PHOTOBIOLOGY/PHOTOMEDICINE

Phototherapy

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The field of photomedicine made tremendous progress at the beginning of the 20th century, owing to heliotherapy as well as to phototherapy of tuberculosis and the prevention of rickets by artificial light sources. In large part, these advances required the expertise of both laboratory scientists and clinicians.

In 1896, modern phototherapy began with Niels Finsen, the father of modern UV therapy. Aware of the bacteria-destroying effects of sunlight, he developed a ''chemical rays'' lamp (a focusable carbon-arc torch), with which he treated over 800 patients with lupus vulgaris in his Phototherapy Institute in Copenhagen. Eighty percent were cured, and Finsen's fame spread quickly (Finsen, 1896; Finsen and Forchhammer, 1904). He was awarded the nobel prize in Medicine in 1903, ''in recognition of treatment of lupus vulgaris, with concentrated light rays''. So far, this is the only nobel prize ever awarded for photomedicine. Suffering from debilitating Pick's disease, he was too ill to travel to Stockholm to receive his Prize. Finsen's work led to the founding of the so-called ''School of the Sun'' in the Swiss Alps for tuberculosis patients (Roelandts, 2005).

In 1923, Goeckerman (1925) introduced his regime (artificial broadband UVB plus coal tar) for psoriasis and published his first results in 1925. This treatment became very popular, particularly in the United States, and it was used for decades to treat psoriasis.

Later, Ingram (1953) combined this regime with dithranol in the United Kingdom. Amazingly, neither of these quite effective phototherapeutic approaches for psoriasis were in use in central Europe. Rather, broadband UVB on its own was quite popular. This therapy was originally proposed in the 1960s by Wiskemann (1963) in Hamburg, who constructed a phototherapy system utilizing Osram Ultravitalux lamps and another using fluorescent UVB tubes.

Photochemotherapy dates back to ancient times. As far back as 2,000 B.C., Indian and Egyptian healers used the pigment-stimulating properties of the psoralen-containing Bavachee plants (*Psoralea corylifolia*) and *Ammi majus*, respectively, to treat vitiligo (Pathak and Fitzpatrick, 1992).

Modern photochemotherapy was born in 1947 when the active ingredients of *Ammi majus*, 8-methoxypsoralen (methoxsalen; 8-MOP) and 5-methoxypsoralen (bergapten; 5-MOP), were isolated (Fahmy *et al.*, 1947; Fahmy and Abu-Shady, 1948), and the first trials with 8-MOP and sun exposure were performed in vitiligo patients by El-Mofty (1948) in Egypt. The first oral use of 8-MOP to treat psoriasis was reported in 1967 at the 21st American Academy of Dermatology Meeting (Allyn, 1962). In 1972, in Germany, Mortazawi (1972) used blacklight UVA tubes in a total-body-irradiation unit with topical 8-MOP to treat psoriasis. However, the UVA output of these tubes was insufficient for clinical efficacy when 8-MOP was administered orally.

In the 1970s, a cooperation of lighting engineers, photophysicists, and dermatologists led to the development of a high-intensity UVA source. These UVA irradiators made oral psoralen photochemotherapy possible. The pivotal publication of Parrish *et al.* (1974) reported the use of this new type of UVA tube in combination with oral 8-MOP to treat psoriasis. It proved to be much more effective than the treatment with blacklight lamps. Fitzpatrick coined the term ''PUVA'' as an acronym for ''Psoralen plus UVA''. The effectiveness of PUVA was confirmed by well-controlled clinical trials in thousands of patients (Wolff *et al.*, 1976). The classic multicenter studies, the US Cooperative Clinical Trial (Melski *et al.*, 1977), and the European PUVA study (Henseler *et al.*; 1981) paved the way for the widespread use of PUVA in psoriasis.

Somewhat later a combination of oral retinoids and PUVA contributed to greater effectiveness and long-term safety of PUVA (Hönigsmann and Wolff, 1989). A variant of PUVA originated as early as 1976 in Scandinavia by the use of trimethylpsoralen (trisoralen) baths and subsequent UVA exposure (also called bath PUVA) (Fischer and Alsins, 1976); bath-water delivery is still in use owing to the absence of systemic photosensitization and the lack of gastrointestinal and potential ocular effects, which oral 8-MOP is known to produce. However, probably owing to logistic problems, bath PUVA has not gained popularity among physicians and patients as compared with the oral form.

Since its introduction, oral PUVA has shown excellent treatment results in a considerable number of other dermatoses, such as vitiligo, mycosis

fungoides, and atopic dermatitis, and as a preventive therapy in photodermatoses. In fact, PUVA sparked a whole new series of discoveries such as the high-intensity UV source now known as narrowband UVB (NB-UVB), and later the UVA1 source (340–400 nm) (see below).

Parrish and Jaenicke (1981) defined the action spectrum for psoriasis with a peak at 313 nm. This led to the discovery of NB-UVB (311–313 nm) irradiation, which, being more efficacious, has largely replaced broadband UVB as the first-line therapy for psoriasis. The first commercially produced lamps at this wavelength became available in the 1980s. van Weelden *et al.* (1988) in the Netherlands and Green *et al.* (1988) in Scotland demonstrated in 1984 the clinical efficacy of NB-UVB in psoriasis. As it was shown to be more effective than broadband UVB, it was increasingly used to treat various skin disorders worldwide; its adoption was also encouraged by its ease of use and its much lower risk of photocarcinogenicity (Hearn *et al.*, 2008; Stern, 2012).

In 1992, UVA1 (340–400 nm) was introduced first for the treatment of atopic dermatitis by Jean Krutmann's group. UVA1 penetrates deeper than UVA2 (320–340 nm); thus it is able to reach deep dermal components of the skin (Krutmann *et al.*, 1992). A few studies with small numbers of patients showed efficacy in some other dermatoses such as localized scleroderma, urticaria pigmentosa, and mycosis fungoides. The published evidence on how best to use UVA1 and its dosimetry remains limited and awaits further study. UVA1 is effective in various diseases, but it appears to be the first-line phototherapy for some types of sclerosing diseases such as morphea (Kroft *et al.*, 2008).

In the early 1980s, a new form of phototherapy, extracorporeal photochemotherapy (photopheresis, or ECP), was introduced by Edelson *et al.* (1987) for the palliative treatment of erythrodermic cutaneous T-cell lymphoma (CTCL). Its efficacy was confirmed later by several uncontrolled clinical trials and approved as a device in 1988 by the Food and Drug Administration to treat this disease. In 1994, at the International Consensus Conference on Staging and Treatment Recommendations for CTCL, ECP was recommended as the first-line of treatment for patients with erythrodermic CTCL (Trautinger *et al.*, 2006).

Meanwhile, ECP also has an important role in the treatment of chronic graft versus host disease (GVHD) after allogeneic bone marrow transplantation, with excellent response rates (Greinix *et al.*, 1998); positive results have also been published for acute GVHD (Greinix *et al.*, 2006). ECP has also been used in several other autoimmune diseases, including systemic sclerosis (Knobler *et al.*, 2006), in acute allograft rejection among cardiac, lung, and renal transplant recipients, and in patients with Crohn's disease, with some success (Dall'Amico and Murer, 2002).

CONFLICT OF INTEREST

The author states no conflict of interest.

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