

ERYTHROPOIETIC PROTOPORPHYRIA

VI. *The Synergistic Effect of Ultraviolet and Infrared Radiation and Protection Against These Wavelengths*

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Abstract. The demonstration of the synergistic effect of infrared and ultraviolet radiation in the production of a cutaneous lesion in a patient with erythropoietic protoporphyria confirms similar observations of Runge & Watson (16) in patients with other types of porphyria. From these experiences it can be concluded that a synergistic effect of ambient infrared and ultraviolet radiation may be primarily responsible for producing the polymorphic eruptions of protoporphyric patients. A similar basic photodynamic mechanism may be assumed to be operative in light-sensitive patients with other types of porphyria.

Most medical investigators agree that, based on action spectra, the range of the electromagnetic spectrum which appears to be mainly responsible for the induction of the light sensitivity symptoms in porphyria patients extends from the ultraviolet to the deep blue (10, 11). As a child, one of our patients developed immediate urticaria on exposure to a 100-watt incandescent lamp approximately 30 cm from his skin. Since there is practically no ultraviolet radiation from such a source (2) the possibility exists that another wavelength or combination of wavelengths was causing symptoms. Runge & Watson (16) demonstrated the importance of simultaneous ambient infrared (2 600 nm) and Soret (405 nm) waveband in the production of cutaneous lesions in other types of porphyria. Since patients with erythropoietic protoporphyria have marked photosensitivity symptoms, a demonstration of the synergistic actinic effect would corroborate its validity as a causal factor and broaden our understanding of photosensitivity. In addition, the demonstration of the synergistic effect may focus medical awareness on the recent

change in man's "indoor light environment" (7). Within the last few decades, fluorescent lighting has been replacing the incandescent lamp as a light source and creating a different "light climate" with elevated UV and blue radiation levels. The light exposure of man indoors to both infrared (IR) and UV simultaneously may influence the clinical expression and precipitation of photosensitivity. This paper is concerned with the demonstration and verification of the effects of UV and IR in one case of erythropoietic protoporphyria and eludes to the protection achieved by chemical alteration of the patient's stratum corneum with the topical application of dihydroxyacetone (DHA)/naphthoquinone (8).

MATERIAL AND METHODS

The patient in this study was case number 2 as reported in the first paper of this series (12). A site on each forearm of the patient was exposed simultaneously to UV and IR. In addition, on two other sites on the forearm, the skin was exposed to only one or the other of the light sources. The light sources and conditions used in testing and the normal response were described previously (16). It is important to note that the radiation energy levels used in the test were approximately twice the ambient levels in Minnesota (USA) at 12.00 on a clear mid-summer day. On the day prior to testing, a topical mixture containing 3% DHA and 0.035% juglone (the naphthoquinones, juglone and lawsone are equivalents) in 50% isopropyl alcohol/distilled water was applied to one forearm at the test site which was to receive both IR and UV exposure (6 applications, 1 hour apart and each application consisted of 2 cc of the mixture over half of the forearm). The control and treated forearms were irradiated for 2 min on each of the test sites.



Fig. 1. Note bullous lesion above the crescent dye mark on the unprotected arm.

RESULTS

During the test period while being exposed to combined UV and IR radiation, the patient reported burning and itching on the unprotected site. These symptoms are identical to the photoparesthesia reported as the only symptoms and clinical manifestations in a patient with erythropoietic protoporphyria (5). Immediately after exposure the skin became erythematous and edematous with a surrounding ischemic area. Within an hour the lesion became bullous (Fig. 1). The patient had no symptoms or lesions on the exposed, protected forearm but did develop a transitory erythema (barely visible in Fig. 2) which disappeared after 24 hours. The patient also received UV and IR radiation separately on the unprotected forearm; that is, on one site he was ex-

posed to UV while on the other, IR. Except for a transitory erythema on the IR exposed area, no lesions were observed. Approximately 1 year later, the unprotected site, which received both UV and IR, had a scar.

DISCUSSION

Runge & Watson (16) pointed to the importance of ultraviolet and infrared radiation in the production of cutaneous lesions in three types of porphyric patients. With relatively low radiation levels of UV and IR, they produced consistently typical pathologic photocutaneous responses in porphyrics. Other investigators (1, 3) used only UV exposure and were unable to produce consistently the cutaneous responses with low level



Fig. 2. Note mild erythema (darker area) above the crescent dye mark on the protected arm.

radiation. These authors did not suspect a synergistic effect of different wavelengths in reproducing the photopathologic response in laboratory tests. Also, Runge & Watson (16) demonstrated the importance of careful selection of skin test sites. The indiscriminate selection of skin test sites may be one of the reasons for failure of earlier investigators to produce photo-cutaneous response in porphyrics.

The possible reason for the consistent demonstration of pathologic photo-cutaneous responses by Runge & Watson (16) was the use of the unexposed abdominal skin as the test site. They were unable to produce consistently a cutaneous response on the usual light-exposed skin of their patients. Redeker, Bronow & Sterling (14) reported a patient with erythropoietic protoporphyria. They said, "In our patient (E. W.) suffering from recurrent urticaria, no porphyrin was demonstrable in the skin excised from the dorsal aspect of the forearm. However, a skin biopsy taken 24 hours after exposure of the forearm to unfiltered sunlight, exhibited definite red fluorescence under ordinary fluorescence microscopy. Examination of this tissue by microfluorospectrophotometry (at the University of Minnesota by W. J. Runge) revealed two major peaks—one of which was clearly protoporphyrin (6334 Å) and the other probably oxyporphyrin derived from protoporphyrin (6678 Å). The reason for the discrepancy between the exposed and the unexposed skin is not clear."

We suspect that the reason for the difference between the exposed skin and the unexposed skin (14) can be explained by the earlier observation of Runge & Watson (16). It is well known that light exposure destroys the protoporphyrin and produces oxyporphyrin (4, 6). In addition, the circumstances of tissue collection and handling are critical to the demonstration of the extremely small amounts of the labile protoporphyrin and its primary red fluorescing derivatives. In a separate study, skin specimens (cases 1 and 2) were obtained without anesthesia from the area of the abdomen just above the inguinal ligament and frozen immediately with solid carbon dioxide. The specimens were kept in almost complete darkness and were immediately sectioned (cryostat) and examined under the recording microfluorospectrophotometer (15). The total elapsed time from the surgical excision of the specimen to the completion of the

spectral analysis was between 15 to 30 min. The air-dried, fresh-frozen sections were mounted in 0.1 N HCl just prior to examination. Runge showed that the only porphyrin present was protoporphyrin (9). A comparable study which demonstrates the lability of protoporphyrin was microfluorospectrophotometric analysis of fluorescing red blood cells of protoporphyric patients (9). Even though kept in a dimly illuminated room (less than 0.2 f.c.) and exposed only to the open air, the protoporphyrin in the dried blood smears changed rapidly. Although the smears were studied consecutively, the red fluorescence band of oxyporphyrin became more intense until protoporphyrin was not demonstrable. Within 2 hours, any trace of porphyrin-related fluorescence had disappeared in the specimen. An inference from these laboratory experiences to the skin *in vivo*, would suggest that once the protoporphyrin is altered beyond oxyporphyrin by light and oxygen, the tissue is not capable of showing a photosensitive response until the concentration of protoporphyrin and its primary breakdown products in the skin have risen again to adequate levels. Daily light exposure of the face and hands of protoporphyric patients probably destroys continuously the protoporphyrin (as indicated by the usual absence of protoporphyrin fluorescence in the exposed skin versus its constant presence in unexposed skin (16), hence the porphyrin concentration in the exposed tissue is consistently lower than the concentration in the unexposed skin of the areas of the body normally covered by clothes. Without excitation by light, porphyrins are not able to participate in the chemical reactions possible in the excited state. Elevated porphyrin levels in tissue are usually well tolerated *in vivo* especially in the dark (4). Histologic examination of the exposed and unexposed skin of our protoporphyric patients (13) gave indirect evidence in support of this thesis. The characteristic pathological histochemical findings of the skin of the light exposed areas cannot be found in tissue sections of skin from the areas of the body that rarely receive any light exposure; namely, buttocks, inguinal region, etc. The histochemical findings of normal-appearing skin in these sites suggest that in unexposed areas the presence of protoporphyrins does not destroy the skin; however, in the chronically exposed areas, the exposure of protoporphyrins in the skin to

light probably initiates a damaging chemical reaction between the skin and the porphyrins or its primary derivatives.

The experimental observation on protection against light presented in this paper corroborates the clinical experience with the DHA/naphthoquinone method of sunlight protection in 7 patients with erythropoietic protoporphyria (8). Other topical methods of light protection failed in these patients; however, in using our topical method the patients changed their daily activities from essentially "indoors" to substantially "outdoors".

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