Phototherapy of Atopic Dermatitis with Ultraviolet Radiation

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ABSTRACT

Studies were conducted in order to evaluate the efficacy of different ultraviolet wavelength regions for the treatment of atopic dermatitis, the risks associated herewith and the *in vivo* effect of ultraviolet radiation (UVR) on the bacterial skin flora.

In bilateral left-right comparisons, adult patients suffering from atopic dermatitis were subjected to treatment with lamps mainly emitting ultraviolet radiation A, UVA, (315-400 nm), UVB (280-315 nm) and combined UVA-UVB, UVAB, respectively. UVAB proved to be most efficacious, with objective and subjective statistically significant superiority to the other types of UVR. UVB was found to be the least efficacious of the three, while the efficacy of UVA was found to lie in between UVAB and UVB. UVAB yielded clearing or considerable improvement in 90% of the patients, while UVA and UVB did so in about 70% of the subjects. Objective differences were less pronounced than subjective ones. The two most common side-effects, xerosis and first-degree burn, were tolerable and clearly correlated to the UVB content of the UVR sources. Uncommon side-effects included polymorphic light eruption (all three types of UVR) and folliculitis (UVB).

A typical patient with atopic dermatitis undergoing phototherapy with UVB or UVAB was found to receive an erythemally effective dose of 1 J/cm^2 per year, a figure considerably lower than that for UVB-treated psoriasis patients, who, according to previously reported data, receive an annual dose of 4 J/cm^2. Treatment for 15 years from the age of 25 years will result in an increase in the risk of non-melanoma skin cancer by the age of 60 of 1.15 compared with the risk in untreated individuals. The risks with phototherapy for atopic dermatitis were thus judged to be small.

Phototherapy with UVB radiation was shown to possess *in vivo* antistaphylococcal properties, which were paralleled by clinical efficacy.

It is concluded that phototherapy is an effective mode of therapy in patients with mild or moderate atopic dermatitis.

Key words: atopic dermatitis, ultraviolet radiation, UVA, UVB, phototherapy, risks, antimicrobial effect.

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The thesis is based on the following papers, which will be referred to by the Roman numerals I to VI:

I. Jekler J, Larkö O. UVB phototherapy of atopic dermatitis. Br J Dermatol 1988; 119:697-705.

II. Jekler J, Larkö O. Combined UVA-UVB versus UVB phototherapy for atopic dermatitis: A paired-comparison study. J Am Acad Dermatol 1990; 22:49-53.

III. Jekler J, Larkö O. UVA solarium versus UVB phototherapy of atopic dermatitis: a paired-comparison study. Br J Dermatol. In press.

IV. Jekler J, Larkö O. Phototherapy of atopic dermatitis with UVA, UVB and combined UVA-UVB. Two paired-comparison studies. Photodermatol, Photoimmunol & Photomed. In press.

V. Jekler J, Diffey B, Larkö O. Ultraviolet radiation dosimetry in phototherapy for atopic dermatitis. J Am Acad Dermatol 1990; 23:49-51.

VI. Jekler J, Bergbrant I-M, Faergemann J, Larkö O. The *in vivo* effect of UVB radiation on skin bacteria in patients with atopic dermatitis. Acta Derm Venereol (Stockh). In press.

Contents

ABBREVIATIONS

ΔA_{330}	Increase in absorbance of polysulphone film measured at 330 nm after exposure to ultraviolet radiation
IgE	Immunoglobulin E
J/cm^2	Joules per square centimetre
MED	Minimal erythema dose
PUVA	Photochemotherapy
UV	Ultraviolet
UVA	Ultraviolet A radiation (315-400 nm)
UVA1	Long-wave ultraviolet A radiation (340-400 nm)
UVB	Ultraviolet B radiation (280-315 nm)
UVC	Ultraviolet C radiation (100-280 nm)
UVAB	Combined ultraviolet A and B radiation
UVR	Ultraviolet radiation

Introduction

Definition

Atopy can be defined[1] as a genetically determined disorder with an increased liability to form IgE antibodies and an increased susceptibility to certain diseases, especially asthma, hay fever and atopic dermatitis, in which such antibodies may play some role. Atopic dermatitis is the characteristic clinical dermatosis associated with atopy.

Historical background

The first documented person with atopic symptoms is believed to have been Pharaoh Menes of Memphis,[2] who died in about 2990 B.C., from what is presumed to have been a hornet sting. The earliest description of atopic dermatitis is thought to be the recording of the symptoms and signs of Emperor Augustus (63 B.C. – 14 A.D) by the Roman historian Suetonius.[3]

In 1892, the French dermatologist Besnier[4] described three patients with a familial, pruritic skin disease which he called "prurigo diathésique". The report led to the acceptance of the disease as a separate entity.

Coca and Cooke[5] coined the term "atopy" after a suggestion by Perry of Columbia University in 1923. The word, derived from the Greek "a" (no) and "topos" (place), had been used in the sense of a "strange disease". Coca and Cooke, however, suggested that it be used in a more specific way, restricted to the hay fever and asthma group of diseases.

The term "atopic dermatitis" was introduced by Wise and Sulzberger[6] in 1933.

Pathogenesis

The pathogenesis of atopic dermatitis is unclear. Studies during the past years have, however, in some respects contributed to its elucidation.

A number of defects are known to occur. Immunological abnormalities include a reduced number of T-lymphocytes,[7] particularly of the T-suppressor subset.[8–10] The T-helper/T-suppressor ratio is increased and the function of T-suppressor cells is impaired.[10] The monocyte and granulocyte chemotaxis is depressed.[11] A defect in the cell-mediated immunity has been documented in several studies.[12–14] The increase in serum levels of IgE is well known.[15] Immunological challenge with acetylcholine, ant-IgE and compound 48/80 has shown increased histamine release with skin concentrations twice as high as in healthy controls.[16] A predominance of T-helper cells admixed with Langerhans cells in the dermal infiltrate in atopic dermatitis has been demonstrated.[17] Increased numbers of mast cells have been shown in lichenified atopic skin.[18,19] The role of eosinophils has also been a matter of investigation. A recent finding that eosinophil cationic protein (ECP) levels are increased in patients with atopic dermatitis[20] supports the concept of an active participation of eosinophils in this disease.[21]

A theory that atopic dermatitis is connected with hypersensitivity to exogenous factors, such as

house dust mites, human dander, inhalant allergens, *Staphylococcus aureus* and *Pityrosporum orbiculare* has emerged. This is based on a number of observations.

The cell-mediated hypersensitivity to house dust mites has been found to be increased in patients with atopic dermatitis.[22] A soluble glycoprotein from eggs and feces of house dust mites, designated antigen P 1, has been found to produce high levels of IgE and IgG antibodies in these patients, but not in healthy controls; epicutaneous test with antigen P 1 yielded positive reactions on mild abrasion of atopic skin.[23,24] Furthermore, Young et al[25] found that only subjects suffering from atopic dermatitis are susceptible to sensitization by antigen P 1 and various human dander fractions when these are applied on skin devoid of stratum corneum. Patch testing with inhalant allergens in patients with coexisting allergic rhinitis resulted in positive reactions in four of nine patients.[26] Langerhans cells, antigen-presenting dendritic epidermal cells known to participate in contact hypersensitivity reactions, e.g. to dinitrofluorobenzene (DNFB),[27] have, in lesional as well as in non-lesional skin of patients with atopic dermatitis, been found to exhibit IgE molecules on their surface. This feature seems specific for atopic dermatitis, since the same phenomenon has not been found in healthy controls, nor in patients with allergic asthma, contact dermatitis and schistosomiasis.[28]

The skin of patients with atopic dermatitis is widely colonised with *S. aureus*: lesional, macroscopically non-infected skin has a carriage rate of 80-93%[29–32] and non-lesional skin 51-78%.[29–33] In comparison, the skin of healthy individuals exhibits rates of 3-8%.[32–34] The exact role of this bacterium in the pathogenesis of atopic dermatitis is, however, still unclear.

The lipophilic yeast *P. orbiculare* has also been discussed as a pathogenic factor, especially in patients with atopic dermatitis of the head and neck type. Clemmensen and Hjorth[35] found a statistically significant effect of antifungal therapy in atopic patients with head and neck dermatitis and positive prick tests for *P. orbiculare*. Later, Wærsted and Hjorth[36] investigated the presence of type I sensitivity to this organism in this disease category. They found, that 28% of the patients had positive prick tests, as compared with 6% of patients with atopic dermatitis with little or no involvement of the head and neck area. Patients with atopic mucous membrane manifestations alone exhibited postitive prick tests in 2%, those with uncertain atopy without skin problems in 0%, and those with urticaria in 1%.

Abnormalities in the metabolism of cyclic AMP (cAMP) have also been found. McMillan et al[37] detected increased levels of cAMP-phosphodiesterase in cord blood of atopic babies, thus indicating that it is a hereditary feature. A hypothesis for the mechanism involved is that the inherited phosphodiesterase levels lead to decreased cAMP, which increases the release of histamine from cells. Histamine, in turn, would inhibit T-suppressor cells, leading to increased IgE levels.[38,39]

The importance of essential fatty acids in atopic dermatitis has been debated. Manku et al[40] found elevated levels of the main dietary essential fatty acid, linoleic acid, in the plasma phospholipids of adult patients with atopic dermatitis, but significantly reduced levels of its metabolites, gamma-linolenic acid, dihomogammalinolenic acid and arachidonic acid.

Clinical features

The diagnosis of atopic dermatitis relies on a number of clinical and laboratory features. The most widely used diagnostic criteria are those of Hanifin and Rajka,[41] but others have been elaborated.[42]

Atopic dermatitis has a clear hereditary factor. Studies by Schultz Larsen et al[43] have shown monozygotic twin pairs to be more often concordant for atopic dermatitis than dizygotic twins. Monozygotic twins run a risk of 0.86 of having atopic dermatitis if the twin partner has the disease, whereas the corresponding figure for dizygotic twins is 0.21; this figure does not differ from the frequency seen in ordinary brothers and sisters. Kjellman[44] studied the familial occurrence of atopy. He found that when both parents had an identical type of atopic disease, respiratory or skin, the incidence of atopic disease was higher (72%) than when non-identical types occurred in the parents (21%).

The prevalence and incidence of atopic dermatitis has been subject to numerous surveys, but the differences in methodology make it somewhat difficult to compare the results. It appears, however, that the prevalence/incidence is increasing. In 1955, Walker and Warin[45] found the cumulative incidence among children 1-5 years of age to be 3.1%. Kjellman[44] made a survey in 1975; the cumulative incidence among seven-year-old children was 8.3%. The same age-group was investigated in 1981/82 by Storm et al,[46] who reported a cumulative prevalence of 8.9%. A study of 12-16-year-old adolescents showed a point prevalence of 3.0%.[47] In an American study of children 5-15 years of age the prevalence was calculated to be 4.4%.[48] In adults, atopic dermatitis often manifests itself as hand eczema. Recently, Meding found atopic hand eczema to constitute 22% of all hand eczema cases, an increase compared to previously published studies.[49]

The prognosis of atopic dermatitis has been studied by several investigators. The most favourable results have been obtained by Vickers,[50] who found a clearing rate of 90% at the age of 15. Less encouraging figures have also been reported. Burrows and Penman[51] found clearing of the disease in only 17% of the patients. Rystedt,[52] in a study with at least 24 years' follow-up, noted that 38% of the patients who in the 1950s had been hospitalised in a dermatology ward on at least one occasion were free of dermatitis at the time of follow-up (early 1980s), while 60% of those treated as outpatients achieved healing.

Treatment of atopic dermatitis

During the past years, a great many remedies have been used, many of which have now been abandoned: tuberculin, sulphur, propeptan, pepton, fever therapy, autohemotherapy, internal treatment with hormones (adrenaline, thyroid hormones), vitamins, arsenic and histaminase.[53]

When no ideal treatment exists, numerous modes of therapy are employed. This is also the case with atopic dermatitis.

The basis of all treatment is general measures,[1] such as reassurance, avoidance of factors known to aggravate atopic dermatitis and occupational guidance. Emollients used on a regular basis are also essential.

The most dominating type of therapy today is topical corticosteroids,[54] with which every atopic dermatitis patient makes acquaintance. Another topical agent still used by many dermatologists is coal tar.[55]In clinical trials, several other drugs have been used. Thirty per cent caffeine mixed with 0.5% hydrocortisone has, in one trial,[56] been found to have the potency of betamethasone. Topical sodium cromoglycate is another substance that has been subjected to investigation. The good results reported[57] have, however, not been reproducible in other trials.[58,59]

Systemic therapy includes antibiotics, antihistamines of the H_1 type and oral corticosteroids. Other systemic agents reported to be efficacious include corticotrophin,[60] cytostatics[61] and thymopoietin pentapeptide.[62] A recent contribution to the therapeutic arsenal is gamma-linolenic

acid, used in a particular variety of evening primrose oil (Epogam). This agent has been subjected to several clinical trials. A meta-analysis of these has shown its efficacy.[63] Analogous to its topical equivalent, oral sodium cromoglycate has in the hands of some investigators yielded good results,[64] while others have found it ineffective.[65,66] Systemically administered transfer factor (dialyzable leukocyte extract),[67] levamisole, a nonspecific immunostimulant,[68] cimetidine, an H_2-receptor antagonist,[69]and nedocromil sodium, a mast cell stabiliser,[70] have all been found ineffective.

The role of foods in atopic dermatitis is not completely clear and the subject of diet manipulation is controversial,[71] but it has many advocates.[72]

Increased knowledge of the importance of microorganisms for atopic dermatitis has yielded antimicrobial methods for the treatment of this disease. The antistaphylococcal agent mupirocin has been shown to be effective in the treatment of atopic dermatitis.[31] The head and neck variety has been successfully treated with ketoconazole,[35] an antifungal agent with effect on organisms such as *P. orbiculare*.

X-rays, mainly in the form of superficial radiotherapy (grenz ray therapy; Bucky therapy), have also been employed for e.g. eczema of the hands[73,74] and also for atopic dermatitis.[53]

The use of ultraviolet radiation will be discussed below.

Phototherapy of atopic dermatitis

Historically, there have been deviating opinions on the effect of sunlight in patients with atopic dermatitis. Rasch (1913)[75] believed that the disease was aggravated by sunlight, an opinion shared by Haxthausen (1919).[76] The first known dermatologist to arrive at a diverging conclusion was Buschke, who, at a balneological congress in 1929, stated that the effect of sea climate on atopic dermatitis was "simply surprising".[77] Later (1940s), other investigators, such as Lomholt[78] and Norrlind,[79] came to the same conclusions and stated that most patients improve in the summer months. Nexmand (1948)[53] interviewed 83 patients with atopic dermatitis with regard to influence of the summer season on their disease; in 54% it improved or cleared completely, in 29% it was aggravated and in 17% no change was noted during the summer. Since this period, there has been a consensus on the benefit of sunny climate[77,80,81] but not on the reasons therefore. In particular UV radiation has been regarded with scepticism. In a dermatology textbook from 1956,[80] artificial UV sources are said to be very poor substitutes for natural sunlight and potent UV sources to be sometimes irritating rather than helpful. Hartung[77] classifies atopic dermatitis as a disease favourably influenced by general climatotherapy but unresponsive to UV radiation and also stresses that the UV radiation of the North Sea climate has "not the slightest effect" on the disease. Magnus[82] lists atopic dermatitis under "primarily non-photosensitive dermatoses aggravated or precipitated by sunlight".

The first report on the systematic use of UV radiation for the treatment of atopic dermatitis is from 1948.[53] Nexmand treated 57 patients with a carbon arc lamp, a treatment he called "generalized ultraviolet light". The results were quite encouraging; 17.5% of the patients cleared, 40.4% improved, 8.8% deteriorated, while the remaining 33.3% remained unchanged.

Papers on therapy of atopic dermatitis with modern fluorescent UV lamps started emerging in the end of the 1970s. Apart from the present studies, I have found 2 reports on treatment with UVA,[83,84] 5 on UVB,[85–89] 7 on combined UVA and UVB (UVAB)[84,86–91] and 8 on PUVA.[85,90,92–97] Furthermore, one study deals with the use of infrared rays.[83] These studies will be discussed further below.

Properties of ultraviolet radiation

Ultraviolet radiation (UVR) is the part of the electromagnetic spectrum which is surrounded by X-rays and visible light. UVR is traditionally subdivided into three spectral regions depending on wavelength; UVA, 400–315 nm, UVB, 315–280 nm, and UVC, 280–100 nm.[98,99] UVA passes through window glass and is considered to be the least harmful of the three wavebands. UVB, attenuated by window glass, is responsible for the formation of vitamin D, but has negative effects in the form of reactions such as burning, photoaging of the skin and skin cancer formation. UVC rays are filtered by the ozone layer and thus do not reach the surface of the earth. However, humans can be exposed to UVC, since this can be produced by artificial sources.[99] Sunlight encompasses the wavelengths between about 290 nm and 2,500 nm. In northern Europe, the irradiance at noon during the summer is 40 W/m^2 (4 mW/cm^2) UVA and below 3 W/m^2 (0.3 mW/cm^2) UVB.[99]

The only well-established benefit of exposure of normal skin to UVR is production of vitamin D.[99] However, it can be used for the treatment of numerous skin diseases,[100] a typical one being psoriasis.[101] The risks, which will be further elaborated below, include photoaging and production of non-melanoma and melanoma skin cancer.[102] In addition, UVR is known to aggravate or precipitate certain skin diseases, e.g. lupus erythematosus, porphyria cutanea tarda and actinic reticuloid.[103]

Aims of the study

The aims of the study were:

- to determine whether ultraviolet light has any effect in the treatment of atopic dermatitis, and, if so, which wavebands are the most efficacious,
- to evaluate the risks with phototherapy of atopic dermatitis, and
- to investigate the *in vivo* effect of ultraviolet radiation on the bacterial skin flora of patients with atopic dermatitis.

Material and methods

A. Common features (I–VI)

Patient selection

All patients fulfilled the diagnostic criteria of atopic dermatitis of Hanifin and Rajka.[41]

UVR sources

The following fluorescent UVR tubes were used. (All of the lamps emit, besides UVR, also visible and infrared rays, but only the UVR content is commented on.)

Philips TL 12. The TL 12 tubes (Philips, Roosendaal, The Netherlands) have a continuous emission spectrum from about 270 nm into the visible light region, with a peak at 313 nm. Most of the output is in the UVB region; this lamp is therefore referred to as a UVB lamp. UVB constitutes 61.6% of the output, UVA 31.3% and UVC 7.1% (*paper V*; UVB here defined as 290-320 nm and UVA as 320-400 nm).

Wolff Helarium B1-12. The Helarium lamps (Cosmedico, Stuttgart, Germany) have an emission spectrum ranging from 280 nm to the region of visible light. The peak is at 325 nm. The output comprises UVA, 74.0%, and UVB, 26.0%. This lamp is referred to as a UVAB lamp.

Philips TL 09. The TL 09 tubes have an emission spectrum from 290 nm to the visible light region. Their output is concentrated to the UVA band, the UVB content being only about 0.35% (measurements by the Swedish Radiation Protection Institute). They are commonly used in commercial UVA solaria. Below, this lamp is referred to as a UVA lamp.

UVASUN 3000. The UVASUN lamp (Mutzhas, Munich, Germany), a high-pressure mercury lamp with heavy metal halides, can be used with various filters. The one used by us, designated as a "UVA filter", eliminates wavelengths shorter than 345 nm permitting treatment with pure UVA. The emission spectrum ranges from 345 nm to 445 nm, the peak being at 370–375 nm. The designation UVA1 lamp is used below.

UVR radiometry

Irradiance measurements were performed with an International Light (International Light Inc., Newburyport, Mass., U.S.A.) Radiometer/Photometer IL 1350. The UVB output was measured using the IL SED 240 probe with a sensitivity of 230–330 nm and peaks at 285 and 295 nm. For UVA irradiance measurements the IL SED 015 probe was utilised; the sensitivity of this sensor is 300-400 nm, its maximum being at 355 nm.

Patient evaluation

Assessment of patients' clinical status relied on eight effect variables, namely pruritus, lichenification, scaling, xerosis, vesiculation, excoriations, erythema and overall (global)

evaluation. Each variable was assigned a score from 0 to 3: 0, none; 1, slight; 2, moderate; and 3, severe. The sum of these scores was designated as the total score. The scale allowed 0.5 subdivisions.

Healing was evaluated using a scale from 3 to –1: 3, completely cleared; 2, considerably improved; 1, somewhat improved; 0, unchanged; and –1 deteriorated.

Statistical analysis

Wilcoxon's matched-pair signed rank test was used in *papers I-IV*. In order to avoid the problem of mass significance, an analysis of only the variables considered to be of greatest importance was performed. In *paper VI* the following tests were employed: Student's t-test for comparison of bacterial densities, Wilcoxon's matched-pair signed rank test for analysis of clinical variables and Spearman's rank correlation test for correlation analysis. A difference was considered statistically significant when $p<0.05$ (two-tailed).

B. Specific features

I. UVB versus visible light; medium-dose UVB versus high-dose UVB

Two paired-comparison left-right randomised studies (1 and 2) were undertaken.

The following exclusion criteria were developed: oral corticosteroid therapy; use of topical agents other than mild corticosteroids (hydrocortisone 0.5–1%) and emollients during and two weeks prior to entry into the study; asymmetric dermatitis lesions; exposure to UVR (delivered in a sunbed or while sun-bathing) 4 weeks before the study; and patient age below 15 years. No phototherapy was performed in the summer months.

In **study 1**, 17 patients with a mean age of 24.9 years and a mean total disease duration of 20.1 years were treated for 8 weeks with UVB on one body-half and with Osram L 36W/30 tubes emitting visible light without any measurable UV content (by us considered as placebo) on the other. Treatments were given three times a week for a maximum of 8 weeks, or until the clearing of at least one side. The patients were phototested and randomised into two treatment groups, one receiving 0.5 of an assessed minimal erythema dose (MED) and the other receiving 1.0 MED. A 20% dose increment schedule was applied.

Study 2 comprised 25 patients with a mean age of 25.9 years and a mean disease duration of 21.4 years. They underwent treatment 3 times a week for up to 8 weeks using UVB tubes. MED testing was performed every other week on the left and right side separately. One body-half received 0.4 MED and the other 0.8 MED, dose adjustments being made at two-week intervals.

II. UVAB versus UVB

Thirty patients with a mean age of 24.8 years and a mean disease duration of 20.5 years were treated in a left-right randomised fashion with UVB on one side of the body and with UVAB on the other. Phototherapy was given three times a week for up to 8 weeks or until the clearing of at least one body-half. With both types of irradiation, the aim was to deliver approximately 0.8

MED. With UVAB treatment, the dose was increased each treatment session to a maximum of 30 mJ/cm^2 UVB and 8.3 J/cm^2 UVA (25 minutes in the UV cabinet). The upper limit for UVB dosage, 765 mJ/cm^2, was not reached by any subject.

After termination of the treatment period, each patient was asked which of the two treatments he had found most effective. In addition, each patient was asked to complete an assessment form. The questions concerned comparison of the two treated sides with regard to preference ("which treatment do you prefer?") and side-effects.

The same exclusion criteria as in *paper I* were employed.

III. UVA versus UVB

Twenty-one patients aged 23.3 years (mean) with a mean disease duration of 19.6 years participated in this left-right paired-comparison study. They were treated with UVA on one body-half and with UVB on the other thrice weekly for up to 8 weeks. On the UVA-treated side the initial dose of 7 to 11 J/cm^2 was adjusted at each treatment session in 2 J/cm^2 increments to a maximum of 15 J/cm^2. The UVB treatment, preceded by phototesting, aimed at delivering approximately 0.8 MED. The assessment made by patients after completion of the therapy was identical to that in *paper II*.

Exclusion criteria identical to those of *paper I* were used.

IV. Low-dose UVB versus UVAB; UVA versus UVAB

Two left-right paired-comparison studies were performed.

In **study 1**, 18 patients with a mean age of 28.3 years and a mean disease duration of 24.8 years were irradiated with UVB on one half of the body and with UVAB on the other. The UVB dose was increased every other week depending on the results of MED testing, each time adjusting it to the level of 0.2 MED. The UVAB treatment was performed in a way similar to that described in *paper II*, but without phototesting. The initial exposure time was determined depending on each patient's skin type.

Study 2 comprised 25 patients aged 24.0 years (mean) with a mean disease duration of 20.4 years. The arms or legs of participating patients were treated 5 times a week for 3 weeks with UVA1 on one side of the body and with UVAB on the other. Due to the small size of the UVA1 lamp (24 x 29 cm), half-body treatment could not be given. Untreated areas were covered with a two-layered thick dark cotton sheeting, except for the face, which was irradiated with UVAB light but not evaluated. In 19 patients, dermatitis patches extending beyond the areas to be treated were found. These served as untreated controls. UVA1 therapy commenced with a dose of 10 or 20 J/cm^2. It was increased each treatment session by 10 J/cm^2 to a final dose of 30 J/cm^2. The set-up of the UVAB therapy was similar to that described in *paper II*.

The evaluation after termination of the therapy made by the patients was identical to that in *paper II*.

Exclusion criteria identical to those described in *paper I* were employed.

V. Dosimetry

Thirty-four patients undergoing phototherapy for atopic dermatitis were subjected to UVR dose measurements during treatment. Of these, 23 were were irradiated with UVB lamps and six with UVAB lamps. The remaining five patients, who also were enrolled in the study described in *paper II*, received treatment with both lamps, UVB on one body-half and UVAB on the other. Treatment was given two to three times a week for a maximum of eight weeks.

At each treatment session, the doses received at the shoulder, hip and knee of each patient were recorded using the polymer film polysulphone.[104] The 40 μm thick polysulphone film was mounted in cardboard mounts with a central aperture of 12 x 16 mm. This type of film can be used as a UVR dosimeter by relating the incident radiation exposure to the increase in optical absorbance of the film at 330 nm (ΔA_{330}) measured before and after irradiation.[104] The film was calibrated by exposure for varying times to the UVB and UVAB lamps, respectively, and the relation of the ΔA_{330} to erythemally effective doses determined spectroradiometrically.[105] One MED in unacclimatised white skin corresponds to 30 mJ/cm^2 (300 J/m^2). The advantages of the film dosimeter were that it provided a simple means of integrating UVR exposure continuously and allowed the three anatomical sites to be compared simultaneously.

With UVB treatment the aim was to give suberythemal doses of 0.5–0.8 MED with a dose increment schedule of 20%. The UVAB treatment regimen was similar to that of *paper II*.

The risk for the development of non-melanoma skin cancer was calculated using a previously described mathematical model.[106]

VI. Skin bacteria and UVB treatment.

Fourteen patients with a mean age of 22.9 years and a mean disease duration of 19.1 years were treated with UVB tubes three times a week for eight weeks.

The exclusion criteria set up were: UVR treatment or sun-bathing one month prior to the study, use of systemic corticosteroids, use of oral or topical antibiotics or antimycotics during and one month before enrolment in the study, use of topical preparations containing salicylic acid one week before and during the study, and age below 15 years. A requirement for inclusion was the presence of dermatitis lesions on the patient's chest. Use of topical preparations other than Uniderm® ointment (containing only hydrocortisone 1%, liquid paraffin and white petrolatum), Essex ointment (the base of Uniderm® ointment) and white petrolatum on the chest was banned.

Bacterial culture samples were collected from the chest area before the start of phototherapy, midway (4 weeks) and after termination of therapy (8 weeks). On the latter two occasions, cultures were performed 30 min and 24 h after UVB irradiation. Twenty-four hours prior to this irradiation and 24 h prior to the pre-treatment sampling, no topical preparations, including the use of soap, were allowed. Samples were recovered from lesional and non-lesional skin at approximately the same location each time.

The technique for quantitative bacterial cultures used was that described by Williamson & Kligman.[107] Samples were collected using a stainless steel ring covering an area of 5.5 cm^2 skin, a glass rod and 1 ml of sterile 0.075 M phosphate buffer, pH 7.9, containg 0.1% Triton X-100. Ten-fold dilutions were inoculated on to a blood agar medium. After an incubation at 37°C for two days, the dishes were examined. Colonies of different morphological types were counted and selected for identification. Gram staining was done and appropriate biochemical tests performed for identification as described by Stockes.[108]

Results

I. UVB versus visible light; medium-dose UVB versus high-dose UVB

Study 1 - UVB versus visible light

Clearing: UVB treatment yielded clearing or considerable improvement in 13 of 17 patients as compared with one patient with placebo irradiation ($p<0.0001$).

Clinical scores: The better effect of UVB treatment compared to placebo was also reflected in significantly lower clinical posttreatment scores: total score, 5.0 and 8.0, respectively ($p<0.001$); pruritus score, 0.8 and 1.8, respectively ($p<0.001$); and overall evaluation score, 0.7 and 1.4, respectively ($p<0.001$). The activity of the patients' dermatitis as measured by the total score improved significantly with both types of irradiation when pretreatment values were compared with posttreatment ones. A decrease from 9.9 to 5.0 (UVB; $p<0.001$) and 8.0 (placebo; $p=0.008$) was observed.

Dermatitis extent: The percentage of dermatitis skin involvement was reduced with UVB treatment from a mean of 13.0% to 2.5% and with placebo tubes from 13.1% to 7.5%. This difference in effect in favour of UVB is statistically significant ($p<0.001$).

Dosage regimens: No statistically significant difference between treatment with 0.5 and 1.0 MED could be detected. However, the number of patients analysed was small.

Consumption of topical preparations: Ten of 17 patients reported having used more topical corticosteroids on the placebo-irradiated side, one had used more on the UVB-treated side, while the remaining six had used equal amounts bilaterally or used no steroids whatsoever. Emollients were used by all patients; two subjects used more on the placebo side, four on the UVB side and 11 used equal amounts on both body-halves.

Side-effects: The side-effects reported were burning (over-exposure erythema) and xerosis. Thirteen of 16 patients who answered a questionnaire stated they had been burnt on the UVB-treated side on some occasion. Two of the patients, both receiving 1.0 MED, considered this side-effect to be severe. Burning was not reported by any patients with placebo irradiation. This difference was statistically significant ($p<0.0001$). Eleven subjects complained of xerosis with UVB treatment, while 4 did so with placebo irradiation. This difference was not statistically significant.

Patient assessment: Out of the 16 patients who completed an assessment form given to them after completion of the therapy, 15 stated they would prefer to be treated with UVB, while 1 subject, who failed to respond to UVB therapy, preferred visible light. When asked which of the two types of irradiation had been most efficacious, 13 replied UVB, none replied visible light, while 4 found both equally efficacious.

Study 2 – Medium-dose UVB versus high-dose UVB

Clearing: Clearing or considerable improvement was achieved in 15 of 25 patients with 0.8 MED and in 16 with 0.4 MED treatment. This difference was not statistically significant.

Clinical scores: No significant differences in analysed clinical scores, i.e. total score, pruritus

score and overall evaluation score, could be detected. The mean total score improved with both treatments when pretreatment and posttreatment values were compared ($p<0.01$).

Side-effects: The side-effects reported were similar to those seen in study 1.

II. UVAB versus UVB

Clearing: Twenty-six of 30 UVAB-treated body-halves cleared or improved considerably, as compared with 25 UVB-treated ones. The difference was not statistically significant.

Clinical scores: UVAB treatment reduced the analysed clinical scores significantly more than did UVB, the mean posttreatment values being: total score 5.2 vs. 6.1 ($p=0.002$), pruritus score 1.0 vs. 1.2 ($p=0.04$), and overall evaluation score 0.65 vs. 0.80 ($p=0.03$). Both therapies improved the total score significantly, with a reduction from a mean pretreatment value of 10.8 to 5.2 (UVAB) and 6.1 (UVB) (both $p<0.001$).

Dermatitis extent: No statistically significant difference in the effect of the two treatments on extent of dermatitis could be detected, both reducing the mean pretreatment extent of 12% to 3% of body surface (hands and head excluded).

Consumption of topical preparations: Twenty of 30 patients were using hydrocortisone at the termination of therapy. Three of these stated they used more on the UVB-treated side, one patient used more on the UVAB-treated side, while the remaining 16 used equal amounts bilaterally. Nine of 29 patients using emollients reported having used more on the UVB side, whereas the remaining 20 used equal amounts on both body-halves.

Side-effects: Burning (over-exposure erythema) and xerosis were the two most common side-effects. Of the 24 patients who answered an assessment form, 21 reported having been burned with UVB treatment, a side-effect considered to be severe by 6 patients, as compared with 3 with UVAB therapy, none being severe. This difference is statistically significant ($p<0.001$). Xerosis was also more common with UVB treatment, being reported by 20 patients with UVB and by 15 with UVAB phototherapy ($p=0.006$). With UVB treatment, two other adverse events were noted: polymorphic light eruption (one patient) and folliculitis of the leg (one patient).

Patient assessment: According to 24 completed assessment forms, 23 patients stated they would prefer to be treated with UVAB, while one patient preferred UVB. Questioned which of the two treatments had been most efficacious, 16 of the 30 participating patients stated UVAB, 14 found both equal, but none stated UVB.

III. UVA versus UVB

Clearing: Fifteen of 21 patients cleared or improved considerably with UVA, as compared with 13 patients with UVB treatment, a difference without statistical significance.

Clinical scores: The effect on the total score was greater with UVA than with UVB therapy, the posttreatment figures being 5.5 and 6.4, respectively ($p<0.02$). The corresponding figures for the overall evaluation score, also these in favour of the UVA treatment, were 1.0 and 1.3, respectively ($p=0.01$). No statistically significant differences in posttreatment pruritus scores could be detected between the two types of UVR. When comparing the mean initial (10.3) with the mean final (UVA, 5.5 and UVB, 6.4) total scores, both treatments were seen to yield significant improvement (both $p<0.001$).

Dermatitis extent: The extent of dermatitis decreased from a mean of 10.1% to 5.4% with UVA

treatment and from 10.0% to 6.2% with UVB irradiation. The greater reduction seen with UVA is statistically significant ($p<0.05$).

Consumption of topical preparations: Fifteen of 21 patients used hydrocortisone topically; 5 of these stated they had used more on the UVB-treated body-halves, while the remaining 10 had used equal amounts bilaterally. All patients had used emollients; 4 reported a greater consumption with UVB treatment, while the remainder had used the same amounts with both therapies.

Side-effects: Burning (over-exposure erythema) and xerosis were the only two side-effects encountered. Burning was reported by 2 of the 17 patients who completed an assessment form with UVA treatment and by 13 patients with UVB treatment. Xerosis of the skin was noted by 8 patients with UVA and by 15 patients with UVB.

Patient assessment: Patient ranking according to 17 completed assessment forms revealed that 13 patients would prefer to be treated with UVA, 4 had no preference, but none preferred UVB. Questioned which of the two therapies had been most efficacious, 17 of the 21 patients replied UVA, 2 UVB, while 2 found the two treatments equal in this respect.

IV. Low-dose UVB versus UVAB; UVA versus UVAB

Study 1 – Low-dose UVB versus UVAB

Clearing: Seventeen of 18 patients cleared or improved considerably with UVAB treatment, as compared with 5 patients with low-dose UVB treatment ($p<0.001$).

Clinical scores: UVAB treatment produced significantly better results concerning all three analysed variables than low-dose UVB treatment: total score, 5.3 and 8.8, respectively; pruritus score, 0.8 and 1.5, respectively; overall evaluation score, 0.9 and 1.8, respectively (all $p<0.001$). Bilateral improvement, measured as reduction of the total score after treatment with UVAB and low-dose UVB, respectively, was statistically significant (both $p<0.001$). Mean pretreatment values of 10.8 were thus reduced to 5.3 (UVAB) and 8.8 (UVB).

Dermatitis extent: The extent of dermatitis decreased with UVAB treatment from a mean of 9.3% to 2.8% and with low-dose UVB therapy from 9.2% to 7.2%. The difference in favour of UVAB phototherapy is statistically significant ($p<0.001$).

Consumption of topical preparations: Of the 15 patients who were using topical hydrocortisone during the study, 9 stated they had used more on the UVB-treated side at some point, while no patient had used more on the UVAB-treated side. No difference in emollient consumption was noted between the two treatments.

Side-effects: The two side-effects reported by the 14 patients who completed a questionnaire were dryness (experienced by 4 patients with UVAB and 4 with low-dose UVB) and what was perceived as burning (2 patients with UVAB and 2 with UVB).

Patient assessment: All 14 patients who completed the assessment form after termination of therapy stated they would prefer to be treated with UVAB lamps. Questioned which of the therapies had yielded the best results, 16 stated UVAB, 2 found both equal, but none found low-dose UVB treatment more efficacious.

Study 2 – UVA versus UVAB

Clearing: With UVAB irradiation, 23 of 25 patients cleared or improved considerably, as compared to 17 patients with UVA1. This difference in favour of UVAB is statistically significant ($p<0.01$).

Clinical scores: Compared with UVA1, UVAB yielded a better reduction in total score, with mean posttreatment values of 7.2 and 6.0, respectively ($p<0.05$) (pretreatment values 12.3), and in overall evaluation score, with mean values of 1.4 and 1.0, respectively ($p<0.01$) (pretreatment 2.1). The difference in pruritus score, 1.3 versus 1.1 (pretreatment 2.3), was not statistically significant.

When comparing the treated areas with untreated control patches, statistically significant differences in favour of active treatment, UVAB as well as UVA1, could be seen for all three analysed variables, with p-values for the pruritus score <0.01 and the remaining variables $p<0.001$.

Consumption of topical preparations: Of the 10 patients, who at some point during the study had used topical hydrocortisone, one stated he had used more on the UVAB-treated side, while the remaining 9 had used equal amounts bilaterally. There was no difference in the consumption of emollients, which were used by all 25 participating patients.

Side-effects: Burning and xerosis of the skin were the two most common side-effects. Burning was reported by 7 of 16 patients who completed an assessment form with UVAB therapy and by 4 with UVA1 therapy. Xerosis was noted by 8 subjects with UVAB and by 7 with UVA1 treatment. None of the patients found these side-effects severe. Bilateral polymorphic light eruption was noted in one patient with skin type I after two weeks of treatment. This patient was subsequently withdrawn from the study.

Patient assessment: In 16 completed assessment forms, 11 patients stated they would prefer to be treated with UVAB, 4 preferred UVA1, while one had no preference. Of the 25 participating patients, 18 judged UVAB to be most efficacious, 5 UVA1 and 2 judged both therapies equally efficacious.

V. Dosimetry

The erythemally effective doses received by the patients during an 8-week course of phototherapy were with UVB lamps 0.8–1.0 J/cm^2 and with UVAB lamps 0.7–0.9 J/cm^2. The shoulder received about 20% less radiation than the hip and the knee. The mean doses per treatment session were 75 and 56 mJ/cm^2 from the UVB and UVAB tubes, respectively. It was calculated that treatment for 15 years from the age of 25 years will result in an increase in the risk of non-melanoma skin cancer by the age of 60 of 1.15 compared with the risk in untreated individuals.

VI. Skin bacteria and UVB treatment

The total bacterial counts of non-lesional skin were not affected in any significant way by the UVB irradiation. The effect on lesional skin was also limited, with moderate decrease of total bacterial counts. These consisted mainly of *Staphylococcus epidermidis*.

The effect of UVB irradiation on *S. aureus* counts was more pronounced. The population of lesional skin was especially affected. Bacterial densities of this microorganism were reduced from a pre-study mean value of 1.3×10^3 bacteria per cm^2 skin to 12 bacteria/cm^2 at the 8-week 30min

count ($p<0.01$) and 75 bacteria/cm^2 at the 8-week 24h count. *S. aureus* was recovered from lesional skin of 12 of 14 patients, and from non-lesional skin of 11 patients.

Lesional skin responded with a greater decrease in *S. aureus* counts, as could be seen when the density reduction from pretreatment counts to 8-week 30 min counts of non-lesional skin were compared with those of lesional skin ($p=0.004$).

The clinical response to UVB phototherapy was reflected in a decrease in total score (from a pretreatment mean of 9.2 to 4.7) and overall evaluation score (reduced from 1.7 to 0.9), and a reduction in dermatitis extent (from 14.6 to 6.1%) (all $p<0.001$).

A correlation analysis showed that patients with stable week 8 *S. aureus* counts, i.e. counts that did not increase from the 30 min to the 24 h sampling, were the ones to reach the best overall evaluation score results.

Summarised results of paired-comparison trials (I–IV)

Table 1 shows the patient characteristics and doses in the paired-comparison studies.

Table 2 summarises the results of these studies.

In table 3, efficacy of the different UV regions and their side-effects have been compiled. Treatment with low-dose UVB (*paper IV*, study 1) has not been included in the UVB group, since the low efficacy found can scarcely be attributed to the lamp used, but rather to the dosage regimen.

Table 1 Summary of patient chracteristics and total doses (Papers I–IV)

Paper (study)	**Patient no.**	♂/♀	**Mean age**	**Mean disease duration**	**Mean total doses (in J/cm^2)**			
					UVB	**UVA**	**UVB**	**UVA**
I. (1) UVB vs. placebo	17	10/7	24.9	20.1	3.18			
(2) UVB 0.4 vs. 0.8 MED	25	5/20	25.9	21.4	0.44/1.08			
II. UVAB vs. UVB	30	11/19	24.8	20.5	2.47		0.47	130
III. UVA (TL 09) vs. UVB	21	12/9	23.3	19.6	1.59	255		
V. (1) UVB 0.2 MED vs. UVAB	18	8/10	28.3	24.8	0.28		0.56	130
(2) UVA (UVASUN) vs. UVAB	25	8/17	24.0	20.4		361	0.47	109

Table 2 Summary of results achieved with lamps dominated by UVB, UVA and UVAB, respectively (Papers I–IV).

Predominant UV-type	Paper/study	Lamp (Dosage)	Cleared or much improved (n)	Total score*	Pruritus score*	Overall evaluation score*	Dermatitis extent*	Side-effects Burn (n)	Xerosis (n)	Other**
U V B	I/1	TL 12 (0.5–1 MED)	13/17	9.9→5.0	2.2→0.8	1.5→0.7	13→2.5%	13/16	11/16	–
	I/2	TL 12 (0.4 MED)	16/25	10.7→6.6	2.4→1.2	1.6→1.0	n.a.	n.a.	n.a.	–
	I/2	TL 12 (0.8 MED)	15/25	10.7→7.0	2.4→1.2	1.6→1.1	n.a.	n.a.	n.a.	–
	II	TL 12 (0.5–0.8 MED)	25/30	10.8→6.1	2.4→1.2	1.7→0.8	12→3%	21/24	20/24	PMLE, Foll.
	III	TL 12 (0.8 MED)	13/21	10.3→6.4	2.2→1.3	1.8→1.3	10.0→6.2%	13/17	15/17	–
	IV	TL 12 (0.2 MED)	5/18	10.8→8.8	2.4→1.5	1.9→1.8	9.2→7.2%	2/14	4/14	–
U V A	III	TL 09	15/21	10.3→5.5	2.2→1.1	1.8→1.0	10.1→5.4%	2/17	8/17	–
	IV/2	UVASUN 3000	17/25	12.3→7.2	2.3→1.3	2.1→1.4	–	4/16	7/16	PMLE
U V A B	II	Helarium	26/30	10.8→5.2	2.4→1.0	1.7→0.65	12→3%	3/24	15/24	–
	IV/1	Helarium	17/18	10.8→5.3	2.4→0.8	1.9→0.9	9.3→2.8%	2/14	4/14	–
	IV/2	Helarium	23/25	12.3→6.0	2.3→1.1	2.1→1.0	–	7/16	8/16	PMLE

*First figure denotes value before treatment; second figure denotes value after completion of study; n.a. = not assessed
**PMLE = polymorphic light eruption. Foll. = folliculitis

Table 3 Summary of the efficacy and side-effects of treatment with UVB, UVA and UVAB, respectively (Papers I–IV).

UV range	Cleared or considerably improved		Side-effects			
			Burn		Xerosis	
	n**	%	n	%	n	%
UVB*	82/118	69.5%	47/57	82.5%	46/57	80.7%
UVA	32/46	69.6%	6/33	18.2%	15/33	45.5%
UVAB	66/73	90.4%	12/54	22.2%	27/54	50.0%

*0.2 MED dosage excluded
**n denotes body-halves

Discussion

Methodological considerations

A. Paired-comparison studies (I–IV)

A number of sources of error can be detected when the material and the methods are analysed.

Patients: The studies were aiming at practically applicable results. Thus, only outpatients were included. This is, however, associated with greater sources of error – inpatients can, in contrast to outpatients, be controlled in a better way, and the risk of infringement of inclusion/exclusion criteria is minimised.

As a rule, patients with severe disease were not included in the studies, since it was considered unethical to withhold potent corticosteroids from these patients. Use of potent steroids would have violated the inclusion criteria. Thus, a tendency toward treatment of moderate or mild disease has been maintained, especially in the study comparing the efficacy of UVB with that of visible light. It was also obvious that the drop-out rate in that study was high; even though no patients stated the reason for withdrawal had been lack of efficacy, this may have been a contributing factor. There has certainly also been a selection towards patients without previous negative experiences of phototherapy or solarium use. It must, however, be pointed out that patients with a history of unimprovement during the summer were not excluded.

With a disease without specific histopathological features, where the diagnosis relies upon a number of criteria, there is always the risk of including patients with other types of eczema. This possibility has been considered, and only patients who without difficulty fulfilled the diagnostic criteria of Hanifin and Rajka[41] were included. When in doubt, participation in the study was not permitted.

Study design: The study design was a left-right comparison. The main disadvantage of this is the risk of the UVR systemic effect interfering. This aspect will be discussed below. A definite advantage, however, is the relative ease with which differences can be detected. Each patient is, furthermore, his own perfect match, an advantage when analysing statistically.

Ideally, all studies should be performed in a double-blind manner. However, when studying clinical effects of UVR, this is not always possible, due to differences in pigmentation elicited by the different wavebands. It is, thus, as a rule, difficult to blind the investigator. Blinding of the patient presents equally great difficulties, at least when we are dealing with relatively well-informed patients.

The use of topical corticosteroids was in the present studies limited to the mild ones (hydrocortisone 0.5–1%). Ideally, no steroids should be used during these studies. The reasons for permitting these preparations were ethical. This could naturally influence the results. However, it should make differences *less* prominent. Moreover, in no cases did patients report having used more of the steroid on the side obtaining the best result; the opposite, on the other hand, was seen in some studies.

Phototherapy: The lamps used in the present studies were designated as UVA, UVB and UVAB sources according to their emission spectrum. There is always the possibility that the spectrum may not have been an optimal one. Also, the dosage regimen may have been inappropriate. In the case of UVB treatment, different dosage regimens have been employed. This has, however, not been the case with the other UV sources. In fact, Krutmann et al,[84] using equipment similar to ours (*paper IV*) for treatment with UVA1 and UVAB, respectively, but with considerably higher UVA doses, achieved results opposite to ours. The interpretation of the results must thus be made with caution.

UVR has been found to have systemic immunological effects, and the impact, if any, on the results of the present studies is of crucial importance. In 1976, Kripke[109] found that UV irradiation of the shaved dorsum of mice produced systemic effects in the animals, effects that impaired the normal rejection of squamous cell carcinomas and fibrosarcomas. These systemic effects have also been observed in animal experiments as diminished reactivity to dinitrochlorobenzene after UV irradiation.[110] The results are supported by subsequent animal[111] and human[96] studies. The presence of systemic immunological changes does not necessarily mean that this has any significant *clinical* implications in humans. In fact, PUVA therapy, in experiments shown to exert systemic effects,[112] has not exhibited this property in clinical trials where patients with atopic dermatitis have been subjected to treatment.[85] Morrison et al[85] treated the entire skin surface except for a small patch on a buttock of four patients with PUVA. An excellent result was seen in 20–58 treatments; the control patches, however, deteriorated in all subjects. Furthermore, in paired-comparison trials, PUVA given to one body-half without irradiating the other yielded excellent results on irradiated sides, while untreated sides showed no improvement.[85] UVB has likewise been shown to have systemic effects in animal experiments.[112] In the present studies, differences between treatments *have*, in general, been found. With a clinically significant systemic effect, this would probably not have been the case. A systemic effect would act in a levelling direction, rather than in the opposite one. Thus, the present results can scarcely have been influenced in any decisive way by the above-mentioned phenomenon of immunological systemic changes.

Assessment: The mode of assessment has the advantage of it having been perfomed by the same investigator in practically all instances. However, the method, being based on subjective judgement, is a natural source of error, since the possibilities of objective evaluation are lacking. With our scoring system, the numerical differences in scores may seem quite small. Had some other system been employed, e.g. that developed by Costa et al,[113] using scores ranging from 0 to 6 for ten severity variables and ten topographic sites, the differences between different modes of treatment would have been numerically greater. When the studies were performed, no uniform scoring system had been agreed upon. Later, a scoring system was elaborated in a workshop at the Third International Symposium on Atopic Dermatitis.[114] This system bears great resemblance to the one used in the present paired-comparison studies.

The use of the rule of nine for estimation of extent of dermatitis constitutes another source of error. Also here, however, it is difficult to find objective methods which at the same time are applicable in clinical practice.

Follow-up was not included in the studies, due to their design. The type of treatment found most efficacious was continued, but given to the whole body, after termination of the study.

Statistical analysis: Wilcoxon's matched-pair signed rank test (two-tailed) has been employed in analysis of differences in clinical variables. This non-parametric test has been chosen because it is well established and because a normal distribution could not be presumed. One alternative would have been Student's t-test, which, however, is a parametric test intended to be used on values with normal distribution.

A source of error is patient selection, since individuals with known intolerance to sun-light did not participate. However, the paired-comparison design and the fact that the main conclusions were drawn from comparisons between body-halves, rather than comparing pre- and posttreatment values, makes the selection problem a minor one.

The population of excluded subjects may be another source of error. However, an analysis of the reasons for exclusion/drop-out shows a vast dominance of factors unrelated to UVR treatment.

B. Dosimetry study (V)

Use of the polysulphone film for dosimetry is a well-established method in the hands of B. Diffey,[105] who has conducted the calibrations as well as the spectrophotometry. A limitation of the film is that its spectral sensitivity extends to wavelengths up to 330 nm. Other sources of error associated with polysulphone film dosimetry include within-batch variation, limitations in length of storage, a possibility of film saturation and a risk of surface contamination.[105] The latter three factors were controlled during the studies.

It is to be noted that the dose values calculated in this study are not directly comparable with those of measurements performed in the paired-comparison studies, where a photometer was used.

C. Bacteriological study (VI)

Assessing clinical variables presented the same sources of error as those discussed above.

In the bacteriological part of the study, there are a number of potential sources of error. The collecting of specimens is one. Two laboratory assistants were responsible for this work, but the fact that the same assistant was involved in the sampling of each patient minimises this problem. The method of sampling, counting bacterial colonies and identifying these, is a recognised and widely employed one. For a trained laboratory assistant, the identification of *Staphylococcus aureus* colonies, with the aid of the coagulase test, is a routine task.

General discussion

No definite cure exists today for atopic dermatitis, a troublesome, pruritic disease. Instead, treatment is symptomatic. The standard treatment, consisting of topical corticosteroids, is sometimes disappointing in efficacy; furthermore, it is afflicted with well-known side-effects. There has therefore been a need for alternative modes of therapy. Phototherapy has emerged as one alternative.

The phototherapeutic approach thus far drawing the greatest attention has been UVA in combination with psoralens, also called photochemotherapy or PUVA. PUVA, originally

developed for the treatment of psoriasis,[115] has ever since its introduction broadened its spectrum of indications.[116–119] Atopic dermatitis also turned out to respond to PUVA and the results have been quite impressive.[85,90,92–97] However, the relapse rates are unfavourable.[93,120] Unfortunately, PUVA is a treatment with potential long-term side-effects, such as production of aging of the skin and skin cancer.[121–125] Since atopic dermatitis mainly affects young people and can persist a lifetime, it is to be expected that many treatment periods will be required. Considering the risks, it constitutes a less attractive alternative in the long run.

The present studies have aimed at finding less hazardous phototherapeutic treatments.

The conclusions from the comparison of the different UV wave-bands, reported in *papers I–IV*, allowing for the methodological pitfalls discussed above, are in summary as follows: UVAB seems to be the most efficient wavelength region, UVA the second most efficient one, while UVB, traditionally the most frequently used type of radiation, is the least efficacious one. All three, have, however, been shown to be efficacious for the treatment of atopic dermatitis. The compilation shown in table 3 gives us a rough idea of the benefits and side-effects of the three types of UVR treatment. The advantages and disadvantages of each can thus be summarised.

UVB treatment requires little time, but it gives rise to frequent short-term side-effects, xerosis and first-degree burn. Also, it is the least efficient of the three wave-bands.

UVA treatment is more effective than UVB, it gives relatively few and mild short-term side-effects, but it is time-consuming.

UVAB treatment seems to be the most efficient of the three wave-bands, it is relatively little irritating, but, like UVA, it is quite time-consuming.

In the present studies, UVAB treatment was found more efficient than treatment with UVB-dominated tubes. These results are supported by the studies of Falk[87] and Midelfart et al.[88] In a study by Hannuksela et al,[86] equally good results were obtained with both types of irradiation, but patient preference was in favour of UVAB treatment. In these three studies, results with UVAB are similar to those in the present studies, over 90% of the patients achieving good results. The beneficial properties of UVAB have been confirmed in other studies.[84,89,91] The positive effects of "generalized ultraviolet light", used by Nexmand in 1948,[53] may also be mentioned in this context.

UVA therapy has attracted little attention in the literature. Pullmann[83] used a UVA source with less than 0.02% UVB content to treat 40 patients. Patients were allocated to two treatment groups, one receiving treatment 5 times a week for 3 weeks and the other twice weekly for 6–8 weeks. The former was found most efficacious; 15 of 20 patients achieved >90% improvement, as compared with 11 of 20 with the latter. Krutmann et al[84] recently published a study comparing the efficacy of UVAB with that of high-dose UVA1 therapy. The lamps used are comparable with those of *paper IV*, UVA vs. UVAB. However, the design was not a paired comparison and the doses used for UVA treatment were more than 5 times higher. With high-dose UVA1 therapy, excellent results were achieved, results superior to those obtained with UVAB. Thus, these results are in discordance with those obtained in the present study. The remarkable difference in dosage regimen can probably account for this discrepancy.

The efficacy of the phototherapeutic treatment traditionally used in Scandinavia for atopic dermatitis, UVB, has been shown in the present studies. Other investigators have reported comparable experiences.[86–88,126] The most current investigations are those of George et al,[126] who, using a newly developed fluorescent UVB lamp, Philips TL-01, with a narrow emission peak around 311–312 nm,[127] have treated atopic dermatitis patients with success.

Different results have obviously been achieved with different treatments. The reasons for this

are unclear. Some of the differences between UVA and UVB may be ascribed to the differences in penetrating properties, the longer wavelengths penetrating more deeply.[128] Furthermore, it can be speculated that a photoaugmentation takes place, UVA and UVB combined being most effective.

In the present studies, conclusions have mainly been drawn from comparisons between different types of UVR. It is nevertheless interesting to note that irradiation with lamps emitting in the visible light region also yielded substantial improvement. Apart from the well-known placebo effect, this can be attributed to the more frequent use of hydrocortisone and emollients by subjects participating in a study. The preservatives of these preparations may add to the beneficial effect by their antimicrobial properties, the possible importance of which will be discussed below.

The safety aspect is important when ultraviolet radiation is used for therapeutic purposes. In laboratory animals, UVR is known to have carcinogenic properties.[129–131] Action spectrum studies in mice have shown maximal carcinogenic efficacy at approximately 300 nm,[132] i.e. in the UVB region. UVA, however, has also been found to be carcinogenic in experimental animal models, but it is less effective than UVB.[133,134] Corresponding experiments have, for natural reasons, not been conducted on humans. Epidemiological data, however, point towards an association between non-melanoma skin cancers and cumulative effects of long-term sun exposure.[135,136] Whether these data are directly applicable to phototherapy is a matter of discussion.

The dose for clearing or considerable improvement of atopic dermatitis has in our study been calculated to be 1 J/cm^2. A patient with this disease receives a median of one treatment course per year (unpublished data). The dose delivered is thus considerably lower than the median dose of 4 J/cm^2 required to clear psoriasis.[137] The increased risk of non-melanoma skin cancer by the age of 60 has been calculated to be 1.15 compared with the risk in untreated subjects.[106] Since phototherapy in many patients is of great benefit, this risk must be considered low. UVB therapy has been subjected to risk evaluation. Larkö and Swanbeck[138] investigated 85 heavily UVB-exposed psoriasis patients without finding any increase in the prevalence of cutaneous cancers. Since UVA has not been employed for more than a few years – mainly in cosmetic solaria – the potential long-term side-effects are unknown. A few anecdotal reports are published concerning the emergence of melanocytic lesions[139] and melanoma[140] in conjunction with UVA solarium use, but whether this connection is causal or not is conjectural. A study on the use of sunbeds with UVA tubes with slight UVB contamination has been performed on healthy subjects.[141] Among the side-effects observed were freckles.

The mechanism of action of phototherapy of atopic dermatitis is not fully understood. UVR has been shown to have immunological, epidermal-thickening and antimicrobial properties, all of which may be of importance.

Toews et al[27] demonstrated in mouse experiments that UVR is capable of damaging epidermal Langerhans cells as well as decreasing their density. Aberer et al[142] showed that this property also applies to human skin. Interestingly, UVB has been shown to reduce the Langerhans cell count in epidermis of patients with atopic dermatitis.[143] The importance of Langerhans cells in the pathogenesis of atopic dermatitis has been discussed above. UVR has also been shown to inhibit mast cell-mediated whealing,[144] which may have some implications, since mast cells participate in the inflammation in lichenified atopic dermatitis.[18,19] Serum interferon levels increase when healthy individuals are exposed to UVB radiation, as demonstrated by Livden et al.[145] Hypothetically, this could be of importance, because interferon has immunomodulatory functions, some of which are suppressive, inhibition of delayed type hypersensitivity being such a

function.[146] Furthermore, UVR has been found to modulate the epidermal cytokine production.[147] Since some of these cytokines are immunosuppressive, it could be of benefit. Recent investigations indicate that the intercellular adhesion molecule-1, ICAM-1, is an important target structure in the immunosuppression brought about by UVB.[148,149] In atopic dermatitis, this receptor is located at the surface of keratinocytes. ICAM-1 has been found to play a key role in formation of an inflammatory infiltrate in the epidermis.[150] The cytokine-induced ICAM-1 expression is inhibited by UVB.[149] Studies have, as mentioned above, indicated an active participation of eosinophils in the pathogenesis of atopic dermatitis.[20,21] High-dose UVA1 therapy has recently been shown to significantly reduce elevated levels of eosinophil cationic protein, indicating that this may be at least a part of the mechanism of action of this therapy.[84]

The antimicrobial action exerted by UVR may be another mechanism of action. *Staphylococcus aureus* is the bacterium most often encountered in discussions on the pathogenesis of atopic dermatitis.[151] Previous studies have shown UVR to have *in vitro* antimicrobial effects against this microorganism.[152,153] This UVR property has in the present study (*paper VI*) been seen to apply also to the *in vivo* situation. It has, furthermore, been paralleled by clinical efficacy. Whether this is part of the mechanism of action or an unrelated phenomenon remains unclear. However, the killing of bacteria seems to have positive effects for atopic patients, an assumption clearly supported by a study on mupirocin. This antistaphylococcal agent proved more efficacious than did placebo in clearing atopic dermatitis.[31] In addition, the UVR antimicrobial action also encompasses the yeast *Pityrosporum orbiculare*,[141,153] which has been ascribed pathogenetic importance.[35,36,154]

UVR causes the epidermis to thicken. Human studies have shown that after a single exposure to UVB, the stratum spinosum thickens twofold and the stratum corneum thickens by a factor of 1.5 to 3 in one to three weeks.[155] An increased thickness of especially the stratum corneum should make the skin less prone to react with an inflammatory reaction on introduction of antigens, such as the house dust mite, an organism also claimed to play a role in the pathogenesis of atopic dermatitis.[156,157]

Phototherapy has in no studies been compared with conventional topical corticosteroid treatment. On empirical grounds, it can be said that phototherapy has a slower effect than potent steroids. The efficacy seems to be somewhere in the vicinity of moderately potent corticoids, although UVR surpasses them in many cases, especially when UVAB is employed. The differences in side-effects are obvious and dependent on the type of UVR and strength of the steroid, respectively, and will therefore not be discussed further in this context. Disadvantages of phototherapy include the time it consumes, and, if the patient purchases his own equipment, the cost it brings. On the other hand, many patients are happy to switch to some other treatment, especially one that gives them a tan and reduces the need for local corticosteroid application.[86] Bearing the economical realities of society in mind, home treatment with UV sunbeds may prove to be advantageous, as has previously been shown for UVB treatment of psoriasis.[101]

Summary and conclusions

In these studies, the efficacy of different types of phototherapy, without using psoralens, in the treatment of atopic dermatitis in adults was evaluated. Lamps emitting primarily in the UVA-UVB spectrum were found to be the most efficacious ones, followed by UVA-dominated tubes. Least efficacious were lamps mainly emitting in the UVB region. However, all three types of radiation were seen to be of benefit. Objective differences were less obvious than subjective ones.

During a normal, eight-week-long, treatment course with UVB and UVAB an erythemally effective dose of about 1 J/cm^2 was seen to have been received. This is also a normal annual dose for UVR-treated atopic patients. Analysis of the risk of developing non-melanoma skin cancer shows it to be small. The hazards with UVA-containing fluorescent tubes are, however, yet to be elucidated. Regular check-ups by a dermatologist are to be recommended.

UVB phototherapy was shown to possess *in vivo* antistaphylococcal properties. These were paralleled by clinical efficacy.

In conclusion, phototherapy for atopic dermatitis is a suitable mode of therapy. For mild to moderate cases, it can be used as monotherapy; for severe cases, it is to be regarded as an adjuvant.

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