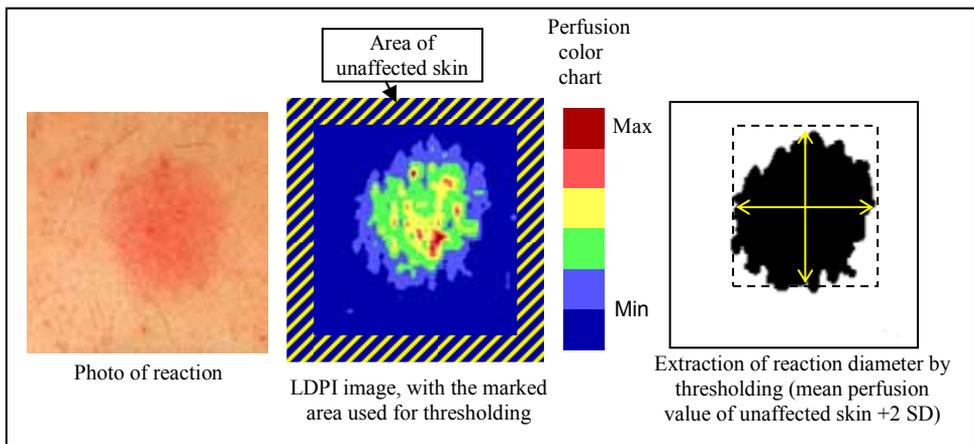


Fig 8. Illustration of a divergent beam phototest reaction, LDPI image and how LDPI diameters were extracted by thresholding.

Naked eye reading of the divergent beam test reactions by a trained observer showed promising results, with high reproducibility between double-provoked reactions for both naked eye and LDPI readings, and with no systematic difference when comparing the two reading assessments. However, when investigating inter-observer variability among a larger number of observers (11 dermatologists) without specific familiarity with the test, this was shown to be substantial. Additionally, in the same study (*paper II*), we investigated inter-observer agreement for readings of erythemas that, in contrast to the divergent

beam reactions, had a sharply delineated border, and found this to be excellent (standard deviations ranging from at maximum 0.6 mm for mean values of readings of sharp-bordered reactions to at maximum 2,9 mm for readings of divergent beam reactions). The conclusion from these findings was that the nature of the erythema border is of major importance for naked eye reading of a phototest. Mapping of the borders of the two reaction types by plotting of LDPI perfusion profiles revealed that the increase in blood perfusion seen over a distance of 1 mm at the edge of the sharp-bordered reaction was spread over a distance of 2.5 – 3.5 mm at the border of the divergent beam reaction (see Fig 9). Since the divergent beam method by its nature produces a diffusely demarcated erythema, the conclusion was drawn that, for a broader use of the method, a skin physiological technique such as LDPI for the assessment, was required.

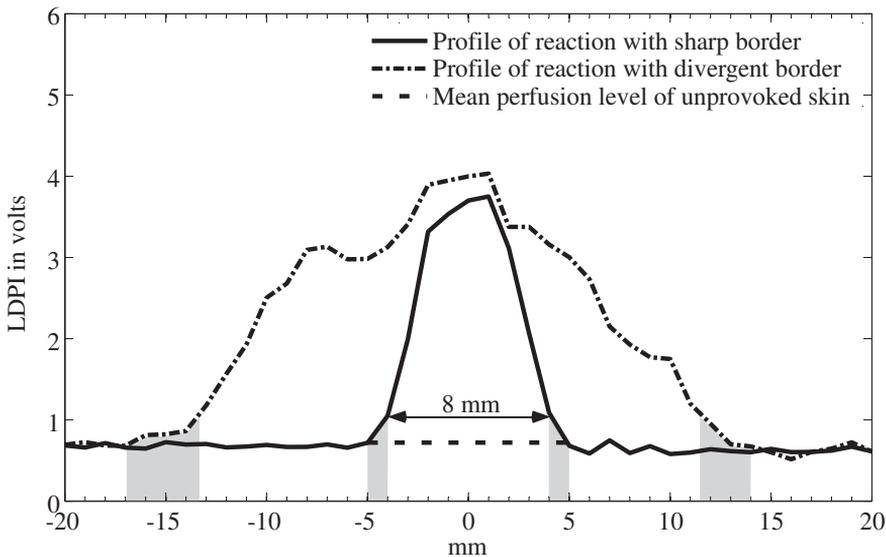


Fig 9. LDPI plot of the two-dimensional distribution of the divergent beam and sharp-bordered reaction, illustrating the different characteristics of the edges (grey areas). To achieve in the divergent beam reaction the same change in LDPI intensity as over the 1 mm edge of the sharp-bordered reaction, a 2.5 – 3.5 mm linear distance was required.

As a complement to the estimation of MED, it is of interest to investigate the erythematous response within the erythematous reaction, i.e. for doses above the MED. Assessment of dose-response data was achieved by matching the LDPI data against the dosimetry of the UV beam. For each scanned erythema reaction, the LDPI doses within 1 mm concentric circles were averaged, and plotted

against a spatially corresponding UV-dose. Thus, a specific UV-dose could be related to skin blood perfusion response at a specific point within the reaction. Associating the MED value to the plot, separate linear relationships could be derived for doses above and below the MED (see Fig 10).

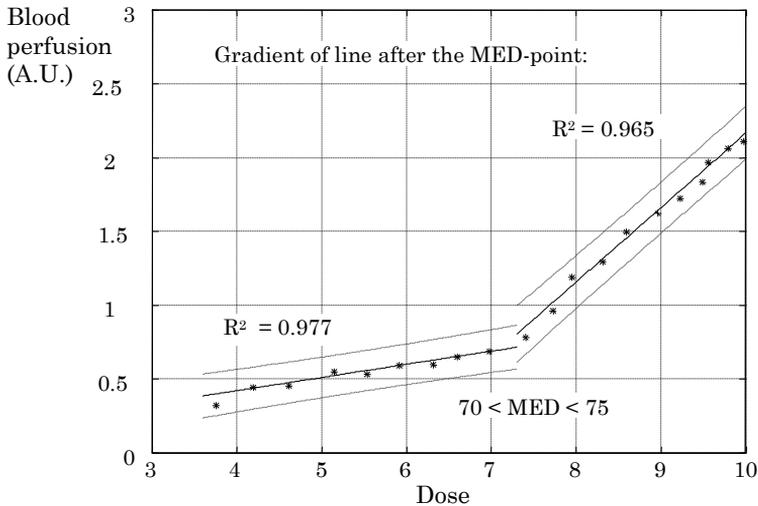


Fig 10. Dose-response data for one subject, illustrating a linear relationship for doses above and below the MED. R^2 regression values displays the statistical level of linear curve fitting.

The gradient of the post-MED line was considered to be a measure of the aggression of the reaction, i.e. a higher gradient representing a tendency to react more intensely to the increasing UV-dose. As a complement to determination of the MED, the approach constitutes a possible new way to grade the erythema response, of potential importance for the greater understanding of UV-induced erythema characteristics.

3.2. Divergent beam phototesting for investigation of effect of topically applied substances (*Paper III*)

Erythema, (increased superficial skin blood perfusion) is one of the components of the inflammatory response. It is thus likely that the quantification of erythematous response could be used as a parameter for investigation of anti-inflammatory effect of topical agents. For this purpose we wanted to investigate the utility of the divergent beam phototest technique as a model for this. In a study on 16 subjects, a substance with a strong and well-known anti-inflammatory effect, the topical steroid *clobetasol dipropionate* (Dermovate[®]), was used as a reference together with two test agents (*acetone* and a *citric ester gel vehicle*). The divergent beam was provoked on the upper back of the subjects, and immediately after provocation, the provoked skin areas were treated with *clobetasol dipropionate* or one of the test agents, under occlusion (Tegaderm[®], 3M Health Care, St Paul, MN, USA) for one hour. Test reading was performed after 6 and 24 hours, by LDPI, and the treated erythema reactions were compared to an untreated control reaction provoked on the same subject.

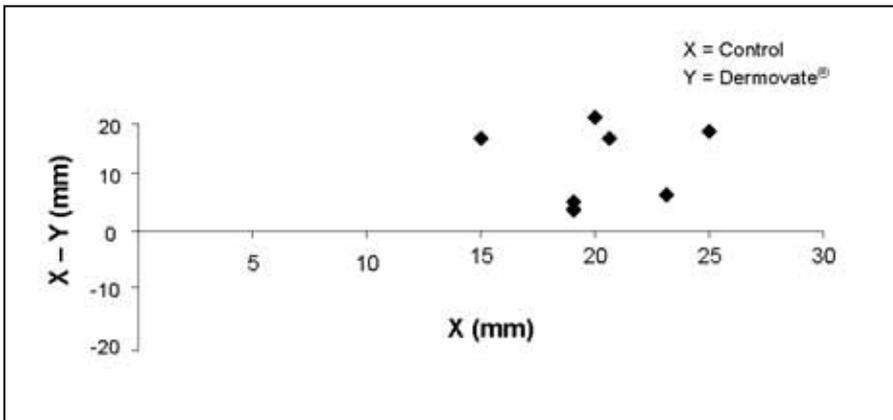


Fig 11. Demonstrated effect of *clobetasol dipropionate* (Dermovate[®]) on reaction diameters, illustrated as the difference between LDPI-diameters of control (X) and treated (Y) reactions plotted against the control diameters (X). Clearly, Dermovate[®]-treated reactions display smaller diameters than control reactions.

Anti-inflammatory effect was estimated from three parameters: reaction diameter, mean perfusion and gradient of the dose-response line above the MED. Reaction diameters and dose-response gradients were assessed as previously

described. Mean perfusion values were calculated within a 20 mm in diameter circle centred over the provoked area.

For *clobetasol dipropionate* anti-inflammatory effect could be shown for all three measurement parameters, expressed as markedly smaller reaction diameters (see Fig 11), lower perfusion mean values and lower dose-response gradients (see Fig 12), compared to the untreated control reactions. The two test agents also showed mild anti-inflammatory effects on reaction diameter and dose-response gradient.

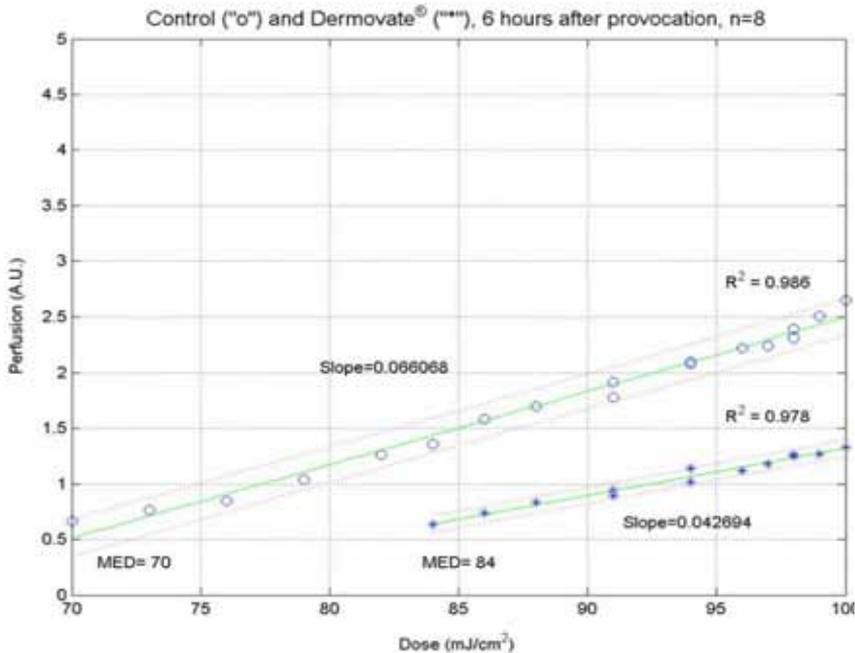


Fig 12. Demonstrated effect of clobetasol dipropionate (Dermovate®) on dose-response gradient of the divergent beam reaction. R^2 regression values displays the statistical level of linear curve fitting, and the slope values (gradients) of the lines are also presented.

4. Patient-performed self-reading of skin tests (*Paper IV*)

Photo-testing and indeed all types of skin testing are probably performed less often than would be optimal for high quality patient care. The chief impediment is the lack of time and resources but a perception of too little gained information is also relevant. Normally skin testing requires both a provocation- and a reading occasion, and both parts demand the participation of experienced personnel. Reading of a phototest is usually performed by a dermatologist. In many cases, for both clinical reasons and perhaps also in prevention situations, an extended use of phototesting could be valuable. One way to accomplish a broader use of skin testing would be to save time and resources by allowing patients themselves to read the test and report test results to the clinic.

In order to evaluate the reliability of patient-performed self-reading, determination of irritation threshold for *sodium lauryl sulphate* (SLS) and *minimal erythema dose* (MED) for UVB were chosen as suitable test protocols. For the phototest assessment a “traditional” technique was used, with the provocation on the ventral side of the right upper arm of four separate, increasing, UV-doses (3, 4, 6 and 9 seconds in provocation time, corresponding to doses 42, 56, 84 and 126 mJ/cm²). For the patch test, applied on the left arm, 20 µl of four different concentrations of SLS (0.5, 1.5, 3.0 and 6.0 %) were used (see Fig 13). 26 subjects provoked with the two test protocols were instructed in “present” or “absent” reporting of test reactions, a positive reaction being defined as any visible change in skin morphology. Test results were then compared to the blinded reading of a trained observer using currently applicable reading guidelines.

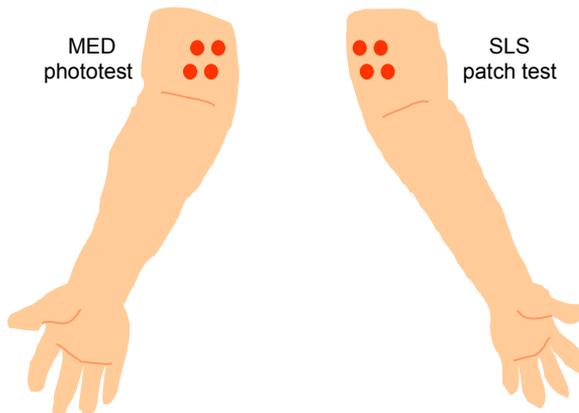


Fig 13. *Provocation sites for the patient performed self-reading of the MED phototests and SLS patch tests.*

Absolute agreement between subject and trained observer reading was found in 76.9% of the SLS reactions, and in 85% of the UVB reactions. Calculation of weighted Kappa for the agreement between observations showed values of 0.76 for the SLS reactions, and 0.83 for UVB reactions. Especially for the SLS patch test, there appeared to be a tendency by subjects to underreport reactions that were weaker. In many cases the difference between subject and trained observer reading was based on barely perceptible findings, and in no case was the difference between subject and trained observer reading greater than one reaction.

The level of agreement found for the two selected skin test protocols is well comparable to the levels of inter-observer agreement even between trained observers reported in previous studies [32, 89].

5. Implementation of phototesting in skin cancer prevention (*Paper V*)

The increasing skin cancer incidence, its correlation to increased sun exposure habits and efforts aiming at early detection have been described, as well as attempted preventive measures (chapters 1.3 and 1.6). Primary health care constitutes a strategic base for prevention. The extent to which resources can be used for prevention is variable, but usually limited. In an increasingly challenged health economic climate, preventive measures (for skin cancer and a long list of other conditions) need to be used effectively and with forethought. For that reason, we wanted to investigate the impact of differentiated levels of preventive efforts focussing on skin cancer, and how level of effort could affect the propensity of the patient to change sun habits/sun protection behaviour and attitudes towards sun bathing. Furthermore, we wanted to investigate whether the addition of a phototest with a self-reading assessment by patients could be a complementary tool in skin cancer prevention.

All patients >18 years of age visiting a primary health care centre in Linköping, Sweden, during 3 weeks in the month of February were given the opportunity to fill in a questionnaire concerning sun habits, sun-protection behaviour and attitudes towards sun bathing (n = 308), and then randomized into one of three groups, each representing an increasing level of effort in time and use of

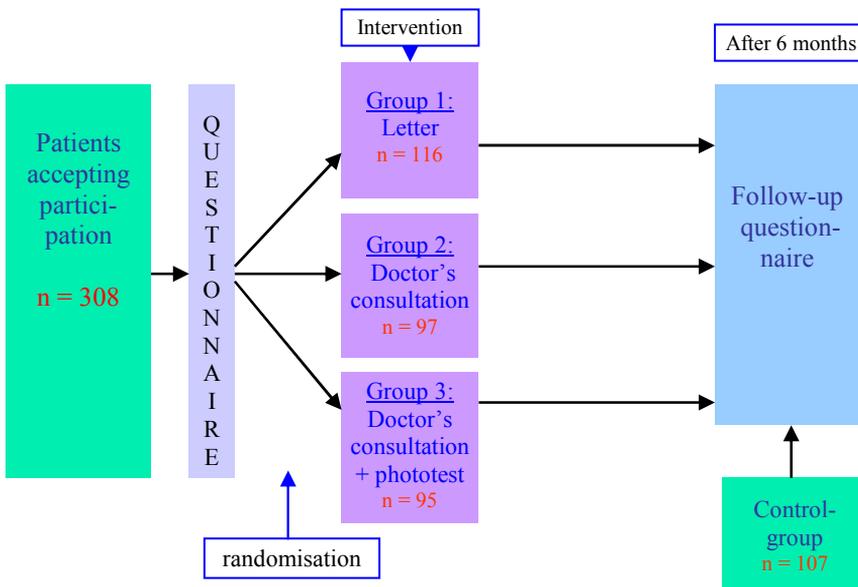


Fig 14. Study design for evaluation of skin cancer prevention in primary health care.

resources. All subjects in the three groups received adjusted feed-back on their questionnaire together with general preventive information/advice about sun protection. In group 1 this was achieved solely by means of a letter. In group 2 and 3 the written information was augmented by a personal doctor's consultation and in group 3 also by the performance of a phototest with a self-reading assessment and a written feed-back of the reported phototest result. Change of sun habits, sun protection behaviour and attitudes towards sun exposure was evaluated after six months, i.e. after the following summer season, by a repeated questionnaire. A further group of subjects filled in the same questionnaire for the first time, serving as a control group.

Questionnaire items: The initial questionnaire consisted of four parts: demographic questions, questions on sun habits/sun protection behaviour, mapping of readiness to change behaviour based on the *Transtheoretical Model of Behaviour Change*, and questions concerning attitudes towards sun bathing. It constituted a set-up of questions based on the experience from previously performed studies [43, 75, 77, 95, 101, 102].

For questions on sun habits/sun protection behaviour and attitudes toward sun bathing, answer alternatives were expressed in terms of 5-graded Likert scales (e.g. *never, seldom, sometimes, often, always*). For sun habits/sun protection behaviour, the following questions were included:

1. How often do you sunbathe with the intention to tan during the summer in Sweden?
(*never, seldom, sometimes, often, always*).
2. How often do you usually go on sun vacation abroad?
(*never, seldom, 1-2 weeks/year, 3-5 weeks/year, >5 weeks/year*)
3. Do you usually use a sunscreen when sunbathing?
(*never, seldom, sometimes, often, always*).
4. If you use sunscreens, which sun protection factor do you choose?
(*I don't use sunscreens, SPF 1-5, 6-10, 11-15, >15*).
5. When in the sun, without intention to tan, how often do you use any of the following ways to protect from the sun: A) sunscreens, B) shirt or sweater with short sleeves, C) shirt or sweater with long sleeves, D) sun hat or cap, E) trousers with long legs, F) staying in the shade?
(*never, seldom, sometimes, often, always*).
6. How many times have you been sunburnt (redness and smarting pain) during the past year?
(*never, 1-2 times, 3-5 times, 6-10 times, >10 times*).
7. How often do you use a sunbed?
(*never, 1-2, 3-5, 6-10, 10-20 or >20 weeks/year, frequency: 1-2, 3-4, 5-7 times a week*)
8. How long do you usually stay in the sun between 11 am and 15 pm, during a typical day-off in the summer (June-Aug)?
(*<30 min, 30 min -1 h, 1-2 h, 2-3 h, >3 h*).

For attitudes towards sun exposure, the following questions were included:

1. How do you like sunbathing?
(*I dislike it very much, I rather dislike it, I neither like nor dislike it, I rather like it, I like it very much*)
2. Do you think that the advantages of sun bathing outweigh the disadvantages?
(*there are many more disadvantages, there are a few more disadvantages, advantages and disadvantages are equal, there are a few more advantages, there are many more advantages*)
3. How extensive do you consider the health risks of sun bathing to be?
(*very high, rather high, not very high, very low, no risk at all*)
4. How extensive do you consider the risk for you to develop skin cancer?
(*very high, rather high, not very high, very low, no risk at all*)
4. How important is it for you to get tanned during the summer?
(*very important, rather important, not very important, not important at all*).

Four questions were based on the *Transtheoretical Model of Behaviour Change*. The theory behind the model proposes that the individual is in one of five schematic stages of behaviour change, for which each stage is represented by a statement. To determine which stage of change the individual is in, for chosen behavioural items, he/she is instructed to mark the statement best fitting his/her own attitude.

The five stages are:

1. *Pre-contemplation stage*: The individual has no intention to change behaviour.
2. *Contemplation stage*: The individual is seriously considering to change behaviour.
3. *Preparation stage*: The individual has decided to change behaviour.
4. *Action stage*: The individual have taken action to change behaviour.
5. *Maintenance stage*: The individual works to prevent relapse and consolidate the gains attained during action.

The four behavioural items investigated were: a) giving up sun bathing, b) using covering clothes for sun-protection, c) using sunscreens, and d) staying in the shade during the hours of strongest sun light. For each item the subjects were asked to mark the statement alternative best corresponding to their own attitude, each statement representing the different stages of change.

Question no.	Behavioural item	Change of mean value		
		Gr. 1 (n = 116)	Gr. 2 (n = 97)	Gr. 3 (n = 95)
17 a)	Giving up sun bathing	-0.19	-0.57 **	-0.42 *
b)	Using covering clothes for sun-protection	-0.12	0.08	-0.27
c)	Using sun screens	-0.19	-0.04	-0.09
d)	Staying in the shade	-0.25	-0.72 ***	-0.31

Table 2. Change in mean values, between the initial and the follow-up questionnaire in each group, for the five stages of change scored as 1-5 (from maintenance to precontemplation stage) and for each of the four behavioural items. Significance levels are displayed as: * = $p < 0.05$, ** = $p < 0.005$, *** = $p < 0.0005$. A negative value indicates change towards a lowered risk behaviour. Index of groups: 1 = letter group, 2 = doctor's consultation group, and 3 = phototest group.

Role of phototesting: For the *phototest* group (group 3) as a whole, the addition of a phototest did not seem to reinforce the preventive effect, but closer investigation of the results for the phototest group (Table 3), revealed differences in results based on UV-sensitivity. Low UV-sensitivity, according to the phototest result, was associated with a lower tendency to improve sun protection behaviour, compared to high UV-sensitivity subjects. Additionally, high UV-sensitivity subjects showed significant change of behaviour even for items for which the two doctor's consultation-groups as a whole did not.

Question no.	Sun habits / sun protection behaviour and attitudes towards sun bathing	Phototest result	
		Low UV-sensitivity (0-2 reactions) n = 41	High UV-sensitivity (3-5 reactions) n = 54
9	How often do you sun bathe with the intention to tan during the summer in Sweden?		-0.32 *
11	Do you usually use a sun screen when sun bathing?	-0.30 **	
12	If you use sun screens, which sun protection factor do you choose?		-0.60 ***
13b	When in the sun, without int. to tan, how often do you use shirt with short sleeves?		-0.30 *
14	How many times have you been sunburnt during the past year?	-0.37 *	
15	How often do you use a sunbed?	-0.13 *	
21	How extensive do you consider the risk for you to develop skin cancer?	0.23 **	
	Stage of change for		
17a	Giving up sun bathing		-0.46 *
17b	Using covering clothes for sun-protection		-0.55 *
17d	Staying in the shade		-0.38 *

Table 3. Change of mean values of the 5-graded Likert scale scorings (upper part) and for the five stages of change scored as 1-5, from maintenance to precontemplation stage (lower part), between the initial and the follow-up questionnaire in group 3 (phototest group), subdivided to show UV-sensitivity according to the number of reported reactions by the phototest. A negative value indicates change towards a lowered risk behaviour. Only statistically significant changes are shown (* = $p < 0.05$, ** = $p < 0.005$, *** = $p < 0.0005$).

In conclusion, a personally mediated prevention message concerning sun exposure, delivered during a doctor's consultation, appeared to be significantly more effective than a corresponding prevention message presented in letter-form. The addition of a phototest to the consultation improved outcome in individuals with high UV-sensitivity, but not for the group as a whole. Thus, since high UV-sensitivity individuals constitute a specific risk group, the phototest can be viewed as a tool to improve the outcome in terms of preventive behaviours for these susceptible individuals.

6. Discussion

6.1. General remarks

Use of phototesting in clinical practice and research is in general limited, by time and resource related factors, insufficient clinical experience, or unfamiliarity with the technique but perhaps also by perceived lack of relevant information delivered by traditional phototesting. Given the increase in western society of both UV-exposure and the diseases related to it, a broader utilisation of phototesting would seem warranted. Worldwide there has been an increasing interest both in the mapping of underlying bio-physiological mechanisms of UV-erythema and UV-carcinogenesis, as well as in finding effective and practicable ways of preventing skin cancer. In recent years the “innate immune response” mechanisms of the skin have caught growing attention in studies illuminating the inflammatory response to external provocation, including UV-radiation [20, 21] and ways in which this may contribute to disease pathogenesis. UV reactivity is known to differ from one person to another. The increase in knowledge at a cellular and bio-molecular level coupled to our ability to determine genotype [19, 23], places increased relevance on our ability to grade and classify the functional biological UV-response both at a group and an individual level. Relevance can also exist in the clinical situation in regard to diagnosis, therapy and prevention. The knowledge base needs to increase, which will only happen if we test individuals more frequently and with a higher content of accuracy and information. This process includes both simplifying procedures at one end of the spectrum (e.g. self reading of traditional UVB testing) in order to broaden our knowledge base and, at the other end of the spectrum, increasing the quality and amount of information gained on individual variability in sensitivity (e.g. from the divergent beam method).

6.2. Divergent beam phototesting – a beneficial complement to traditional phototesting?

With the divergent beam protocol, we have demonstrated how phototesting technique can be modified to achieve more detailed information on UV-sensitivity in the skin, and how dose-response data above the MED can be generated and interpreted. The added information opens up for application of the protocol in clinical research situations as well as improving the quantification of UV-sensitivity in clinical practice. Since the irradiance dose increases in a continuum, the MED determination can be more exact.

MED-estimation by the divergent beam showed good agreement with traditional phototesting for higher MED values, but in the lower region the

divergent beam gave in general higher MED values than traditional phototesting. The explanation for this is probably related to optical factors of the lens and differences in the spectral distribution along the UV-field radius. This has been confirmed by Ilias et al, who found that the erythema effectiveness, due to spectral UV-distribution, was lower in the periphery of the divergent beam than in its centre [103]. From this knowledge, dosimetry data and MED-values of the divergent beam can be weighted according to the relative erythema effectiveness within the dose-field, thereby adjusting for the lens defect. Whether this correction needs to be applied or whether newer, better UV-radiation delivery techniques will ultimately be used is as yet undecided.

An important advantage when compared to traditional phototesting, is the ability of the divergent beam method to explore the skin blood perfusion response within the erythematous reaction, i.e. for UV-doses above the MED. The generation of dose-response curves, and the interpretation of dose-response gradient data constitutes a new approach that might be a valuable complement for the understanding of the UV-erythematous response, or perhaps even in the investigation of photodermatoses. In phototherapy for psoriasis, eczema and other dermatoses, two bits of information are helpful in planning therapy. The first, the MED, can be provided by traditional phototesting. The second, the rate of increments of UV-dose to be used during therapy, is at present decided empirically. Dose-response information from the divergent beam phototest may be of use here.

Another interesting area is the UV-provoked non-erythematous skin closest to the outside border of the reaction in which, though no visible redness can be detected by naked eye, sub-clinical and homeostatic bio-physiological mechanisms are logically taking place. In Paper I, MED dose-response curves of the divergent beam erythemas in this area revealed different perfusion patterns, in some cases plots with a slight slope and in others a flat response. The chronology of erythema development is another issue for which the divergent beam method, with its dose-response assessment capability, might be useable.

MED-estimation of the divergent beam performed by naked eye did not prove to be fully reliable, due to high inter-observer variability. This can be explained to a great extent by the diffuse nature of the reaction border. The ability of the human eye to demarcate a continuous transition from reddened to unaffected skin is considerably poorer than for a sharp delineation. In terms of ophthalmophysiology this can be explained by the fact that colour contrasts are reinforced by the structure and function of the retina [104]. This phenomenon was clearly illustrated in Paper II, by the excellent inter-observer agreement for naked eye readings, as well as the agreement with LDPI measurements, of the sharp

bordered “band”-reactions, compared to the diffusely demarcated divergent beam erythemas. Thus, for all test readings intended for naked eye assessment, provocations or protocols producing as distinct borders as possible are advantageous. This circumstance is undoubtedly a weakness of the divergent beam method, but an exception must be made for trained observers, who perform much better. For a broader use, however, the performance of some kind of objective, skin physiological method, such as LDPI would be necessary. A bioengineering technique is also a prerequisite for the generation of dose-response data in the area above the MED.

The divergent beam protocol is developed for broad band UVB-provocation, but it is possible that the method would be applicable also for broad band UVA, or even for other specific, narrower wavebands. For broad band UVA and narrower wavebands, high doses would need to be delivered, which may mean that the protocol would be of use only for patients/subjects with enhanced UV-sensitivity. Use of alternative, more powerful light sources, may solve this problem.

As conceivable alternatives to LDPI measurement, polarisation spectroscopy and colorimetry appear to be interesting methods, since they have a similar ability to present quantifiable outcomes of erythema intensity [105, 106]. An advantage of LDPI, however, is that it actually measures the biological cause of the erythema, i.e. skin blood perfusion (more precisely the amount of red blood cells times their velocity in an area of tissue), instead of just the colour effect. On the other hand, techniques such as polarisation spectroscopy [105] are considerably more accessible and robust, for which reason further investigation is warranted.

6.3. Can divergent beam phototesting be used to quantify the effect of topically applied substances?

As well as a more precise and detailed estimation of MED and dose-response, the quantitative outcome of the divergent beam assessed by a bioengineering measurement technique, such as LDPI, also facilitates presentation and statistical interpretation in scientific research situations. As a concrete example of this, we have in Paper III been able to demonstrate how the divergent beam protocol can be utilised for the evaluation of the effect of topically applied substances. For the tested topical steroid *clobetasol dipropionate*, profound anti-inflammatory effect was shown for all three examined measurement parameters: reaction diameter, mean perfusion and dose-response gradient. Though to a much lesser extent, effects of the two other test agents – acetone and a gel vehicle – were also seen,

which illustrates that the method appears to have potential even for evaluation of agents with a markedly less pronounced therapeutic efficacy.

The method also has the benefit of being non-invasive and well-tolerated by the individuals subjected to testing. This is an advantage in the consideration of ethical issues and may allow a broader use of testing in product development and basic research.

Another potential field for use is the study of the efficacy of sunscreens. In an unpublished pilot study, application of a sunscreen prior to UVB-provocation diminished erythema diameter as expected. Of course, closer investigation in this matter is needed.

6.4. Can patients read their own phototests?

In an increasingly challenged health economic climate, not the least in primary health care, available resources have to be used effectively. Insufficient time and personnel capacity may lead to a restrictive usage of clinical investigations and evaluations that might actually be valuable for the patient and for the physician.

In Paper IV, we have been able to demonstrate how a traditional phototest can reliably be assessed by patient self-reading and reporting of test results, a procedure that, since the test provocation *per se* only takes a few seconds, could lead to a more frequent use. Self-reading of test protocols with a result communicated by post, email, telephone or fax obviates the need for return visits and might thereby increase the frequency with which dermatological patients could be subjected to actual testing of skin function, which would be a qualitative advantage for diagnosis and management of skin diseases. Additionally, population studies and even prevention initiatives might be facilitated. Naturally, the outcome of patient-performed self-reading does not have the potential to be as informative as expert reading, in which not only the presence or absence of a reaction is established, but also reaction intensity and morphology. It is important to emphasize that patient-performed self-reading is not intended to replace expert reading, but rather to find its own place in a broader perspective of clinical practice or prevention. In Paper V, the self-reading procedure has successfully been implemented in a primary health care situation, something that would have been practically impossible to achieve if expert test reading had to be performed. The phototest equipment needed for the performance is easily handled, and can be obtained at a low cost for the clinic.

6.5. Does phototesting have a place in skin cancer prevention?

The importance of preventive measures to counteract the increasing skin cancer incidence can not be underestimated. Primary health care constitutes one of the basic platforms for prevention, in a multiplicity of medical fields. In this thesis it has been shown that prevention mediated in a primary health care situation, during a doctor's consultation, had significant effect both on patient propensity to change behaviour in terms of improved sun habits/sun protection and on attitudes toward sunbathing. It is likely that a similar approach could be used for a range of other targets of prevention – tobacco smoking, alcohol overuse, physical inactivity and other health risk behaviours. The encouraging results presented in Paper V may thus be of general relevance for all health care professionals involved in reducing health risk behaviours.

The finding in Paper V that solely written information, mediated in the *letter group*, was insufficient to achieve significant change of behaviour, strongly indicates that this information form alone has difficulty in reaching its aims in the competitive climate of information to which the individual is subjected, including other preventive messages.

In this study, the personally mediated preventive message was delivered by a doctor, but it cannot be excluded that this could equally have been achieved by other health care personnel, such as nurses. Whether the better impact was an effect of the personal meeting with the doctor, or of the way of mediating the preventive message orally *per se*, is at this point not fully clear. However, a patient's individual consultation with the doctor constitutes a uniquely integrating occasion for delivering a preventive message, and adjusting the message in accordance with the personality, individual risk factors and receptive communication abilities of the patient.

Though primary prevention of skin cancer was the dominating element in the study, the two *doctor's consultation* groups were also subjected to secondary prevention, by means of nevi inspection, aiming at early detection of malignant melanoma. An interesting detail not mentioned in the paper, is that among the 192 patients subjected to nevi inspection, two cases of malignant melanoma were found and could rapidly be referred for dermatological assessment and surgery. In both these cases the patients filled in the study questionnaire while visiting the primary health care centre for a completely different purpose, and their participation in the study precipitated the melanoma diagnosis.

Finally, we could demonstrate a place for phototesting in skin cancer prevention, with results indicating a significant impact on reported behaviour for individuals with heightened UV-sensitivity. In the *phototest* group as a whole,

however, this effect was diminished, possibly explained by the subgroup of low UV-sensitivity individuals being led into a false feeling of security from the phototest result. Thus, since high UV-sensitivity individuals constitute a specific risk group, the phototest can be viewed as a tool to improve the outcome in terms of preventive behaviours for these susceptible individuals, a result of high preventive value.

7. Conclusions

Divergent beam phototesting, patient-performed self-reading, and the application of phototesting in skin cancer prevention constitute three novel, previously sparsely investigated, aspects of phototesting, for which promising results have been demonstrated.

- The single dose divergent beam UVB phototest protocol enables the two-dimensional association of administered dose to the erythematous response.
- The human eye assesses size of erythematous reactions with sharp borders more efficiently than reactions with diffuse borders, a fact of relevance for protocol design.
- The divergent beam UVB phototest enables the determination of MED in a continuum of doses by naked eye reading performed by a trained observer or by use of a skin physiological method such as LDPI.
- LDPI divergent beam testing allows the determination of a dose-response curve for UVB reactivity which gives quantitative data on individual response above the MED.
- The divergent beam protocol can be used for evaluation and quantification of the effect of topically applied substances, by interpretation of the three parameters *reaction diameter*, *mean perfusion* and *dose-response gradient*.
- A traditional MED phototest and an irritant patch test constitute two skin test methods that can reliably be assessed by patient-performed self-reading and reporting of test results.
- Patient self-reading of a traditional MED phototest reduces considerably the resources utilised to perform the test, and opens for the broader use of phototesting clinically, in population studies and in preventive initiatives.
- A preventive message focussing on sun habits, sun protection behaviour and attitudes towards sunbathing was considerably more effective when mediated during a personal doctor's consultation, than the corresponding preventive message presented solely in written form.
- When targeting individuals with heightened UV-sensitivity, and thus a greater risk for skin cancer, a phototest in conjunction with structured preventive information can be used to improve results in regard to sun habits and sun protection behaviour.

8. Future issues

The promising results with the divergent UVB beam concept are encouraging. Continued development and refinement of the method will probably occur on several fronts such as technical modifications of the light source, adjustment of the spectral distribution of the UV-field as well as optimisation of the test reading procedure by use of simpler and more robust methodology.

For phototesting in clinical practice, determination of UVA sensitivity in a similar fashion would be an important element. Existing light sources can probably only generate enough energy to induce reactions in UVA-sensitive individuals. This is an area for development which will, hopefully, be facilitated by access to alternative, more powerful light sources.

The divergent beam phototesting concept has in this thesis been tested on a material of healthy subjects with normal skin UV-sensitivity. An important and logical target group for further study is patients being investigated for suspected photodermatoses. Here the dose response in the dose-range above the MED may provide information characteristic for the particular dermatosis and thus be of diagnostic value. Testing can be performed on unaffected skin as well as on skin lesions.

In phototherapy, information from the divergent beam test may be incorporated into management routines with a view to optimising outcome and minimizing dose. Modifications of the protocol might be interesting for “toxicity” testing prior to PUVA therapy or in PDT – topical applications reducing erythema have been trialed in this thesis, so why not topical (or systemic) applications which increase erythema?

In basic research, the innate UVB-induced inflammatory capabilities of the skin can be studied at an individual level. An exciting possibility is that the individual may be genotypically, phenotypically, and then functionally characterised in more detail than previously possible. Multi-parametric study of the reaction could include histological examination – even here with two dimensional spatial discrimination and association to dose and skin physiological response as shown in this thesis.

Patient self reading of phototesting based on traditional dosimetry and MED estimation can allow phototesting of a much broader group of patients, which might be a valuable complement in the management and classification of patients with a range of dermatological conditions. Rationales may develop for a place for phototesting of this sort in primary care.

The implementation of self-read phototesting in skin cancer prevention is probably one of the largest areas of potential use of the methodology studied in this thesis. From a prevention perspective, it would be of great interest to more efficiently target the subject group with the greatest risk for the development of skin cancer (sun-sensitive individuals) and those with the greatest propensity to behavioural change (logically patients consulting their general practitioner or doctor for suspected skin cancer). Use of the questionnaire from the present study, or perhaps a shortened version of it, coupled to self-read phototest might prove to be a practical and valuable instrument to communicate risk, influence attitudes and suggest behavioural change whether the patient be met in primary care or in dermatology.

Technical development of the divergent beam methodology will probably in time lead to simpler, less expensive, more user friendly testing apparatus which may also find a role at primary health care centres or at other logical places where individuals/potential patients can have easy access, such as the chemist or other health facilities.

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Sammanfattning på svenska

Under de senaste årtionedena har insjuknandet i hudcancer ökat dramatiskt i västvärlden, detta till stor del beroende på förändrade solvanor. Exponering för solens ultraviolettera strålning (UV-strålning) samt den individuella ljuskänsligheten i huden utgör två viktiga faktorer av betydelse för uppkomsten av hudcancer. Individer med ökad benägenhet att bli rödbrända i solen löper också ökad risk för hudcancer av solexponering, och behöver således vara extra noga med att skydda sig mot solen. Hur känslig man är mot solljuset kan bedömas antingen genom självskattning (klassificering enligt *Fitzpatrick*), eller genom att använda ett ljustest. Det sistnämnda är en betydligt mer objektiv metod, men används ändå relativt sparsamt, sannolikt ofta beroende på brist på resurser, tid eller klinisk rutin.

Det övergripande syftet med avhandlingen var att utveckla och förbättra aspekter på ljustestningsförfarandet med inriktning på att kunna bredda användningen av ljustest inom forskning, klinisk verksamhet och hudcancerprevention. Som ett första steg undersöktes och utvärderades en ny ljustestteknik, baserad på en divergent (spridd) UV-stråle. Genom att belysa huden med ett cirkulärt UV-ljusfält framkallas en cirkulär rodnad (*erytem*), där diametern på rodnaden står i relation till den individuella ljuskänsligheten i huden. I jämförelse med traditionell ljustestningsmetodik visade sig metoden resultera i en noggrannare uppskattning av ljuskänslighet, samt möjligheten att beskriva ett dos-responsförhållande inom det rodnade hudområdet. Eftersom kanten på den framkallade rodnaden tenderade att bli ganska diffust avgränsad framkom dock, med undantag för speciellt tränade avläsare, svårigheter att läsa av testet med enbart ögats hjälp. Av den anledningen krävdes mer objektiv, hudfysiologisk mätmetodik. I de genomförda studierna användes så kallad *Laser Doppler perfusion imaging* (LDPI) för detta. Förutom uppskattning av ljuskänsligheten testades den divergenta UV-strålen också som modell för skattning av anti-inflammatorisk effekt av ämnen som appliceras på huden, exempelvis cortison, och visade sig användbar för detta.

I syfte att öka förutsättningarna för bredare användning av ljustest, genomfördes en studie där försökspersonerna själva fick avläsa ett traditionellt ljustest och rapportera in testresultatet. Resultaten jämfördes med avläsningar utförda av en kunnig avläsare, och visade på god tillförlitlighet.

Slutligen, med hjälp av den beskrivna självavläsningsproceduren, undersöktes i en primärvårdspopulation, om ljustestning kan vara användbart för att förebygga hudcancer, med inriktning på att påverka individers solvanor, solskydds beteende och attityder gentemot solning. I studien jämfördes även olika modeller för att presentera ett preventionsbudskap, och där ett muntligt sådant, förmedlat vid ett läkarbesök, hade ett betydligt bättre genomslag än motsvarande, enbart skriftlig, information. För individer med hög ljuskänslighet bidrog ljustestet till ökat solskydds beteende, vilket indikerar att ljustest skulle kunna vara ett användbart verktyg i eftersträvan att förebygga hudcancer speciellt i denna grupp av individer med förhöjd hudcancer risk.

Sammanfattningsvis utgör ljustestning med divergent UV-stråle, självavläsning av ljustest samt användning av ljustest vid hudcancerprevention tre nya, tidigare sparsamt undersökta aspekter på ljustestning, för vilka den här avhandlingen visar lovande resultat.

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