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PHOTOMEDICINE

Volume II

Ehud Ben-Hur
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Photomedicine

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Editors

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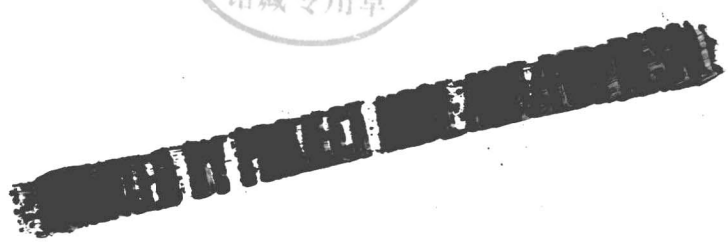

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INTRODUCTION

Go outside and play in the sun. It's good for you.

My mother

The use of sunlight and drugs for the treatment of skin diseases has been documented for over 3400 years; for an even longer time, the reddening, blistering, and tanning effects of sunlight have probably been known. With the discovery of lasers a new dimension was added in the study and application of light in medical therapy. Ophthalmologists adopted the laser in the clinic as a photocoagulator for the treatment of detached retina, and the use of laser as a scalpel for noncontact, noninvasive, and even subcellular surgery is at an earlier state of acceptance. In addition to surgical uses, new, promising ideas are continuing to emerge. Thus, laser can be used to diagnose and treat malignant tumors using photoradiation therapy. This renewed interest, stimulated by the mutual interplay of both scientific and technological innovations, is characterized by a multidisciplinary approach involving physicists, chemists, biochemists, and physicians.

Our objective has been to collect in these three volumes the most up-to-date assessment of our understanding of light in medicine. Since *Photomedicine* was defined as an informative guide to practical applications rather than an esoteric study of medical discipline, the level of medical rigor was reasonably relaxed.

Given limitations on length, the chapters are not intended to be all embracing reviews of the field, but rather to present an overview of key ideas and directions with the objective of delineating the most promising and exciting problems. We hope that the text is sufficiently introductory to stimulate the curiosity and interest of a neophyte, and to simultaneously provide the specialist with a rather short, but current summary of the status of this field. Most important, we hope that the volumes will further highlight this rapidly developing science and spur current and new researchers and ideas.

Ehud Ben-Hur
Ionel Rosenthal

THE EDITORS

Ehud Ben-Hur, Ph.D., was born in Israel in 1940. After graduation from the Hebrew University of Jerusalem in 1965, he went on to study biochemistry at the Technion, Israel Institute of Technology at Haifa, where he obtained his M.Sc. and doctorate degrees. He then joined the Biology Department of Brookhaven National Laboratory as Research Associate where he completed postdoctoral work on the radiobiology of cultured mammalian cells under the auspices of Dr. M. M. Elkind. Upon returning to Israel in 1973, he first joined the Department of Cellular Biochemistry at the Hebrew University and then the Nuclear Research Center-Negev, in 1975, where he is currently engaged in studies of biological effects of ionizing and nonionizing radiations.

The main thrust of his research activity in the past was related to radiation-induced damage in DNA and its repair. During the last few years he has become interested in photodynamic therapy of cancer and is actively involved with Dr. I. Rosenthal in developing new and improved photosensitizers for this purpose.

Dr. Ben-Hur is affiliated with the Department of Radiation Biology, Colorado State University. He is also affiliated with Ben-Gurion University, Beer-Sheva, Israel, where he teaches photobiology. Dr. Ben-Hur has published over 80 papers in scientific journals, is a member of the American Society for Photobiology and the Radiation Research Societies of both the U.S. and Israel, and is on the Editorial Board of the *International Journal of Radiation Biology.*

Dr. Ben-Hur is married with two children and lives most of the time in Beer-Sheva.

Ionel Rosenthal, Ph.D., received his degree in Chemical Engineering from the Polytechnic Institute in Bucharest (Romania) and Ph.D. degree from the Freinberg Graduate School of the Weizmann Institute of Science, Rehovoth, Israel. Dr. Rosenthal has had a very colorful professional career which has included Plant Engineer at "Mahteshim" Chemical Co. and Senior Scientist at the Department of Organic Chemistry at the Weizmann Institute of Science and at the Department of Organic Chemistry, Nuclear Research Center-Negev. Currently he is Principal Scientist at the Department of Food Science, Agricultural Research Organization, Bet-Dagan, and Professor in the Department of Agricultural Biochemistry at the Faculty of Agriculture of the Hebrew University, Jerusalem.

His scientific interests in organic photobiochemistry and food chemistry (and its spin-off: cookery) have resulted in more than 100 research publications in these areas.

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TABLE OF CONTENTS

Volume I

Volume II

Volume III

Chapter 1

THE IDIOPATHIC PHOTODERMATOSES

I. A. Magnus

TABLE OF CONTENTS

I. PHOTODERMATOSES OF UNKNOWN ETIOLOGY

Earlier recent reviews on the photodermatoses include the relevant chapters and sections in the books of Harber and Bickers[1] and of Johnson.[2] This chapter will be dealing with only four types of photodermatoses (Table 1). These may be called the "primary" or idiopathic photodermatoses. See Table 2 for a summary of their main features; this table is necessarily oversimplified and the full text must be consulted.

The secondary photodermatoses, which are dealt with elsewhere, are briefly listed in Table 3. In addition (not shown in these tables), chronic, life-long exposure to sunlight is associated with (1) aging changes and (2) skin cancer. These may be considered "normal" responses in that probably all normal people with a pale skin would be subject to these changes given sufficient radiant exposure. The relative absence of melanin pigment in white skin must lead to impaired photoprotection against aging and cancer as compared with Asiatic or Negroid skin, and this is surely important. However, other genetic factors, as yet undetermined, also play a part in "normal white populations". These seem to include, as well as having a pale skin, being of "Celtic" heritage. As yet, what the relevant qualities of being Celtic are have not been isolated, let alone quantified or scientifically characterized.

Table 1
THE PRIMARY PHOTODERMATOSES

1. Polymorphic light eruption (Rasch)
2. Actinic or summer prurigo (Hutchinson)
3. Chronic actinic dermatitis (actinic reticuloid and photosensitive eczema)
4. Hydroa vacciniforme (Bazin)

II. POLYMORPHIC LIGHT ERUPTION

A. Introduction

More or less minor rashes of the skin, thought to be associated with solar exposure, had been described from the start of what may be called modern dermatological literature, viz., Robert Willan[4] wrote in London, just before the turn of the 18th century, on "eczema solaris". Willan is credited as the pioneer of a proper classification of skin eruptions, and it is to him that credit is probably due for first associating solar exposure with a skin disorder. Other early writers were Rayer[5] in Paris and Veiel[6] in Vienna. Presumably, all these observers were writing about what is here termed polymorphic light eruption, but this is not always certain. Uncertainty has long bedeviled early medical classifications. The position is not much better today, where the main difficulty remains putting an agreed terminology to an agreed morphological and clinical state, where mechanism is unknown.

1. Terminology and Relation to Other Photodermatoses (Especially Actinic Prurigo)

The story of this has been reviewed previously by several writers, viz., Rasch[7] and also Magnus.[8] The term polymorphic light eruption (PLE) was introduced by Carl Rasch in 1900 in a brief note describing two patients, mother and daughter, who had what he called an "eczema-like polymorphic light eruption". In a later review, Rasch[7] tells how earlier, his pupil Haxthausen[9] in 1918 had proposed the forming into one disease group the eczematous condition with another pruriginous condition described by Hutchinson.[10] This has turned out to be an unfortunate disservice to clear nomenclature.

Thus, seemingly was the beginnings of a widespread and continuing confusion of two separate dermatoses. In retrospect, it is tempting to ask how such distinct skin disease pictures could possibly be confused for so long.[2]

In spite of the confusion, there had always been some who had emphasized the distinctions between the various solar-induced rashes on the basis of morphology, e.g., Epstein,[11] who wrote about "solar erythema and eczema" and "summer prurigo" as separate clinical entities.

With the more recent observation of sun-induced rashes in indigenous races of the New World, the muddle of nomenclature has returned. The solar-induced prurigo in patients of North, Central, and South America has been called PLE. This has continued the confusion.[12–16]

Magnus strongly supports the view that summer (or actinic) prurigo and PLE must be separated on the grounds of their (1) having different morphology, (2) taking a different clinical course, (3) responding to a different therapy, and (4) reacting with possible differences in T cells.[17–19]

B. General Features

1. Racial and Geographical Distribution

The racial and geographical distribution of PLE has received little or no notice. This is, presumably, partly because of differences in terminology. Such an endeavor, to

Table 2
SUMMARY OF CHIEF CHARACTERISTICS OF THE FOUR PRIMARY PHOTODERMATOSES

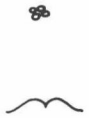
	Prevalence	Characteristic primary lesion	Diagrammatic view from above and profile	Progression of lesion	Other skin lesions	Body surface distribution	Demonstrable photosensitivity	Characteristic lesion histology
Polymorphic light eruption	Common	Papule, 1—2 mm		Resolves 1—2 weeks, without scars	Rare, urticarial, target-like	Diffusely; exposed limbs, V of neck, trunk; not face	+ or ±	±
Chronic actinic dermatitis	Less common	Varied and not specific		Persistent	Reticulosis-like papules (2—5 mm) or plaque (1—3 cm)	Diffusely; not strictly on exposed areas	+++ or ±	+++ or ±
Actinic prurigo	Uncommon	Prurigo papule, 1—3 cm, with surmounting scratched vesicle 1—2 mm		Slowly resolves, ± superficial scars	Not usual, except in exacerbation, edema, and papules	Diffusely; mostly exposed limbs and face; also covered areas	+ or ±	±
Hydroa vacciniforme	Very rare	Closely grouped tense vesicles, 1—2 mm each; umbilicated larger edematous papule, 1 cm		Lesions coalesce, form scabs; resolves 2—4 weeks; depressed scars, 3—6 mm	Lesions often in different stages, some umbilicated, some scabbed	Lesions in restricted number of groups; exposed limbs and face	±	+

Table 3
THE SECONDARY PHOTODERMATOSES

I. Photodermatoses associated with known external or exogenous chemicals or chemical photosensitizers
   - A. Therapeutic drugs, which include the following
     1. Certain antibiotics, especially tetracyclines and in particular demethyloxytetracycline
     2. Tranquilizers, especially chlorpromazine and protriptyline
     3. Antibacterials, namely nalidixic acid and sulfonamides, especially with trimethoprim
     4. Oral diuretics such as hydrochlorothiazide and furosemide
     5. Oral antidiabetics such as chlorpropamide
     6. Other miscellaneous drugs[3]
   - B. Industrial chemicals or products, which include the following
     1. The products of the destructive distillation of coal, e.g., pitch, anthracene, and related substances
     2. Dyes, e.g., of the hydroquinone and triphenylmethane families
   - C. Botanical products: some plants of the parsley, celery, figs, citrous families. The known active photochemical agents are nearly always psoralens as in bergamot oil. Of unknown importance is hypericin, an established photosensitizer in cattle but very doubtful in humans
   - D. Cosmetics: these include ingredients incorporated into soaps, perfumes, etc. of which the incriminating agents may include halogenated salicylanilides, certain nitromusks, *p*-aminobenzoic acid, cinnamates, and psoralens (bergamot oil)

II. Photodermatoses associated with endogenous photosensitizers or metabolic abnormalities
   - A. The porphyrias
   - B. Certain genodermatoses, associated mostly with dwarfism, including xeroderma pigmentosum, Cockayne, Bloom, and Rothmund-Thomson syndromes, ataxia telangiectasia, Hartnup disease, and dyskeratosis congenita. In the first five of these, there is evidence of either abnormal mechanisms associated with DNA repair or synthesis, or RNA synthesis, or of features such as highly abnormal spontaneous sister chromatid exchange
   - C. Pellagra

III. Dermatoses, usually not associated with UVR, but liable to exacerbation or precipitation by solar exposure[2,3]

determine world prevalence in a relatively uncommon dermatosis, would necessitate a multicenter cooperative project. Some suggestive points, however, can be made.

PLE occurs essentially in places of mild temperate climate, e.g., in Europe, mostly in regions higher than about latitude 50° N, as in Holland, England, and Scotland, southern Scandinavia, and northern Germany; and in North America, near latitude 42° N upwards on the West and East Coasts. However, PLE does not seem to occur nearly as often in regions of similar latitudes in the Southern Hemisphere, as amongst the Europeans of South Africa. PLE is rare also in Australia and New Zealand.

PLE seems to be more common in the relatively pale-skinned people, as is evidenced by case collections written up by Haxthausen[9] of Copenhagen and by Wiskemann and Wulf[20] of Hamburg. It would be surprising if genetic pigmentation did not play a decisive protective role, and indeed, PLE is almost unknown in the natives of India.[21] Wiskemann and Wulf[20] had noted that their white-skinned patients failed to show the normal immediate pigmentation reaction in response to irradiation with UVA and wondered whether this had a causative role. However, PLE can occur in the very dark skinned, e.g., it occasionally has been described in Black Americans,[22] and in Central Africa, Verhagen et al.[23] noted a number of cases. In St. John's Hospital, London, nine cases of PLE among Asian immigrants have been seen in a period of about 15 years. The clinical picture in the cases the author saw is identical to that of the pale-skinned native.

An important part is played by seasonal changes in sunshine. Magnus[8] previously discussed this point when the apparent absence of PLE had been noted in parts of the

Table 4
AGE OF ONSET OF PLE IN TWO LARGE STUDIES

	0—10	11—20	21—30	31—40	41 and over
Dundee, Scotland	50%	23%	27% (21 years and over)		
London and southern England	9%	27%	33%	16%	15%

world that did not have marked seasonal changes in sunlight. Generally, the sun is more or less uniformly strong. This condition occurs in the southern U.S., e.g., Texas, parts of southern Africa, and Australasia. A proper survey of the prevalence of PLE in such geographical sites, where there is an Anglo-Saxon or Nordic population, would be valuable. If, as one suspects, PLE is rare or unknown in these regions, the relationship of this disease to the phenomenon of seasonal "hardening" or "habituation" in patients with PLE is of interest. Some earlier writers had noted the tendency of PLE to be less severe in many patients toward the middle and end of the sunny season; this suggests some kind of hardening process.

2. Prevalence

In the majority of cases, PLE does not seem to cause significant disability and probably many cases are too mild to attract dermatological consultation. It has been claimed, though seemingly on no ascertainable published authority, that including the very mildest cases, PLE may affect about one in ten of the population as a whole. This very high figure applies supposedly only to a racial stock predominantly Caucasian in mild, northern temperate climates. A proper survey on this would be valuable.

3. The Seasonal and Long-Term Course of the Disorder

PLE, as defined here, is commonly a relatively mild recurrent condition, occurring in short attacks each lasting several days. Sometimes there are individual attacks which reduce in number or cease before the middle or end of the sunny season, Thus, there may be season amelioration earlier than would be expected from the amount of sunlight available.

The long-term tendency for the disorder is for it to persist indefinitely; this has been shown by a follow-up study[24] on some 300 cases of PLE observed for varying times up to 30 years at St. John's Hospital, London. There was almost no predilection to the disease undergoing natural termination. Smaller surveys by others have given essentially the same result.

4. Age of Onset

This is very variable and is probably mostly due to variation in diagnostic criteria for PLE (see Table 4). Onset appears to be in an earlier group in Scotland, compared with the more general spread noted in England.

5. Sex Distribution

Wiskemann and Wulf,[20] Frain-Bell et al.,[25] Magnus,[8] and Jansén[26] all found female patients to be much commoner, approximately two to one. However, this is to be contrasted with the findings of Epstein,[22] who alone found the sex incidence about equal in his study of about 80 patients. There seems to be very little other data available in the literature on large studies of cases.

6. Family Prevalence

This seems to occur not uncommonly, but with what frequency it is difficult to say