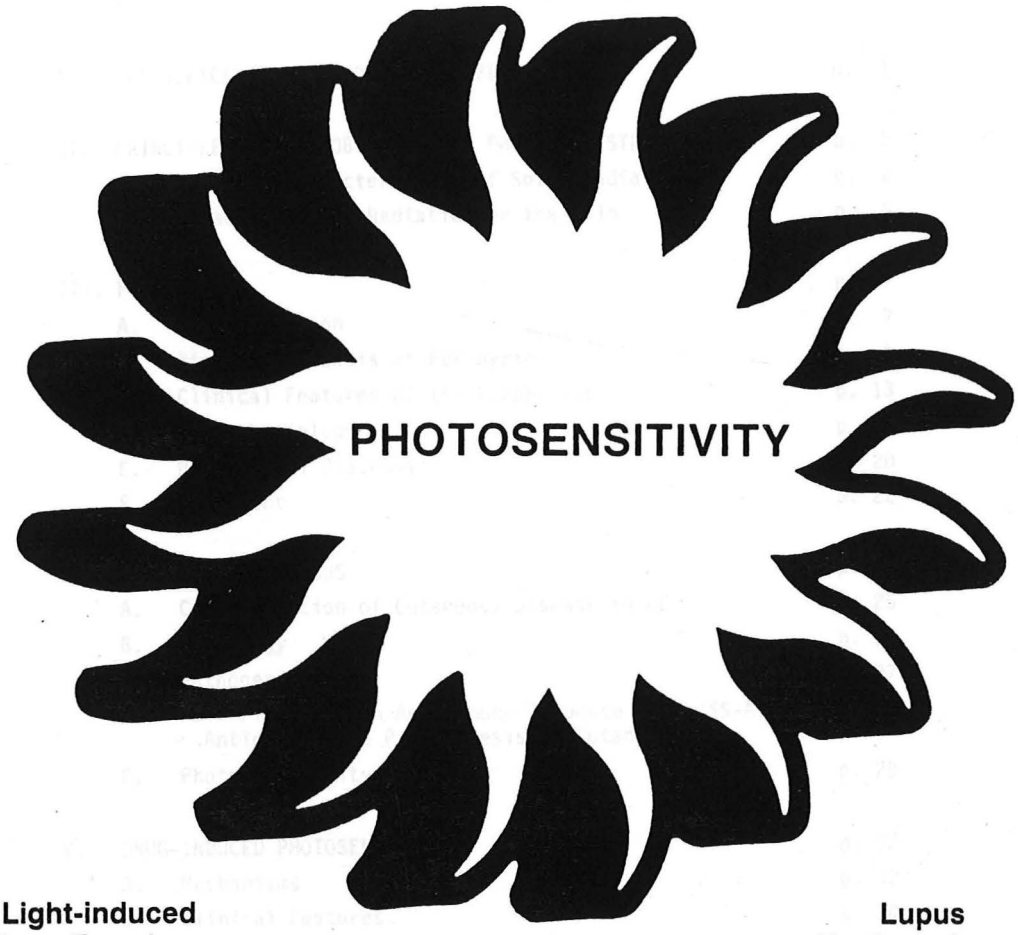
Porphyrias



Light-induced
Drug Eruptions

Lupus
Erythematosus

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I. CLASSIFICATION OF PHOTOSENSITIVITY DISEASES

There are a number of clinical disorders which are either induced or aggravated by exposure to natural sunlight or artificial sources of radiant energy. Table I lists one classification scheme for the photosensitivity diseases.

Table 1

CLASSIFICATION OF PHOTOSENSITIVITY DISEASES

Type	*Disease*
1. Genetic and metabolic	Xeroderma pigmentosum Erythropoietic protoporphyria Erythropoietic porphyria Erythropoietic coproporphyria Porphyria cutanea tarda Albinism Pellagra Kwashiorkor Hartnup disease
2. Phototoxic and photoimmunologic	(a) *Phototoxic* Internal (drugs) External (drugs, plants, fruits) (b) *Photoallergic* Solar urticaria* (immediate hypersensitivity) "Drug" photoallergy (delayed hypersensitivity)
3. Degenerative and neoplastic	Squamous cell carcinoma Malignant melanoma Actinic keratosis Basal cell epithelioma
4. Idiopathic	Polymorphous light eruption Hydroa aestivale Hydroa vacciniforme Actinic reticuloid Actinic prurigo
5. Photoaggravated	Discoid lupus erythematosus Systemic lupus erythematosus Dermatomyositis Herpes simplex Darier's disease Bloom's disease Acne vulgaris Atopic dermatitis Disseminated superficial actinic porokeratoses (DSAP) Hartnup disease Lichen planus actinicus Pellagra Pemphigus foliaceus Transient acantholytic dermatosis (TAD)

*Only one of the six types is definitely immunologic.

(Ref. #1)

Many of these entities are of interest only to the patient and his dermatologist. However, certain of these disorders have both cutaneous and systemic manifestations, and should thus be of interest also to the Internist. Table 2 lists those photosensitive disorders that an Internist is likely to encounter.

Table ?

PHOTOSENSITIVITY DISEASES OF INTEREST TO THE INTERNIST

Genetic and Metabolic

Porphyrias

Phototoxic and Photoimmunologic

Photo-induced drug eruptions

Degenerative and Neoplastic

Malignant melanoma

Photoaggravated

Lupus erythematosus
Dermatomyositis

It is my goal today to provide you with an overview of three of these disorders: porphyria, lupus erythematosus and photo-induced drug eruptions. This discussion will focus particularly on the mechanisms by which light energy triggers the clinical manifestations of these disorders. To effectively communicate our state of knowledge concerning these conditions, I must begin by reviewing certain principles of photobiology and photochemistry.

II. PRINCIPLES OF PHOTOBIOLOGY AND PHOTOCHEMISTRY

A. PHYSICAL CHARACTERISTICS OF SOLAR RADIATION.

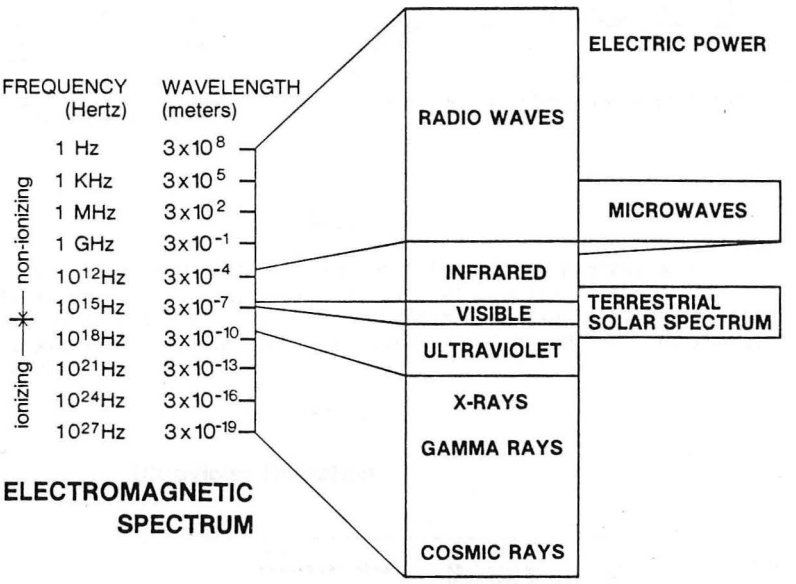
Solar energy can be conceptualized as radiation emanating from a solid, black body heated to a vapor stage by a temperature of approximately 6,000 degrees C. (1). At this temperature, an infinite number of wavelengths are emitted; the emission spectrum is thus called a continuous spectrum. The proportions of the wavelengths are temperature dependent; at the sun's present temperature, approximately 40-50% of the emitted light is visible and 40-50% is infrared, with ultraviolet radiation making up the remainder. Although solar radiation is relatively constant, the amounts reaching the earth's surface vary widely, owing to differences in altitude and latitude, atmospheric conditions, environmental pollution, and seasonal changes.

Light can be thought of as a wave form of electromagnetic energy which is defined by wavelength (λ) and frequency (ν) characteristics that can be related by the following equation:

$$C = \lambda \nu$$

where C is the speed of light (186,000 miles per second; 3×10^8 meters per second). Therefore, the wavelength of light is inversely related to the frequency. This reciprocal relationship between wavelength and frequency of electromagnetic radiation is a fundamental concept. Traditionally, electromagnetic radiation has been defined in terms of wavelengths because this property can be measured rather easily. A classification of electromagnetic radiation based upon wavelength and frequency can be seen in Figure 1.

Fig. 1



Electromagnetic spectrum can be described in units of either frequency (Hertz) or wavelength (meters). The terrestrial solar spectrum contains essentially non-ionizing radiation.

(Ref. #1)

As can be seen, the terrestrial solar spectrum represents only a small fraction of the electromagnetic spectrum. The portion of the electromagnetic spectrum which reaches the earth's surface is better illustrated in Figure 2.

Fig. 2

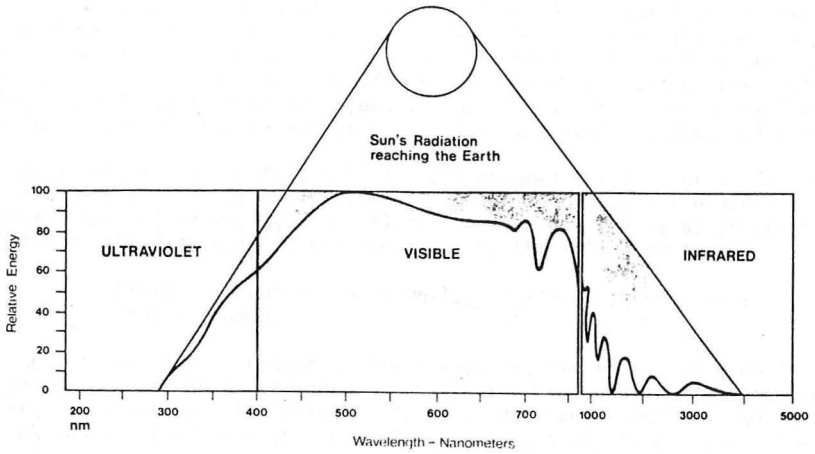
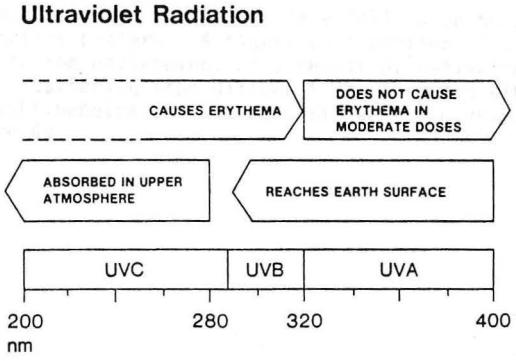


Figure 2–1. Electromagnetic radiation reaching the earth from the sun contains wavelengths from 290 nm to 4000 nm (long-wave infrared).

(Ref. #1)

The wavelengths of electromagnetic energy of the greatest medical and photobiologic importance fall into the ultraviolet portion of the spectrum predominantly and to a lesser degree in the visible portion. As can be seen in Figure 3, ultraviolet radiation can be divided into 3 broad bands of energy: UVC, UVB, and UVA.

Fig. 3



(Ref #1)

Although the shorter wavelength, higher energy UVC portion of the ultraviolet spectrum can produce significant biologic effects, this is of little clinical relevance since virtually all of this portion of the spectrum is absorbed in the ozone layer of the upper atmosphere. The UVB portion of the spectrum is predominantly responsible for inducing sunburn erythema and increase melanin production, and is the portion of the clinically relevant ultraviolet spectrum which is felt to be most injurious to the skin (skin cancer formation, premature aging). However, UVA wavelengths can also contribute to these clinical effects.

Another convenient way to think of electromagnetic radiation is to consider the possibility that light energy travels in individual discrete packets or quantum units (photons) of energy. Max Planck related the energy of an individual photon to the frequency of the radiation by the following formula:

Energy of Photon = H ν; where H = Planck's Constant (6.63×10^{-34} joule-second).

Since λ is inversely related to the frequency, the energy of a photon also equals h divided by λ. Therefore, the shorter the wavelength, the greater the energy of a photon. For example, twice as many white photons (800 nm each) as black photons (400 nm each) are needed to impart the same amount of energy.

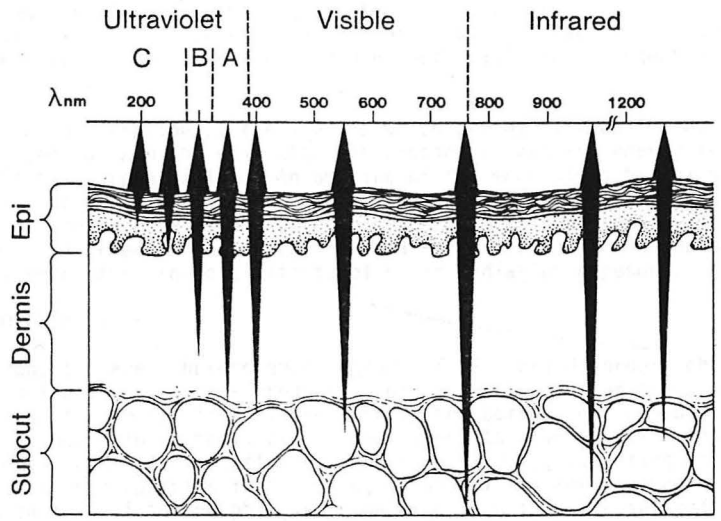
In clinical photobiology one is concerned with two characteristics of the radiation that effects biologic systems. One characteristic is the wavelength distribution, or the spectrum, of the radiation. The second characteristic is the amount, or dose, of radiation. The dose can be determined from measurements of the radiation's intensity or irradiance (power/area = watts/centimeter^2) Intensity can be easily measured with a radiometer. The dose can then be calculated by the following formula:

dose = intensity x time
dose = power/area x time
dose = watts x seconds/centimeter^2
dose = joule/centimeter^2.

B. IMPACT OF SOLAR RADIATION ON THE SKIN.

Solar radiation reaching the earth's surface falls upon human skin in a clinically distinctive pattern. A significant portion of light striking the skin is remitted to the environment as a result of reflection at the surface of the skin and back scattering from different compartments within the skin. The depth to which light penetrates cutaneous tissue is inversely related to the wavelength (Figure 4).

Fig. 4



Shorter, more energetic wavelengths of ultraviolet radiation (UVC and UVB) are absorbed primarily by the epidermis. Longer wavelengths (UVA and visible) penetrate to the lower dermis and to subcutaneous fat.

(Ref #1)

Approximately 90% of UVB energy is absorbed by the stratum corneum and epidermis whereas significantly greater proportions of longer wavelength UVA penetrate well into the dermis. Natural sunlight striking normal skin produces 2 major clinically evident physiologic responses: sunburn (erythema) and tanning (increased melanin pigment formation and distribution). Sunburn erythema is produced predominantly by UVB, and is mediated predominantly by increased prostaglandin formation within the skin. UVC can also induce erythema quite efficiently, however this is not relevant to natural sunlight-induced human sunburn. UVA is also capable of inducing an erythema reaction when delivered artificially in much higher doses than are routinely present in sunlight at the earth's surface. The mechanism of increased melanin pigment formation by ultraviolet radiation appears to involve two types of reactions: 1) new tyrosinase and new melanin synthesis, which leads to delayed tanning, and 2) activation of previously synthesized melanin pigment, which produces immediate tanning. New melanin synthesis is triggered predominantly by UVB while UVA contributes greatly to immediate tanning.

The first law of photochemistry states that only absorbed light can cause a photochemical change. Thus for light to trigger a clinical response in the skin it must be absorbed at the molecular level. As a result of absorption, the energy of a photon is taken up by a molecule and the photon ceases to exist. Different molecules in the skin have characteristic light absorbing properties. Thus the absorption spectrum of a given molecule is defined as the summation of

the probabilities with which it absorbs various light wavelengths. This is to be contrasted to the action spectrum of a certain photo-induced disease process: the summation of those wavelengths which trigger the pattern of clinical response. The action spectrum of a photosensitive disease is often a clue to the identity of the cutaneous molecule responsible for triggering the disease process.

A detailed description of the ways in which energy is transferred between compartments within the skin after absorption of radiant energy is beyond the scope of this presentation. An outline of the mechanisms by which some of these processes occur is presented in the discussion of the mechanisms of cutaneous injury in the porphyrias discussed elsewhere in this protocol. The stimulated reader is referred to references #1 - #3 for a more detailed and documented discussion of the biologic effects of solar radiation exposure.

III. PORPHYRIAS

The porphyrias are a heterogeneous group of clinical disorders characterized by a common finding of excess production of porphyrins and/or their precursors which result from specific alterations in the pathway of heme biosynthesis. The defect in heme biosynthesis can be due either to a genetically based emzymatic deficiency or drug/toxin effects. Photosensitivity, resulting from the action of light upon porphyrins in the skin, is one of the most common clinical manifestations of the porphyrias. The exception is acute intermittent porphyria, a disorder where photo-inactive porphyrin precursors are produced in excess rather than photo-excitable porphyrins.

A. CLASSIFICATION

Porphyrias have been traditionally classified as either hepatic or erythropoietic, depending upon the primary site of porphyrin overproduction. (Table 3).

Table 3

CLASSIFICATION OF THE PORPHYRIAS*

Erythropoietic	Erythropoietic porphyria (uroporphyria; Günther's disease)
	Erythropoietic protoporphyria
	Erythropoietic coproporphyria
Hepatic	Porphyria cutanea tarda
	Acute intermittent porphyria
	Variegate or mixed porphyria
	Hereditary coproporphyria

(Ref. #1)

This classification scheme has been challenged recently by the realization that some porphyric patients appear to have equivalent degrees of heme synthesis abnormalities in both the erythroid and hepatic compartments. Other workers have more recently suggested that porphyria might be best classified into acute and non-acute types, based upon the presence or absence of the acute attack where associated neurologic and psychologic disturbances are coupled with hugh increases in the production and excretion of porphyrin precursors (Table 4).

Table 4

Classification of Porphyria

Acute intermittent porphyria (Intermittent acute porphyria)	Acute porphyrias
Variegate porphyria (Porphyria variegata)	
Hereditary coproporphyria (Harderoporphyria)	
Plumboporphyria (ALA dehydratase-deficient porphyria	
Porphyria cutanea tarda (Symptomatic porphyria, cutaneous hepatic porphyria)	Non-acute porphyrias
Erythropoietic protoporphyria (Erythrohepatic porphyria)	
Congenital erythropoietic porphyria (Gunther's disease)	

(Ref. #4)

Another approach which I have found useful is a system of classification based upon the type of cutaneous involvement present. This classification system includes three categories: 1) acute cutaneous flare pattern, 2) vesiculo-bullous/erosive/scarring pattern, 3) no cutaneous disease. The pattern of skin involvement appears to depend greatly upon the lipid/water partition co-efficients of porphyrins which accumulate in the skin (5) (Table 5).

Table 5

CLASSIFICATION OF PORPHYRIA BASED UPON CUTANEOUS ABNORMALITIES

Acute Cutaneous Flare Pattern
- Erythropoietic protoporphyria (erythrohepatic protoporphyria)

Vesiculo-Bullous/Erosive/Scarring Pattern
- Porphyria cutanea tarda (symptomatic porphyria)
  - Hepatoerythropoietic porphyria (homozygous PCT)
- Congenital erythropoietic porphyria (Gunther's Disease)
- Variegate porphyria
- Hereditary coproporphyria (harderoporphyria)

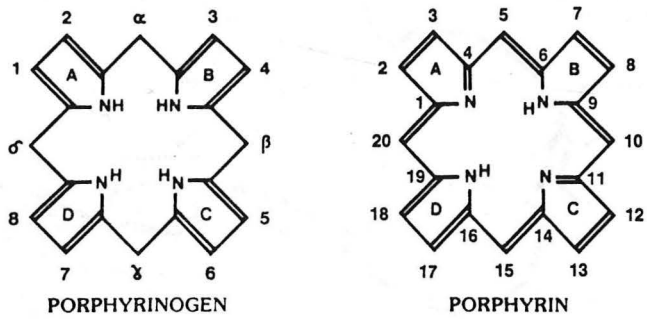
No cutaneous manifestations
- Acute intermittant porphyria
- Plumboporphyria

B. BIOCHEMICAL BASIS OF PORPHYRIAS

1. Structure and function of porphyrins.

Porphyrins are found ubiquitously in nature, their principle role being the control of biologic oxidation and oxygen transport. The basic porphyrin nucleus is a unique biologic structure consisting of a macrocycle of 4 pyrrole rings linked by 4 methine bridges (Figure 5).

Figure 5



(Ref. #4)

This is a rigid planar structure onto which 8 side chains can be attached at positions 1 to 8 in the Fischer nomenclature. The type of side chain determines the physical characteristics of the porphyrin. The normal biologic intermediate is not this highly conjugated porphyrin, but the hexahydro-porphyrin, porphyrinogen, in which each of the methine bridges is reduced. Porphyrinogens are colorless and unconjugated compared with the conjugated and brightly colored porphyrins, which fluoresce in light around 400 nm.

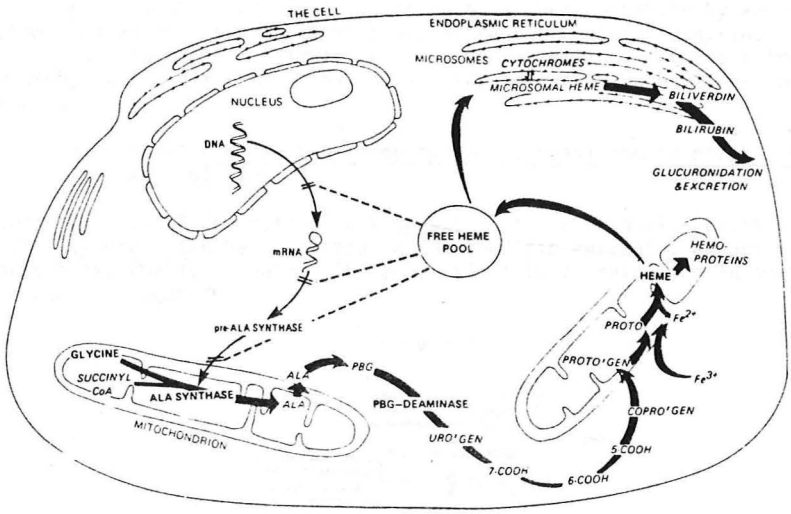
An important attribute arising form this complex ring structure and the available ligand binding sites within it, is their capacity to bind metals, the most common being iron and magnesium. Heme, an iron-containing complex usually bound to various proteins, is central to all biologic oxidations, especially those associated with drugs. In addition, heme is also an efficient oxygen carrier. The chlorophylls are the magnesium-porphyrin compounds, which are central in solar energy utilization in the biosphere.

In addition to the systematic formation of porphyrins by biological systems, abiotic synthesis has been described (6-7) in which a primitive chemical system has produced porphyrin-like compounds through the high entropy of their formation. Such synthesis is important in the ontogenesis of terrestrial life, since it would have facilitated the emergence of life forms by increasing the efficiency of oxido-reductive processes.

2. Normal pathway of heme synthesis.

Figure 6 illustrates our current understanding of the normal pathway of heme biosynthesis.

Figure 6



(Ref. #4)

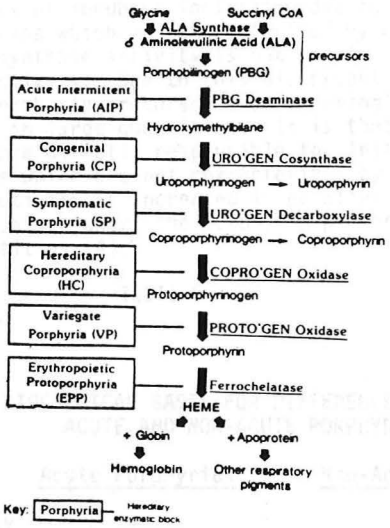
The rate limiting enzyme in heme synthesis is delta-aminolevulinic acid (ALA) synthase. The synthesis of this enzyme is under feedback control at the transcriptional and translational levels by the free heme pool within the cell. ALA synthase catalyzes the condensation of glycine and succinyl Co-A within the mitochondrion to form the compound delta-aminolevulinic acid (ALA). This reaction requires pyridoxal phosphate as a cofactor. The activity of ALA synthase may be markedly altered by various drugs and foreign compounds, including lead. Delta-aminolevulinic acid is then transported into the cytoplasm where, in the presence of ALA dehydratase, it is converted to the monopyrrole, porphobilinogen. Defective ALA dehydratase activity has been linked to a rare form of porphyria, plumbo porphyria (8-9). In normal systems, 2 other cytoplasmic enzymes, porphobilinogen deaminase and uroporphyrinogen 3 co-synthase, act in concert to condense 4 molecules of porphobilinogen to hydroxymethylbilane and cyclize them to form the first of the porphyrins, uroporphyrinogen III. The importance of this combined reaction is that the tetrapyrrole produced in normal biologic sequence is not the symmetrical uroporphyrinogen I, but the assymetrical uroporphyrinogen III because the normal limiting enzyme of the paired reaction is PBG deaminase. Uroporphyrinogen III but not uroporphyrinogen I can proceed past the stage of coproporphyrinogen in the biosynthetic sequence that will form heme. At this stage in the reaction sequence, the basic structure of the porphyrins has been produced and all that remains before iron is inserted to form heme is that a series of decarboxylations and oxidations take place to form protoporphyrin. The first of

these decarboxylation sequences is catalized by uroporphyrinogen decarboxylase. In this sequence, 4 moles of carboxyl are lost from every mole of porphyrinogen between the octacarboxylic uroporphyrinogen and tetracarboxylic coproporphyrinogen. Coproporphyrinogen then reenters the mitochondrion where it is further decarboxylated by the enzyme coproporphyrinogen oxidase to form the compound, protoporphyrinogen. This compound is then converted by another mitochondrial enzyme, protoporphyrinogen oxidase, to protoporphyrin. The last step of this biosynthetic pathway involves the insertion of ferrous iron into protoporphyrin to form heme. This final step is catalyzed by the enzyme ferrochelatase.

3. Genetic defects of heme synthesis resulting in porphyrin accumulation.

Our current level of understanding suggests that the metabolic basis of each porphyric syndrome can be localized to one specific enzymatic abnormality within the heme biosynthetic pathway. The enzymatic defects resulting in porphyria are illustrated in Figure 7.

Figure 7



The enzymatic blocks in the porphyrias. The rare variants, plumboporphyria and harderoporphyria, are affected at the levels of ALA dehydratase and the second stage of coproporphyrinogen oxidase, respectively.

(Ref #4)

Most of the porphyrias are inherited as Mendelian, autosomal-dominant characters with one, congenital erythropoietic porphyria, inherited as a mendelian recessive and another, porphyria cutanea tarda, existing in two forms: a

heriditary and an acquired disease. The question of whether homozygous acute porphyria would be lethal has often been raised. Current knowledge would suggest that this is not the case. Homozygous cases of hereditary coproporphyria (10) and familial porphyria cutanea tarda (also referred to as hepatoerythropoietic porphyria) (11-12) have been described and it is probable that cases of plumbo porphyria represent homozygous alterations of ALA dehydratase (8-9). No genetic advantage has every been identified for the porphyrias. The disease incidence of acute intermittent porphyria remains relatively constant throughout the mixed white population in the world at 1-2/100,000 (13). There are however, "hot spots" of the disease that usually can be related to intermarriage in a geographically stable population. The high incidence of variegate porphyria in South Africa, with a rate calculated as high as 1/400 of the white population or acute intermittent porphyria in Lapland, 1/1,000 of the population, are such examples.

4. Enzymatic differences between the acute and nonacute porphyrias.

The presence or absence of acute neurologic and psychologic attacks associated with large increases in the production and excretion of the porphyrin precursors, delta-aminolevulinic acid and porphobilinogen, form the basis of one popular classification scheme for porphyrias. Some insight into the biochemical basis for the presence or absence of the acute attack has been recently gained. As can be seen in Table 6 ALA synthase activity is increased in all forms of porphyria, oweing to the lack of feedback inhibition due to a subnormal free heme pool. In those porphyrias which are characterized by an acute neurologic attack, this increased ALA synthase activity is not coupled to an increased porphobilinogen deaminase activity. Due to this discordant expression of enzymatic activities, the porphyrin precursors, delta-aminolevulinic acid and porphobilinogen, accumulate in large quantities. It is these high levels of porphyrin precursors which are directly responsible for initiating the acute attack. In those porphyrias which are not characterized by the acute attack, porphobilinogen deaminase activity is increased in parallel to ALA synthase activity resulting in a situation where the porphyrin precursors do not accumulate in abnormal quantities (4).

Table 6

BIOCHEMICAL BASIS FOR DIFFERENCES BETWEEN ACUTE AND NON-ACUTE PORPHYRIAS

	Acute Porphyrias	Non-Acute Porphyrias
ALA Synthase Activity	↑	↑
PBG Deaminase Activity	N or ↓	↑
ALA and Porphobilinogen	↑	N

(Adapted from ref. #4)

C. CLINICAL FEATURES OF THE PORPHYRIAS

The clinical findings in the various forms of porphyria are summarized and compared in Table 7.

Table 7

Clinical Features of the Porphyrias and Porphyrinurias

	Inheritance	Usual Age of Onset	Acute Photo-sensitivity	Mechanical Dermatosis	Acute Attack	Other Features
Acute porphyrias						
AIP*	Dominant	Puberty to 30	0†	0	+	0
VP	Dominant	Puberty to 30	+	+	+	0
HC	Dominant	Puberty to 30	+	+	+	0
Non-acute porphyrias						
PCT (A)	0	Over 40	++	+	0	Alcoholic liver disease
PCT (F)	Unclear	Any age	++	+	0	Liver damage
PCT (N)	0	Over 50	++	+	0	Neoplasm
EPP	Dominant	Under 10	++	+	0	Liver disease Cholelithiasis
CP	Recessive	From birth	++	++	0	Hemolytic anemia splenomegaly
Porphyrinurias						
Lead poisoning	0	All ages	0	0	+	Anemia
Iron deficiency anemia	0	All ages	0	0	0	Anemia
Tyrosinemia	Recessive	From birth	0	0	+	

*AIP—Acute intermittent porphyria; VP—Variegate porphyria, HC—Hereditary coproporphyria; PCT—Porphyria cutanea tarda; (A)—acquired, (F)—familial, (N)—from neoplasm; EPP—Erythropoietic protoporphyria; CP—Congenital erythropoietic porphyria.
†0—never present; +—usually present; ++—present.

(Ref #4)

As can be seen, a number of these disorders are characterized by hepatic and hematologic abnormalities. The diagnosis and management of the hematologic, hepatic and acute neurologic manifestations of the porphyrias was addressed in these Grand Rounds by Dr. Rainer N. Zahlten on June 4, 1981. I would therefore at this time like to focus particularly on the cutaneous manifestations of the porphyrias particularly with regards to the role played by solar radiation.

The cutaneous manifestations of the porphyrias can be divided into two categories: 1) The acute cutaneous flare pattern and, 2) the vesiculo-bullous/erosive/scarring pattern. It is generally felt that the acute cutaneous flare pattern results from the accumulation in the skin of more lipid soluble compounds such as protoporphyrin while the vesiculo-bullous/erosive/scarring pattern results from increased skin levels of the more water soluble porphyrins such as uroporphyrin (5).

1. Acute cutaneous flare pattern.

The acute type of porphyrin-mediated phototoxicity occurs most often in patients with protoporphyria (14-15) although it has also been described in patients with other forms of porphyrias who have unusually severe disease and/or who are

exposed to prolonged intense light radiation (16-17). The acute cutaneous flare reaction occurs rather quickly after exposure to light, usually developing within minutes or hours after the onset of exposure. Patients initially note stinging, prickling or burning sensations in their exposed skin. The amount of light exposure necessary to elicit this reaction varies from patient to patient, and from day to day in the same patient. Patients who experience this pattern of cutaneous reaction often note that they are particularly susceptible to severe reactions after small amounts of exposure if they have had sufficient exposure to begin "feeling" the reaction on the preceeding day. Because of this, many protoporphyric patients routinely avoid light exposure on sequential days, knowing that they will again have an increased tolerance after 2 to 5 days of no exposure. If light exposure is prolonged, the skin becomes diffusely edematous within hours. The swelling is usually accompanied by an intense burning pain deep in the skin, which may persist for several hours or occasionally as long as several days. Vesicles and crusted erosions occur only infrequently, chiefly involving the face or hands. The painful edema resolves spontaneously over several days, leaving blotchy petechiae, and occasionally purpura which tends to fade slowly. This pattern of skin reactivity is identical in its morphology and temporal development to the photo-induced skin reactions experienced by individuals who have been artificially sensitized by the administration of hematoporphyrin (18). Hematoporphyrin, a tetrapyrrole derived from acid-treated hemoglobin, has been used in a phototherapy protocol to treat certain tumors, since this compound partitions somewhat selectively to tumor tissue. Patients deliberately sensitized with hematoporphyrin and inadvertently exposed to sunlight have suffered severe, acute phototoxic eruptions.

Erythropoietic protoporphyria is by far the most common form of porphyria in which the acute cutaneous flare pattern is seen. This autosomal dominant disorder is linked to defective ferrochelatase activity (19-20), and as a result, protoporphyrin, the 2-carboxylic, lipophilic immediate precursor of heme, accumulates in several distribution compartments, notably erythrocytes, plasma, liver, bile and feces. The lipophilic nature of protoporphyrin requires its excretion by hepatobiliary mechanisms rather than renal excretion. Protoporphyria is by far the most common of the porphyrias whose major site of porphyrin hypersynthesis is the bone marrow. Individuals with protoporphyria begin to experience during childhood or the early teens typical symptoms of the acute cutaneous flare pattern. Protoporphyric patients also develop chronic skin changes, however these changes tend to result in much less disfigurement than is seen in other forms of porphyria. These changes for the most part consist of shallow, elliptical or linear pits on the forehead, nose, cheeks and perioral skin. Occasionally the skin over the nose, cheeks and forehead develops a roughened, pebbly texture. Hyperkeratotic, thickened skin with a waxy, pebbly, leathery texture is seen most impressively on the dorsal aspects of the hands, giving a prematurely aged or weatherbeaten appearance. These changes are more pronounced over the metacarpophalangeal and interphalangeal joints. Severe scarring, large bullae, hypertrichosis, and milia are rarely ever observed in patients with protoporphyria. The most significant extracutaneous manifestation of erythropoietic protoporphyria is the early onset of cholelithiasis and, less frequently, progressive hepatic dysfunction. Fatal hepatic failure has occurred unpredictably in approximately 10-15% of these patients.

2. Vesiculo-bullous/erosive/scarring pattern.

Vesicles and bullae are the primary lesions seen on the sun-exposed skin surfaces in this pattern of porphyric photosensitivity. These bullous lesions are typically non-inflammatory and are easily ruptured to form erosions which commonly become secondarily infected giving a crusted appearance. Milia (small 1-2 mm hard yellow-white papules) are also frequently seen in areas of vesiculation and erosion. The crusted erosions heal with scarring. The non-involved skin in these areas is very fragile, often rupturing with only minimal trauma. Patients are commonly seen to have vesicles, bullae, erosions, crusts, scars and milia in all stages of development at the same time. Patients with this pattern of porphyric photosensitivity also frequently develop facial hypertrichosis particularly on the periorbital and upper cheek areas. A mottled brown, purple, blackish discoloration of the facial skin is also frequently seen in such patients. This hyperpigmentation is due to increased melanin deposition and has occasionally been sufficiently dark and widespread as to resemble the pigmentary changes of Addison's Disease or hemochromatosis. Scarring alopecia can be severe in such patients. Approximately 15% of patients with this cutaneous reaction pattern will eventually develop sclerodermoid plaques (21), which occasionally are the only skin abnormalities noted. These scleroderma-like skin lesions can be seen not only on the areas exposed to sunlight, but also on relatively light protected sites such as the anterior chest and back and at times have become generalized. Dystrophic calcification can also be seen in patients who are chronically affected by this porphyric cutaneous reaction pattern.

The vesiculo-bullous/erosive/scarring pattern is seen most commonly in patients with porphyria cutanea tarda, the disorder of porphyrin metabolism most commonly seen in dermatologic practices in North America and Europe. However as noted in Table 6, this cutaneous reaction pattern is also seen in variegate porphyria, hereditary coproporphyria, congenital erythropoietic porphyria, and hepatoerythropoietic porphyria.

Acute phototoxicity is quite uncommon in patient with this type of cutaneous reaction pattern. More commonly, these patients have little or no awareness of discomfort during light exposure. Such patients will generally be aware that their disease is worse during the sunnier seasons of the year but some will fail to recognize any association between sun exposure and their skin disorder. The most frequent complaint of patients with this reaction pattern is that their skin has become more fragile. This is manifested by a shearing away of a layer of skin (the entire epidermis) with minimal trauma. The resulting denuded dermal erosions are painful and heal slowly, oozing serum that forms heavy crusts which eventually heal with scarring.

Porphyria cutanea tarda is the only porphyric syndrome that appears to have both inherited and acquired forms. In all cases, the defective enzyme of heme biosynthesis is the same: uroporphyrinogen decarboxylase (22-23). This enzymatic defect results in the accumulation of increased levels of uroporphyrinogen, and 8-carboxylic, hydrophilic intermediate of heme metabolism. Many cases are clearly examples of a genetic defect inherited in an autosomal dominant fashion (24-26). Whether sporadic cases represent the inheritance of a predisposition to overtly express disease after exposure to an acquired factor is not known. It is clear, however, that a number of factors can trigger the identical biochemical and clinical abnormalities seen in genetically determined

PCT. Such agents include alcohol ingestion (27-28) estrogen therapy (27-28), and exposure to various polychlorinated aromatic hydrocarbons (29-30). The primary site of the overproduction of carboxylated porphyrins in PCT is the liver. The porphyrins formed in the liver are released into the plasma, which transports them to other distribution compartments, particularly the skin.

D. PATHOPHYSIOLOGY

1. Pathology

Histologic data indicates that the bulk of acute and chronic porphyric phototoxic skin damage is concentrated in the upper dermis and lower epidermis in all forms of porphyrias. The epidermal basement membrane zone and the upper dermal blood vessels appear to be the specific sites of injury in all forms of porphyria. However the degree of injury in these two areas does varies somewhat between the different types of porphyria (5). In porphyria cutanea tarda lesions, the prototype of the vesiculo-bullous/erosive/scarring injury pattern, damage is particularly severe at the dermal-epidermal junction and in the lower layers of the epidermis. There is reduplication of the epidermal basal lamina resulting in homogeneous thickening of the dermal-epidermal zone. IgG deposition in this thickened basal membrane zone can be routinely observed. Dermal-epidermal junction separation resulting in subepidermal bullae formation occurs regularly in this pattern of reaction, very often in the complete absence of inflammatory cells. In addition, condensation of basal cell cytoplasm, damaged subcellular organelles, and loss of continuity between the lateral membranous walls of the basal cells has been observed. Homogeneous thickening of the upper dermal blood vessel walls is also seen in this disorder but to a lesser degree than as seen in other forms of porphyria, such as erythropoietic protoporphyria. These thickened dermal vascular walls contain mucopolysaccharides and immunoglobulins. Ultrastructurally this thickening consists of finely fibrillar material surrounding the dermal blood vessels with associated reduplication of the vascular basal laminae. In erythropoietic protoporphyria, the prototype of the acute cutaneous flare pattern of porphyric skin injury, the dermal vascular wall abnormalities are present to a greater degree and the dermal-epidermal junctional changes are present to a lesser degree than is seen in porphyric cutanea tarda lesions. Sequential histopathologic and ultrastructural studies of experimentally induced porphyric skin lesions suggest the following mechanism of injury (31). The prime event appears to be damage to the endothelial cells resulting from photo-induced activation of plasma derived porphyrins located near endothelial cell lysosomes. Next, leakage of plasma and erythrocytes ensues through the damaged vessel wall. Finally, phagocytosis of plasma or erythrocyte porphyrin into fibroblasts could cause some photochemical alterations that induce the fibroblasts to synthesize and excrete the amorphous substance into the surrounding dermis. It has also been suggested that the masses of amorphous material found in the dermis have their origins in extravasated intravascular contents and cell debris, rather than in synthesis of this substance by fibroblasts. A similar process of phototoxic injury also occurs in the epidermal basal cell layer resulting in the fragility of this region and the basement membrane zone abnormalities that have been observed.

2. Porphyrin deposition in skin.

It has been well documented that porphyrins do accumulate to excessive degrees in the skin of patients with various forms of porphyria. This has been found to

be the case with fluorescence microscopic studies (32) and by quantitative determinations (33). While there has been some debate as to whether the porphyrins are delivered to the skin via the circulation or are synthesized locally within the skin, the majority opinion at this time would favor the former possibility.

3. Action spectrum.

The action spectrum for the development of erythema and edema in the skin of patients with several forms of porphyria have been determined. Maximal skin reactivity has been shown to occur as a result of exposure with 400-410 nm wavelength light for patients with all forms of porphyria (14, 34-35). The fact that the action spectrum for inducing porphyric skin lesions peaks at precisely the same wavelengths as the most intense absorption bands of all the photoactive porphyrins strongly supports the thesis that porphyrin-sensitized photochemical events are directly responsible for the gross and microscopic tissue damage in light exposed skin of patients with all forms of porphyria having photocutaneous manifestations.

4. Porphyrin induced phototoxic cellular injury.

The photochemical reactions mediated by porphyrins within the skin appear to be examples of energy transfer processes in which singlet-or triplet-excited state porphyrin molecules that are first created by absorption of visible light energy then donate a portion of their absorbed energy to other "acceptor" molecules. The acceptor molecules, which are thought to be involved in these reactions in the skin, include molecular oxygen and various components of the complex biomolecules forming cutaneous structures. The exact mechanism by which the excited-state porphyrins effect the damage to the skin in vivo remains largely theoretical. There is however considerable evidence to suggest the involvement of oxygen as an important intermediary in the chain of reactions. There is in vitro experimental data to support the following scenario. Triplet-excited porphyrin molecules possess adequate amounts of excitation energy to act as donors to ground-state oxygen acceptor molecules (36-37). This energy transfer results in raising the oxygen to the singlet-excited state. Singlet-excited oxygen is a short-lived but highly reactive species, and appears to be the active oxidizing agent in many porphyrin-sensitized photo-oxidation reactions. Singlet oxygen is a powerful oxidizing agent in vitro for many compounds of biologic importance including lipids (38-39), cholesterol (40-41), and amino acids (42-43), particularly histidine, methionine, tryptophan, cystine, and tyrosine. Porphyrin-sensitized, oxygen-dependent mechanisms have been implicated in the peroxidation of cell membrane lipids (38-40), cross linking of cell membrane and intracellular proteins (42, 44), inhibition of cell membrane associated cytosolic and mitochondrial enzymes (45-46), loss of membrane integrity and function (44), disruption of intracellular organelles (45-47), and cell death (48-49). In the biomolecular systems of the skin, propinquity of oxygen, porphyrins, and the appropriate target molecules appears to be sufficient to enable such sequences of energy transfers to occur in vivo, with the ultimate result of acute and chronic damage to the structural and functional integrity of its vital elements. Photodynamic reactions sensitized by porphyrins may also proceed by mechanisms involving electron transfer and free radical formation, such as formation of the superoxide radical.

Since all the photoactive porphyrins that accumulate in the different porphyrias have the potential of initiating photoxidative chemical reactions in the skin by

the same general mechanisms, the question naturally arises as to why patients with different forms of porphyria do not manifest cutaneous lesions of uniform morphology. The probable explanation of the this phenomenon appears to lie in the wide differences in the physiochemical properties of the various types of porphyrin molecules which accumulate in excess in each of the porphyric disorders. Porphyrin compounds become progressively more hydrophilic as the number of carboxyl side groups increases. The uroporphyrin molecule, with 8 such carboxyl groups, is the most water soluble porphyrin. Water solubility decreases as the numbers of carboxyl groups decrease. The 4 carboxilic compound, coproporphyrin has an intermediate solubility and the 2 carboxilic compound, protoporphyrin, is quite insoluble in water. These solubility differences might well relate to differences with which these compounds partition in cutaneous tissue. The weight of evidence would suggest that the more lipophilic porphyrin, protoporphyrin, localizes particularly to the lipoprotein membranes of dermal capillary endothelial cells. Thus, light exposure would produce endothelial cell injury as a primary event. There is considerable data which would suggest that the dermal vasculature is the primary target of injury in prophyric states where the more hydrophobic porphyrins accumulate in access, such as erythropoietic protoprophyria. The more hydrophilic porphyrins, according to this theory would be less attracted to lipophilic membrane sites and would therefore be expected to be less efficient sensitizers of membrane-related adverse events. Thus the more hydrophilic porphyrins, such as those present in excess in porphyric cutanea tarda, would be less likely to produce primary endothelial cell damage. These more water soluble porphyrins would have freer access to the dermal-epidermal junction and epidermal basal cell layer where they might affect phototoxic injury after light exposure. An alternate possibility would be that the more water soluble porphyrins are actually synthesized de novo in the vicinity of the lower epidermis and dermal-epidermal junction, thus preferentially photosensitizing these structures. Thus, it would appear that the accumulation of porphyrins in living tissues is chiefly determined by some combination of the site of porphyrin synthesis and the partitioning of porphyrins within tissues to which they are distributed according to the hydrophobicity or hydrophilicity of the target site. Since the photochemistry of porphyrin-sensitized oxidative damage to the target molecules appears to be similar for all of the 2-8 carboxilic oxidized tetrapyrrole by products of heme synthesis, it is probably the different sites in which they tend to partition and the relative efficiency of the production of photodynamic toxicity at the molecular level in these sites that determines the different morphologies and temporal evolution of the skin lesions (5).

5. Contribution of secondary mediators of inflammation.

a. Lysosomal enzymes.

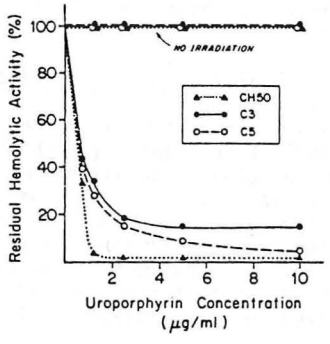
Earlier studies of the contribution of secondary mediators of inflammation to the evolution of porphyric phototoxicity focused on the role of lysosomal hydrolases. It was shown that exogenous uroporphyrin was concentrated by lysosomes of mammalian cells in tissue culture, and that lysosomal acid phosphatase was released into the cytosol after exposure of the cells to 400 nm light radiation (47). Exogenous protoporphyrin was also shown to be accumulated in the lysosomal regions of human fibroblasts that were lethally photosensitized and died after exposure to ultraviolet radiation. These data suggest that release of lysosomal enzymes might contribute to the full development of the clinical phototoxic responses seen in patients with porphyrias. However, more

recent studies have indicated that lysosomal damage is not likely to be either the initial event or the major determinant of cytotoxicity in vivo (46, 49).

b. Complement activation.

A second important inflammatory pathway that has been implicated as a participant in the pathogenesis in porphyric skin lesions is the complement cascade. Involvement of complement in the reaction pattern was initially suggested by the frequent observation of C3 deposition at the dermal-epidermal junction and in and around the thickened upper dermal capillary walls in the skin of patients with different forms of porphyria (50). More recently it has been shown that the addition of uroporphyrin (51), protoporphyrin (52), and hematoporphyrin (53) to human sera, and mixed porphyrins to guinea pig serum (54) followed by exposure of the sera to sources of ultraviolet and visible light radiation consistently produced porphyrin concentration-dependent decreases in the titer of total hemolytic serum complement activity (Figure 8).

Figure 8



Effect of serum concentration of uroporphyrin on total hemolytic complement (CH50), C3, and C5 activities.

(Ref. #51)

Generation of C5-derived chemotactic activity for polymorphonuclear leucocytes has been demonstrated in irradiated sera from patients with protoporphyria and porphyria cutanea tarda (51) and in normal human serum sensitized with exogenous uroporphyrin (55). Human serum genetically deficient in C4 that had been sensitized with the addition of uroporphyrin did not yield C5-derived chemotactic activity after irradiation, indicating that the uroporphyrin-sensitized photoactivation of the complement cascade proceeds by way of the classical pathway (55). Studies have also shown that C5-derived chemotactic activity is also generated in vivo in patients with porphyria who are exposed to long wave ultraviolet invisible light (56). These data clearly support an active role for complement-derived peptides in evoking the acute signs and symptoms of porphyric phototoxicity. Vascular permeability, pain, dermal edema, and recruitment of polymorphonuclear leucocytes in the dermis of

patients with porphyrias exposed to the appropriate wavelength of light could well be augmented by complement-mediated mechanisms.

E. BIOCHEMICAL DIAGNOSIS

When entertaining a diagnosis of porphyria, several things should be kept in mind prior to collecting samples for laboratory analysis. As a group of compounds, porphyrins and their precursor, porphobilinogen are not terribly stable compounds. Porphobilinogen will polymerize spontaneously in acidic conditions, and it has been recommended that urine be collected at neutral pH. Porphyrins are unstable in daylight and are therefore best collected and stored in low light conditions. Urine, for instance, is best collected in brown bottles.

The basic principle behind porphyrin quantitation resides in its ability to absorb light at wavelengths of around 400 nm. This peak of absorption in solution is called the "Soret" band. The absorption spectrum of porphyrins can vary significantly with respect to the relative acidity or alkalinity of the solutions in which they are contained. The most characteristic feature of porphyrins however is their bright red fluorescence. Parallel to the energy absorption of 400 nm, there is reemission of wavelength-shifted light, as red fluorescence at around 600 nm. This property of porphyrins can be used to rapidly screen clinical specimens for elevated porphyrin levels qualitatively (57).

1. Qualitative screening for porphyrins.

To detect abnormal levels of porphyrin in the urine, a solution should be prepared with equal volumes of diethyl ether, amyl alcohol, and glacial acetic acid. Five ml of urine and 3 ml of the above solution are then mixed well in a stoppered test tube, centrifuged to separate the layers, and examined in ultraviolet light of approximately 400-410 nm wavelength (Woods light) for red porphyrin fluorescence. A similar procedure may be applied to fecal samples, blood and other tissues. Elevated protoporphyrin levels in red cells obtained from peripheral blood or bone marrow aspiration can be detected qualitatively by their characteristic red-pink fluorescence under ultraviolet light microscopy.

2. Qualitative screening for porphobilinogen.

As has been previously noted, the most consistent change in the acute porphyrias is the overproduction of porphobilinogen and 5-aminolevulinic acid. The Watson-Schwartz test can be used at the bedside to rapidly identify elevations in porphobilinogen levels qualitatively. Equal volumes of urine and Ehrlich's reagent [2 gm of 4-dimethylaminobenzaldehyde made up to 100 ml with hydrochloric acid (6 moles per liter)] are mixed in a test tube. A pink coloration indicates the presence of an Ehrlich's positive pyrrole. This may be identified as porphobilinogen by the addition of 2 volumes of chloroform; the mixture is shaken and allowed to stand. If the pink coloration is extracted from the chloroform (the lower layer), this is not porphobilinogen but urobilinogen. When urobilinogen concentrations are high, it may be necessary to decant the upper layer and repeat the extraction with chloroform in order to remove all the pigment due to urobilinogen (57).

The changes in porphyrins and enzymatic activities in the porphyrias and porphyrinurias is shown in Table 8.

Table 8

Changes in Porphyrins and Enzymes in the Porphyrias and Porphyrinurias

	Urine				Feces			Erythrocyte		
	ALA	PBG	Uro-porphyrin	Copro-porphyrin	Copro-porphyrin	Proto-porphyrin	X-por-phyrin	Copro-porphyrin	Proto-porphyrin	Enzyme Decrease (White Cell/Red Cell/Fibroblast)
Acute Porphyrias										
Acute intermittent porphyria	Raised; very high in attack	Raised; very high in attack	Usually raised	Sometimes raised	Sometimes raised	Sometimes raised	Sometimes raised	Normal	Normal	Porphobilinogen deaminase ± uroporphyrinogen decarboxylase
Variegate porphyria	Raised; in attack	Raised; in attack	Usually raised in attack	Usually raised in attack	Raised	Raised	Raised; very high in attack	Normal	Normal	Protoporphyrinogen oxidase ± PBG deaminase±uroporphyrinogen decarboxylase
Hereditary coproporphyria	Raised; in attack	Raised; in attack	Sometimes raised in attack	Usually raised; always in attack	Raised	Usually normal	Sometimes raised, especially with photosensitivity	Sometimes raised in attack	Normal	Coproporphyrinogen oxidase ± PBG deaminase
Non-acute porphyrias										
Cutaneous hepatic porphyria	Normal	Normal	Raised; very high in attack	Slightly raised	Raised in remission	Raised in remission	Raised	Normal	Normal	Uroporphyrinogen decarboxylase
Erythropoietic protoporphyria	Normal	Normal	Normal	Normal	Normal	Usually raised	Normal	Sometimes slight raised	Raised; usually very high	Ferrochelatase
Congenital porphyria	Usually normal	Usually normal	Raised; isomer 1	Raised; isomer 1	Normal	Usually raised	Normal	Usually raised	Usually raised	Uroporphyrinogen cosynthase
Other conditions										
Lead poisoning	Raised	Normal	Normal	Sometimes raised	Normal	Normal	Normal	Normal	Raised; when blood lead > 2μM	ALA dehydratase, coproporphyrinogen oxidase ferrochelatase
Hereditary tyrosinemia	Raised	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	ALA dehydratase
Iron deficiency anemia	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Raised	Ferrochelatase

(Ref. #57)

Table 9 lists the normal ranges of urinary, fecal and blood porphyrin concentrations.

Table 9

Ranges of Urinary, Fecal, and Blood Porphyrin Concentrations in Normal Subjects

Porphyrin Concentration	Range
Urine	
Delta-aminolevulinic acid	0–40 μmol/24 h
Porphobilinogen	0–16 μmol/24 h
Uroporphyrin fraction	0–50 nmol/24 h
Coproporphyrin fraction	0–430 nmol/24 h
Total porphyrin	0–300 μg/24 h
Feces	
Coproporphyrin fraction	0–76 nmol/g dry wt
Protoporphyrin fraction	0–200 nmol/g dry wt
"X" porphyrin	0–15 μg/g dry wt
Blood	
Protoporphyrin	0–900 nmol/l
Plasma	
Uroporphyrin fraction	0–1.6 nmol/l
Coproprophyrin fraction	0–2.2 nmol/l
Protoporphyrin fraction	0–3.0 nmol/l

(Ref #57)

The relative diagnostic value of various porphyrin and enzymatic activity estimations in different porphyrias and porphyrinurias is shown in Table 10.

Table 10

RELATIVE VALUE OF VARIOUS PORPHYRIN AND ENZYMATIC ACTIVITY MEASUREMENTS IN DIFFERENT PORPHYRIAS AND PORPHYRINURIAS

1. Acute intermittent porphyria - urine 5-aminolevulinic acid, porphobilinogen and uroporphyrin.
2. Porphyria cutanea tarda - cutaneous hepatic porphyria or symptomatic porphyria-urine uroporphyrin.
3. Hereditary coproporphyria - urine 5-aminolevulinic acid, porphobilinogen and coproporphyrin, fecal coproporphyrin and protoporphyrin.
4. Variegate porphyria - urine 5-aminolevulinic acid, porphobilinogen, and fecal protoporphyrin.
5. Erythropoietic protoporphyria - erythrocyte protoporphyrin.
6. Lead intoxication - urine 5-aminolevulinic acid and erythrocyte protoporphyrin.
7. Hereditary tyrosinemia - urine 5-aminolevulinic acid.
8. Iron deficiency anemia - erythrocyte protoporphyrin.

(Ref. #57)

When evaluating the results of quantitative porphyrin determinations on urine samples, one must keep in mind the fact that there are a group heterogeneous diseases, the porphyrinurias, in which elevated levels of urinary porphyrins can be seen as a secondary effect of the disease. The porphyrin normally excreted in excess in these conditions is coproporphyrin. Lead poisoning (58), hereditary tyrosinemia (59), viral hepatitis (60), and lymphoma (61) are examples of such disorders which are associated with porphyrinuria. In addition, drugs like carbamazepine and other compounds such as polyhalogenated hydrocarbons can also induce excessive urinary porphyrin excretion.

F. TREATMENT

The approach to the management of porphyrias is outlined in Table 11.

Table 11

MANAGEMENT OF PORPHYRIAS

Non-Acute Porphyrias

I. Discontinuation of inciting factors
   1. Drugs, toxins
   2. Avoid light exposure (use sunscreens)

II. Modulation of disordered heme synthesis
   1. Phlebotomy

III. Increased excretion of porphyrins
   1. Urinary
      A. aminoquinoline antimalarials
         chloroquine
         hydroxychloroquine
      B. metabolic alkalinization
   2. G.I.
      A. cholestyramine
      B. activated charcoal
   3. Plasma
      A. plasmapharesis

IV. Systemic Photoprotection
   1. Carotenoids
      A. Beta-carotene
      B. Canthaxanthin
   2. Vitamin E

Acute Porphyrias

Hematin infusions
Carbohydrate loading
Beta-blockers

Of obvious benefit would be the avoidance of any drugs or (e.g. estrogens, griseofulvin) and toxins (e.g. ethanol) that might be inciting the porphyric state. In addition, unnecessary light exposure should be avoided. Topical photoprotection with sunscreens is not very effective since these agents are very poor UVA and visible light absorbers. Opaque sunscreens can be helpful but are often not practical. The most beneficial treatments for the cutaneous manifestations of the non-acute porphyrias such as porphyria cutanea tarda (PCT) is phlebotomy and/or aminoquiniline antimalarials.

1. Phlebotomy

The removal of 500 ml of blood at 1-2 week intervals can produce a complete chemical and clinical remission of PCT. The rate at which blood is removed is adjusted to insure not dropping below 12 gm/dl of hemoglobin. The amount of blood that will need to be removed to attain remission can vary considerably (1.5-16 liters). The beneficial effect of phlebotomy appears to result from a depletion of total body iron stores (62-64) since replenishment of iron following phlebotomy-induced remission of PCT has resulted in biochemical and clinical exacerbation (62-63). The exact mechanism by which phlebotomy induced depletion of excess iron leads to improvement in PCT is not completely clear.

Iron is known to enhance the induction response of ALA synthase to drugs and toxins in experimental animals (65). Thus, depletion of iron could render ALA synthase less inducible and diminish hepatic porphyrinogen synthesis. Iron depletion has also been shown to effect other heme pathway enzymes. The studies of Kushner, et al (66-67) showing that ferrous iron inhibits uroprophyrinogen decarboxylase and increases the rate of hepatic porphyrin synthesis from ALA or PBG suggests that removal of iron can allow uroporphyrinogen decarboxylase activity to return to normal and/or reduce excess porphyrinogen synthesis.

2. Antimalarials.

Chloroquine or hydroxychloroquine can be used as an alternative to phlebotomy to induce remissions of PCT. The mechanism by which these antimalarials act has been reasonably well worked out. Low oral doses of these compounds (125-200 mg) by mouth twice weekly can result in the formation of more water soluble antimalarial-porphyrin complexes within the liver. The complexed porphyrins are then released from the liver and excreted rapidly into the urine (68). However, if the usual antimalarial or photoprotective doses of these drugs are ingested by PCT patients (250-400 mg per day), an acute hepatotoxic reaction consisting of fever, malaise, abdominal pain, nausea, vomiting and high elevations of hepatocellular enzymes in serum is very likely to occur (69-70). Such patients on examination can appear to have an acute abdomen and have been often operated upon unnecessarily when this clinical situation has not recognized.

3. Carotenoids.

Systemic photoprotection with oral carotenoids such as beta-carotene and canthaxanthin (not available in the United States at this time) has been of considerable value in the management of erythropoietic protoporphyria. These compounds are yellow and reddish pigments that are found in nature in many yellow, orange, red and green plant foods. Based upon their ability to protect photosensitive bacterial microorganisms from lethal effects of ultraviolet light (71), beta-carotene was used in clinical trials in protoporphyric patients as an oral photoprotective agent (72). While on beta-carotene, most protoporphyric patients developed increased tolerance to both natural and artificial light exposure when serum carotene levels rose to more than 400 µg/dl (normal values being less than 300 µg/dl). At these serum carotene levels the skin gradually develops a yellow color (carotenodermia). Since these initial studies beta-carotene has become a mainstay for the management of erythropoietic protoporphyric patients. The therapeutic mechanism by which carotinoid compounds exert their effects at the molecular level are largely theoretical. The yellow color imparted to the skin may serve as a physical screen to some of the offensive wavelengths. It is considered unlikely, however, that sufficient photoprotection could be afforded by the barrier effect alone to account for the degree of relief provided to many patients with protoporphyria. In addition, carotene does not dramatically alter circulating protoporphyrin levels (73). The most important function of carotenoids in photoprotection may be their actions as scavengers of highly-reactive free radicals and as quenchers of singlet-excited oxygen generated by photoexcitation of porphyrins in tissue (74-75). Carotenoid compounds have also been tried in patients with other forms of porphyria but with considerably less benefit in comparison to erythropoietic protoporphyria. This may be do to the fact that carotenoids are lipophilic compounds and would be expected to partition into tissues at the molecular level in much the same way as the lipophilic protoporphyrin molecules. Therefore, beta-carotene might naturally distribute in tissue in closer proximation to the

dicarboxilic porphyrin, protoporphyrin, than to the more highly carboxilated, more hydrophilic porphyrins. When used as an oral systemic photoprotectant, beta-carotene is currently administered in doses designed to achieve serum carotene levels of between 600-800 µg/dl. In practice these levels are achieved in most adults by ingestion of 120-180 mg of beta-carotene (as synthetic encapsulated beadlets) per day (two 30 mg capsules three times daily). Doses for children under 14 years of age are scaled down according to weight: 30-150 mg/day. Vitamin E, also a lipid soluble, hydrophobic molecule with anti-oxidant properties, has also been used as a systemic photoprotectant in porphyria. However, this agent has not been nearly as beneficial as beta-carotene in photoprotecting erythropoietic protoporphyric patients.

4. Plasmapharesis.

The cutaneous manifestations of porphyria cutanea tarda have occurred in chronic renal failure patients after starting hemodialysis. In some of these patients there has been clear cut biochemical evidence of PCT (76-77) while in others, such disturbances in porphyrin synthesis have not been evident (78-79) ("bullous dermatosis of hemodialysis"). The management of hemodialysis patients with PCT is complicated by their chronic anemia (obviating phlebotomy) and renal failure (complicating the use of antimalarials). Such patients have been successfully managed with plasmapharesis (80).

IV. LUPUS ERYTHEMATOSUS

Sunlight exposure has long been recognized to be capable of exacerbating both the cutaneous and systemic manifestations of lupus erythematosus. This occurs with a frequency that has justified the inclusion of photosensitivity ("unusual skin reaction from exposure to sunlight, by patient's history or physicians observation") among the 14 preliminary (81) and 11 revised (82) classification criteria for systemic lupus erythematosus. What little we do understand about the mechanism(s) by which sunlight exposure aggravates LE has come from studies which have examined the relationships which exist between solar radiation and the cutaneous manifestations of LE. Therefore to better understand LE photosensitivity, we must first begin with a discussion of cutaneous LE.

A. CLASSIFICATION OF CUTANEOUS DISEASE IN LE.

Cutaneous disease is an exceedingly common manifestation of lupus erythematosus. The skin is the second most commonly injured organ in this disease process. In addition, cutaneous lesions are second only to joint disease as the most common presenting clinical manifestation in systemic LE (SLE) patients (83). Skin lesions in LE patients can be divided into 2 broad categories: those which are 1) histopathologically specific for LE (LE-specific) and those which are 2) not histopathologically specific for LE but are related to this disease (LE non-specific). The LE-specific lesions can be further subdivided into: chronic cutaneous LE (discoid LE [DLE] and its variants), subacute cutaneous LE (SCLE; psoriasiform and annular types) and acute cutaneous LE (localized [malar] or generalized erythema) (Table 12).

Table 12

LE-specific (diagnostic) skin lesions in SLE

Chronic cutaneous LE (CCLE) (15 to 20 per cent[a])
Clinical forms of chronic cutaneous LE
- Localized DLE
- Generalized DLE (lesions above and below the neck)
- Hypertrophic DLE
- Lupus profundus (lupus panniculitis)

Clinical and laboratory features of SLE patients with discoid LE
- Usually localized chronic, scarring lesions of head and/or neck region
- Antinuclear antibodies usually present. The nuclear staining pattern is often particulate (or speckled but may be homogenous
- Anti-dsDNA antibodies rarely present; anti-ssDNA and anti-ENA antibodies may be present
- Subepidermal immunoglobulin deposits are commonly found in lesions (80 per cent) but are uncommon in biopsies of clinically uninvolved skin (20 per cent)
- Simultaneous occurrence of severe SLE with nephritis is rare

Subacute cutaneous LE (SCLE) (10 to 15 per cent[a])
Clinical forms
- Papulosquamous (psoriasiform)
- Annular–polycyclic

Clinical and laboratory features of patients
- Usually widespread, non-scarring lesions on face, neck, upper trunk, upper back, shoulders and extensor arms (photosensitive distribution)
- Severe renal disease is uncommon
- Antinuclear and anticytoplasmic (anti-Ro and anti-La) antibodies are frequently present (>60 per cent)
- Anti-dsDNA antibodies are occasionally present
- HLA-A1, B8 and DR3 are significantly increased
- Subepidermal immunoglobulin deposits are present in only 50 per cent of lesions and 30 per cent of biopsies of clinically uninvolved skin

Acute cutaneous LE (ACLE) (30 to 40 per cent[a])
Clinical forms
- Facial (malar) erythema
- Widespread erythema of face, scalp, neck, upper chest, shoulders, extensor arms and back of hands
- Bullous or TEN-like lesions

Clinical and laboratory features of patients
- Transient (hours to days) erythema and induration
- Multisystem disease is usually apparent and renal disease is common
- Antinuclear antibodies are frequently present in high titre
- Anti-dsDNA antibodies are present in 50 to 70 per cent
- Subepidermal immunoglobulin deposits are commonly found in lesion (95 per cent) and non-lesion (75 per cent) skin

[a] Estimated incidence in SLE.

(Ref. #84)

Since LE-non-specific skin disease (e.g. small vessel vasculitis) can be seen in other disorders, we will confine our attention for this discussion to the LE-specific skin lesions because of their remarkable specificity for LE. All further references to cutaneous LE in this discussion should be taken to imply LE-specific skin disease.

B. PATHOLOGY

LE-specific skin involvement has ? consistent histopathological elements: a highly characteristic lichenoid pattern of inflammatory cell-associated injury at the dermal-epidermal (D-E) junction which is focused at the epidermal basal cell layer and a less specific pattern of dermal perivascular inflammatory cell infiltration (85). Even though this pattern of perivascular inflammation is not specific for LE it does appear to be an integral pathogenetic element since this is the histologic change which has been noted to occur first in experimental ultraviolet light (UVL)-induced cutaneous LE lesions(86).

C. PATHOGENESIS

Speculation regarding the pathogenesis of cutaneous LE in the past has focused upon the immunoglobulin (Ig) and complement component deposits which can frequently be found along the D-E junction of lesions (87-88), and many investigators have merely assumed that LE cutaneous inflammation was simply another manifestation of type II and/or type III mediated humoral autoimmune injury. There are however several lines of investigation which suggest that the D-E junction immune deposits are not responsible for eliciting the characteristic pattern of lichenoid injury that is seen in LE-specific skin disease (data reviewed in literature citation 89). Most telling among these arguments is the observation that in experimental UVL-induced DLE lesions, D-E junction Ig deposits follow the first appearance of an inflammatory response by several weeks (86). In addition the pattern of inflammatory cell response seen in cutaneous LE (i.e. predominately T lymphocytes) is not that which would be expected with immune complex mediated injury (i.e. polymorphonuclear leukocytes).

More recent work by Norris and coworkers has suggested the possibility that another form of antibody dependent immune injury (antibody-dependent cell-mediated cytotoxicity [ADCC]) might be responsible for the elicitation of certain forms of autoantibody-associated papulosquamous cutaneous LE such as SCLE and neonatal LE (data reviewed in citation 90). While certainly an attractive idea, this hypothesis cannot easily explain the etiology of forms of cutaneous LE such as DLE which are only infrequently associated with autoantibodies. Because of these reasons we have also considered the possibility that the predominate infiltrating inflammatory cell type present in cutaneous LE lesions, the T-lymphocyte (91), might be capable of directly effecting cellular injury in response to auto- or neo-antigens present at or near the D-E junction. This view is supported by the striking similarities which exist between the histopathologies of cutaneous LE and graft-versus-host skin disease, a process known to be T-cell dependent in which there is little evidence for a causal role for Ig. There is also increasing evidence from experimental models of human disease which suggests that antigen-specific autoreactive T-cell injury might be responsible for disorders such as multiple sclerosis (92) as well as certain forms of thyroiditis (93) and arthritis (94). In addition, there has been a recent renewal of interest in the possibility that autoantigen-specific T-cells might play a greater role in the B-cell hyperactivity that is seen in SLE than has been previously recognized (95-96). While earlier studies have suggested that DLE patients can mount a delayed hypersensitivity response to nuclear antigens such as DNA (97), there is at this time no direct evidence for T-cell mediated cellular cytotoxic injury triggered by cutaneous auto- or neo-antigens.

D. ROLE PLAYED BY AN AUTOIMMUNE RESPONSE TO RO/SS-A ANTIGEN IN THE PATHOGENESIS OF CUTANEOUS LE.

Work carried out in ours and other laboratories suggest that an autoimmune response to the cellular antigen Ro/SS-A might be involved in the pathogenesis of certain forms of cutaneous LE. Circulating anti-Ro/SS-A antibodies are found in a remarkably high percentage of patients with two forms of photosensitive cutaneous LE: SCLE (98-99) and a related disorder, neonatal LE (100-101) (Table 13).

Table 13

Autoantibodies Seen in SCLE Patients[5,6]

Frequency	Autoantibodies	Incidence
High		
	ANA (>1:160)	81%
	Anti-Ro(SSA)	82%
Intermediate		
	Rheumatoid factor	36%
	Anti-lymphocyte	32%
	Anti-La(SSB)	25%
Low		
	Anti-double stranded DNA	11%
	Biologic false-positive VDRL	8%
	Anti-nRNP	8%
	Anti-Sm	5%

(Ref. #99)

Clinical and Laboratory Findings Noted in Neonatal Lupus Erythematosus*

Significant Finding	*Apparent Sensitivity (%)*
Cutaneous disease†	100
Hepatosplenomegaly†	32
Heart block†	23
Pulmonary disease†	15
Failure to thrive†	9
Serologic evidence of LE (positive LE cell preparation, ANA, or both)‡	61
Thrombocytopenia (platelet counts <100,000)*	11
Leukopenia (WBC <5000)†	9
Antibodies to Ro/SS-A antigen‡	93
Rheumatoid factor positivity‡	38
Antibodies to nDNA‡	9
Antibodies to RNP‡§	0

(Ref #102)

Ro/SS-A antigen has been shown to be expressed in human epidermal keratinocytes both in vivo (103) and in vitro (104-105). Our studies suggest that Ro/SS-A is expressed to a greater degree in rapidly proliferating keratinocytes (106). UVL radiation appears to alter the subcellular distribution of Ro/SS-A in keratinocytes in tissue culture in a manner that would make it more accessible to an immunological attack (104). In addition, anti-Ro/SS-A antibody when passively infused into nude mice bearing grafts of normal human skin preferentially binds to the lower layers of the human epidermal grafts (105). We also have preliminary data which suggest that an autoimmune response to Ro/SS-A occurs more frequently than was initially suspected in another cutaneous LE subset, DLE (107). These studies taken together would suggest that an autoimmune response to Ro/SS-A might well play a role in eliciting the patterns of cutaneous injury seen in SCLE, neonatal LE and possibly even DLE as well. Further characterization of the immune response which occurs to this autoantigen and a more precise delineation of the factors which regulate its expression in cutaneous tissue will be required to more fully understand the role it plays in the pathogenesis of LE-specific skin disease.

E. PHOTOSENSITIVITY IN LE.

Photosensitivity has been reported to occur in 11-58% of SLE patient populations (83, 108-109) and is present in virtually all patients in certain cutaneous LE subsets such as SCLE (99). However, sun sensitivity remains one of the least well studied and understood aspects of LE today. Any comprehensive overview of cutaneous LE must include an explanation of the mechanism by which UV-B (and perhaps UV-A) exposure initiates or exacerbates acute and subacute cutaneous LE (and to a lesser extent chronic cutaneous LE).

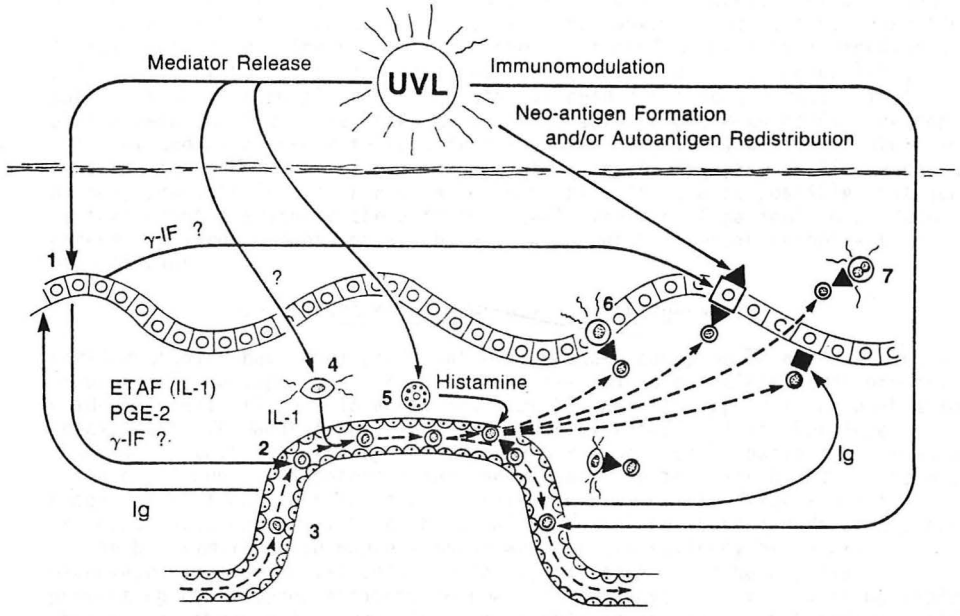
1. Action Spectrum.

While some experienced clinicians have suggested that infrared and x-iradiation can exacerbate LE (110), most of the experimental work carried out to address this issue has suggested that UVB wavelengths are responsible for LE photosensitivity (111-113). The possibility that UVA wavelengths might be important still exists. In general, the mean erythema doses of UVB in LE patients has not differed significantly from that of normal individuals.

2. Pathogenesis of LE photosensitivity.

Investigators in the past have focused on the possibility that UVL exposure might damage epidermal DNA in such a way as to produce highly immunogenic epitopes (e.g. pyrimidine dimers) that would elicit an immune response which would be focused at the D-E junction due to the known binding affinity of DNA for the type IV collagen at this site (114-115). Others have shown that cells of various types from murine SLE models and human SLE patients do not repair UVL-induced DNA damage at normal rates (116-120). Thus, the immune response of an LE patient might have to deal with a greater number of UVL-induced immunogens than would a normal individual. Work in experimental animals has suggested that the immunomodulatory effects of UVL irradiation might be capable of increasing B-cell activity and enhancing anti-DNA antibody production in genetically predisposed individuals (121). Other investigators have suggested that circulating factors present in SLE serum might becapable of enhancing UVL-induced cellular injury (122). In addition, clinical observations have suggested that some LE patients experience an exaggeration of the normal cutaneous inflammatory response provoked by UVL exposure which subsequently leads to the development of LE-specific skin disease (i.e. a sunburn that does not go away). These observations taken together suggest that UVL exposure might trigger cutaneous LE expression by one or a combination of the following four mechanisms: 1) augmentation of inflammatory mediator release from the epidermis or dermis, 2) induction of new antigen formation within the epidermis or at the D-E junction, 3) redistribution of antigens normally present in the epidermis or at the D-E junction, 4) induction of local and/or systemic immunoregulatory abnormalities. My view of how these possibilities might interrelate in the elicitation of cutaneous LE is presented graphically in figure 9 and further discussed below.

Figure 9



Proposed pathogenesis of photosensitivity in lupus erythematosus.

Key to figure

1. epidermal keratinocyte
2. dermal microvascular endothelial cell
3. circulating T lymphocyte
4. dermal perivascular dendritic cell
5. dermal mast cell
6. epidermal melanocyte
7. epidermal Langerhans cells

▲ - neoantigen induced in epidermis by UVL exposure
■ - autoantigen redistributed to surface of a keratinocyte by UVL exposure.

a. Augmentation of inflammatory mediator release.

UVL exposure is known to enhance the release from different compartments within the skin of several cytokines (ETAF [IL-1], PGE-2, histamine) (123-128) which have potent effects on the dermal microvascular unit. Some of these substances

(ETAF [IL-1]) are known to be potent chemoattractants for T-lymphocytes, and can augment binding of lymphocytes to endothelial cell surfaces. Perhaps these substances might enhance cutaneous UVL-induced auto- or neo-antigen-specific T-cell traffic into the skin through their effects on the dermal microvascular unit. Autoantibodies to phospholipase inhibitory protein (lipomodulin), a substance which normally down-regulates arachidonic acid generation in the plasma membrane (129) are known to occur in some LE patients (130). Perhaps such antibodies or other factors from the serum might allow a given UVL stimulus to evoke the generation of greater amounts of cyclooxygenase or lipoxygenase pathway products in the skin of an LE patient. It is also possible that genetic factors might predispose the epidermal cells from an LE patient to produce abnormally large amounts of arachidonic acid metabolites in response to a given UVL stimulus.

b. Induction of new cutaneous antigens.

Earlier studies have indicated that UVL exposure can produce at least one highly immunogeneic epitope (i.e. thymine dimers) within the nucleic acids present in epidermal cells (115). In addition, some LE patients appear to be unable to repair such UVL-damaged nucleic acid at normal rates. It is therefore conceivable that the already-active immune response of LE patients is regularly being challenged with potent immunogens created in the skin by UVL. There are a number of resident skin cells which either constitutively express class II antigens (e.g. epidermal Langerhans cells, dermal perivascular dendritic cells) or can be stimulated to express these antigens (keratinocytes, dermal microvascular endothelial cells, melanocytes) that might be capable of presenting UVL-induced antigens to CD4 + T-lymphocytes. It is also possible that any of these cell types might be capable of presenting UVL-induced antigens to CD8 + T-lymphocytes since they all constitutively express class I antigens.

c. Redistribution of autoantigens in the skin.

Ro/SS-A, an autoantigen normally present in the epidermis, appears to be preferentially expressed in the proliferating, basal cell layer (105-106). It is possible that greater amounts of this autoantigen are expressed in UVL irridiated epidermis, since UVL exposure is known to produce a wave of epidermal cell proliferation. Earlier studies have also suggested that UVL exposure might result in the translocation of Ro/SS-A from the nucleus to the plasma membrane of human epidermal keratinocytes, a site which would be more accessible to specific antibody or T-cells (104).

d. Induction of immunoregulatory abnormalities.

Most of the earlier work which has examined the effects of UVL exposure on immune regulation have been carried out in experimental animals. In such systems short term exposure with low doses of UV-B have generally resulted in decreased class II antigen expression and the generation of antigen-specific suppressor cells. Since LE patients frequently have deficient suppressor cell function, it is conceivable that UVL exposure in an LE patient generates less down regulation in response to UVL induced antigens than would be seen in a normal individual. Recent studies in humans have also shown that in vivo UVL exposure results initially in a decrement of class II antigen expression within the epidermis. However, 72 hours after exposure there is an increase in epidermal HLA-DR antigen-bearing, alloantigen-presenting cells (131). This UVL-induced influx of antigen presenting cells into the epidermis might

facilitate T-cell recognition of UVL-induced auto-/neo-antigen. It is also possible that UVL exposure might increased T-cell traffic to the skin directly through effects on T-cells circulating through the skin or indirectly via UVL-induced alterations in dermal microvascular endothelial cells.

V. DRUG-INDUCED PHOTOSENSITIVITY

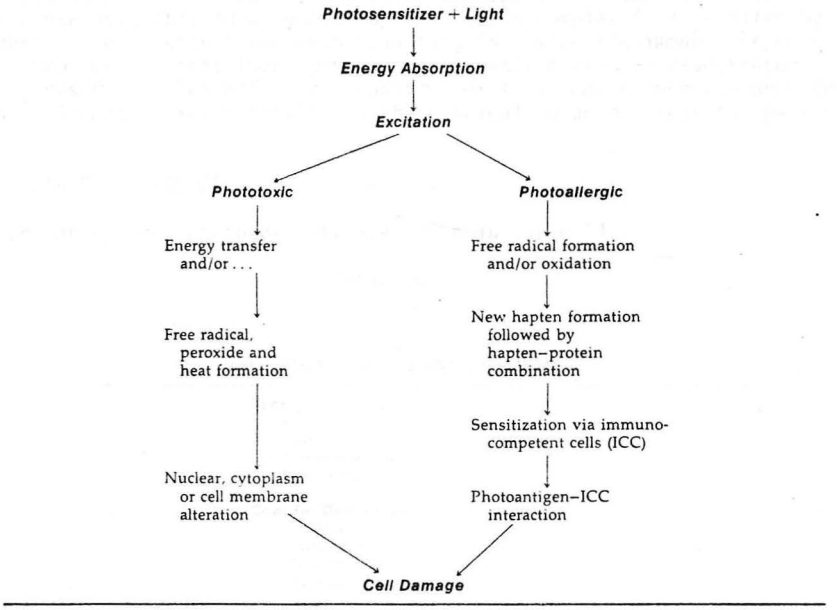
Drug-induced photosensitivity reactions are adverse cutaneous responses to the combined actions of a drug and light exposure. Either agent alone usually evokes no abnormal response, but the two in combination can result in adverse cutaneous syndromes. Drugs or chemicals that can cause photosensitivity may reach the skin either directly following external environmental exposure or indirectly following systemic administration.

A. MECHANISMS

The mechanisms by which drugs induce photosensitive reactions are complex and still not completely understood. Based upon our current understanding, drug induced photosensitive reactions can be subdivided into two broad types: phototoxic reactions and photoallergic reactions. This concept has evolved from the original studies of sulfanilamide photosensitivity by Stephan Epstein in the late 1930's (132). The proposed mechanisms of these two patterns of drug-induced cutaneous photoreactivity are outline in Figure 10.

Figure 10

HYPOTHETIC MECHANISMS OF PHOTOTOXIC AND PHOTOALLERGIC REACTIONS IN PHOTOCONTACT DERMATITIS*



(Ref. #1)

1. Phototoxicity.

Phototoxicity is a dose related response of all individuals to adequate exposure simultaneously to radiant energy and a chemical that is capable of absorbing radiant energy at that wavelength. Clinically, there are two main patterns of response: 1) an immediate burning sensation, erythema, and urticaria; and 2) a delayed reaction resembling sunburn which appears within hours or at the most several days after exposure. The following mechanism for this reaction pattern has been proposed. Light is absorbed by the drug in the skin resulting in an excited, higher energy state. Energy is then transferred from this excited molecule with the resultant formation of free radicals, peroxide and heat within the skin. These are the agents of cell membrane, cytoplasm and nuclear damage which produce the clinical cutaneous response seen.

2. Photoallergy.

Photoallergy is a reaction to a chemical and radiation in which an immune mechanism can be demonstrated. It is therefore a qualitatively different reaction than phototoxicity which may occur in a small minority of exposed individuals. The dose-response relationship is much less evident than in phototoxic reactions and minute quantities of the drug or chemical and radiation

may be adequate to elicit a response. The clinical appearance is more closely related to a dermatitic or eczamatoid reaction compared to the sunburn-like reaction seen in phototoxic drug eruptions. The following mechanism has been proposed for this type of drug photoreactivity. Radiant energy is absorbed by the drug in the skin producing an excited state. Photochemical reactions that are produced by this excited state (free radical formation, oxidation) result in hapten formation within the skin followed by conjugation of the hapten to cutaneous proteins. This immunogenic hapten-protein complex is recognized by immunocompetent cells within the skin resulting in a specific immune response. Subsequent exposure to this immunogen then frequently evokes an exaggerated immunologic response. The effector mechanisms of this immune response produce cutaneous inflammation which results in the clinical cutaneous reaction patterns seen.

B. CLINICAL FEATURES

Drugs which can produce phototoxicity are shown in Table 14.

Table 14

PHOTOTOXIC DRUGS AND CHEMICALS

Dyes
Anthraquinone
Eosin
Methylene blue
Rose bengal
Coal Tar Derivatives
Acridine
Anthracene
Phenanthrene
Pyridine
Furocoumarins
Psoralen
8-Methoxypsoralen
4,5,8-Trimethylpsoralen
Drugs
Nalidixic acid
Phenothiazines
Sulfonamides
Tetracyclines
Thiazides

(Ref. #1)

Those drugs which are capable of eliciting photoallergic responses can be seen in Table 15.

Table 15

PHOTOALLERGENIC DRUGS AND CHEMICALS

Halogenated Salicylanilides
Tetrachlorosalicylanilide
Tribromosalicylanilide
Dibromosalicylanilide
Trichlorocarbanilide
Bithionol
Antifungal Agents
Multifungin
Fentichlor
Jadit
Phenothiazines
Chlorpromazine
Promethazine
Sulfonamides
Sunscreens
PABA esters
Digalloyltrioleate
Whiteners
Stilbenes
Fragrances
Musk ambrette
Methylcoumarin

(Ref. #1)

The comparative clinical characteristics of drug-induced phototoxic and photoallergic reactions are shown in Table 16.

Table 16

CHARACTERISTICS OF DRUG-INDUCED PHOTOSENSITIVITY: PHOTOTOXIC AND PHOTOALLERGIC REACTIONS

Characteristic	Reaction	
	Phototoxic	Photoallergic
Incidence	Usually relatively high (theoretically 100%)	Usually very low
Clinical manifestations	Usually resemble sunburn	Varied morphology
Possibility of reaction on first exposure	Yes	No
Incubation period after first exposure	No	Yes
Development of persistent light reaction	No	Yes
Possibility of "flares" at distant previously involved sites	No	Yes
Cross reactions to structurally related agents	No	Frequent
Broadening of cross reactions following repeated photopatch testing	No	Possible
Concentration of drug necessary for reaction	High	Low
Chemical alteration of photosensitizer	Sometimes	Yes
Covalent binding with carrier protein	No	Yes
Passive transfer	No	Possible
Lymphocyte stimulation test	No	Possible
Macrophage migration inhibition test	No	Possible

(Ref. #1)

The reader is referred to pages 966-968 of reference (3) for a more comprehensive discussion of individual chemical and drug photosensitizers. Most photosensitizing durgs are highly conjugated, heterocyclic compounds. Consequently, the absorption-spectrum of most of these agents peaks in the UVA range. A more comprehensive listing of photosensitizing drugs can be found in the appendix.

C. MANAGEMENT.

Ideal management of light-induced drug eruptions would include identification and avoidance of the offending agent. In the real world, this is often not possible. Identification of the responsible agent can be a challenge at times when a patient is on multiple drugs. Once identified, it is often not practical to find an adequate substitute for an agent that might be vital to the survival of the patient. In such cases, one must resort to non-specific anti-inflammatory therapy (topical and/or systemic corticosteroids) and light avoidance/photoprotection.

VI. PHOTOPROTECTION.

All photosensitive states could be eliminated by completly avoiding exposure to radiant energy. However, in this less than ideal world, a certain degree of compromise from this position is required. The most effective management of patients with light sensitive disorders should therefore include both topical and systemic measures to photoprotect the patient.

A. TOPICAL PHOTOPROTECTION.

The beneficial effects of commonsense, light-avoidance measures such as the use of broad-brimmed hats and long-sleeved clothing whenever possible should not be underestimated. Patients should be instructed to carry out their outdoor activities before 10 am or after 4 pm whenever possible. The more direct angle of inclination of radiant energy during the midday period allows for significantly greater penetration of the atmosphere by ultraviolet energy. For any given duration of exposure, approximately 4 times as much UVB strikes the earth's surface at 12 noon as compared to 4 pm. Sunlight exposure in the context of snow or sand can result in significantly greater amounts of ultraviolet exposure because of the efficiency with which these materials reflect UV light.

Photosensitive patients can benefit significantly by the regular use of topically applied sunscreening agents. Chemical sunscreens fall into 4 categories, as can be seen in Table 17.

Table 17

MAJOR CHEMICAL GROUPS OF SUNSCREENS

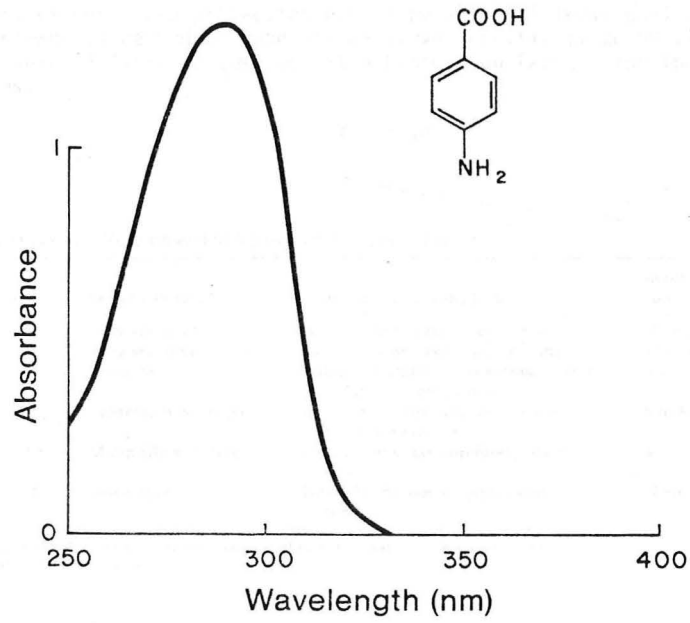
Group 1	
Para-aminobenzoic acid (PABA)	Absorbers (chemical sunscreens)
PABA esters	
Salicylates	
Group 2	
Cinnamates	
Group 3	
Benzophenones	
Group 4	Blockers (physical sunscreens)
Zinc oxide	
Titanium dioxide	

(Ref. #1)

The most effective are the opaque materials that effectively reflect or scatter ultraviolet and visible radiation (Group IV - zinc oxide, titanium dioxide). However, most of these agents are cosmetically unacceptable to patients and therefore are not of practical value. The remaining agents in Table 17, para-aminobenzoic acid (PABA) and its esters, salicylates, cinnamates and benzophenones are better accepted by patients but are of less benefit due to their variable UV absorbing qualities. The most extensively used light

absorbing sunscreen preparations in this country are PABA and its derivatives. Figure 11 illustrates the absorption spectrum of PABA which can be seen to be maximal in the UVB range.

Figure 11



(Ref. #1)

However this compound is not at all efficient at absorbing UVA or visible wavelengths. Thus PABA or PABA esters can be of significant value in protecting against UVB-induced processes (sunburn, skin cancer, premature aging, pigmentary disorders, lupus erythematosus) but would not be of benefit in UVA induced conditions (porphyrias, most photoinduced drug eruptions). The remaining light-abosrbing chemicals (salicylates, cinnamates, benzophenones) in general have a broader absorption spectrum than does PABA or its esters. Even though some of these agents do absorb some UVA wavelengths, used by themselves they are not as substantive or as efficacious as PABA or its esters. The more potent sunscreens used today usually combine PABA or its esters with one or a combination of these other, more broadly absorbing, sunscreening chemicals.

Two issues should be considered when choosing a sunscreen, its Sun Protection Factor and its substantivity. The UV-blocking effectiveness of a sunscreen can be judged by its Sun Protection Factor, or SPF, which is defined as the minimal erythema dose of UVB for the sunscreen-protected skin divided by the minimal

erythema dose of UVB for the non-protected skin. For example, a sunscreen with an SPF of 4 theoretically permits the patient to increase his or her exposure time 4 fold before developing a sunburn. The substantivity of a sunscreen refers to its relative resistance to removal from the skin by perspiration, swimming and washing. Therefore the relative effectiveness of a sunscreen can be thought of as the product of its Sun Protection Factor and its substantivity.

The amount of sunscreen protection needed by a normal individual to retard actinic damage is dependent upon his relative sensitivity to UV light (skin type). Table 18 lists recommended Skin Protection Factors for the different skin types.

Table 18

Skin Types and Recommended Sunscreen Protection Factor

Skin type	Sensitivity to UV[a]	Sunburn and tanning history	Recommended sun protection factor[b]
I	Very sensitive	Always burns easily; never tans	10 or more
II	Very sensitive	Always burns easily; tans minimally	10 or more
III	Sensitive	Burns moderately; tans gradually and uniformly (light brown)	8 to 10
IV	Moderately sensitive	Burns minimally; always tans well (moderate brown)	6 to 8
V	Minimally sensitive	Rarely burns, tans profusely (dark brown)	4
VI	Insensitive	Never burns; deeply pigmented (black)	None indicated

[a]Based on first 30 to 45 minutes' sun exposure after winter season or no sun exposure.
[b]Based on outdoor field studies.

(Ref. #133)

Table 19 lists the Sun Protection Factors of some brand name sunscreens under indoor and outdoor conditions.

Table 19

Sun Protection Factors of Some Brand Name Sunscreens Under Indoor and Outdoor Conditions

Trade name	Ingredients	Type of sunscreen	Sun protection factor (SPF)		Resistance to	
			Indoor solar simulator	Outdoor sunlight	Sweating	Water immersion
PABA sunscreens						
PreSun 15	5% PABA in 50–70% ethyl alcohol	Clear lotion	15	10	Excellent	Poor
Pabanol		Clear lotion	15	6–8	Fair	Poor
Sunbrella		Clear lotion	15	6	Fair	Poor
PABA-ester combination sunscreens						
SuperShade 15	7% octyldimethyl PABA + 3% oxybenzone	Milky lotion	15–18	6–9	Excellent	Good
Total Eclipse 15	2.5% glyceryl PABA + 2.5% octyldimethyl PABA + 2.5% oxybenzone	Milky lotion	15–18	9–12	Excellent	Good
MMM What-A-Tan!	3.0% octyldimethyl PABA + 2.5% benzophenone-3	Milky lotion	15–20	10	Excellent	Good
PreSun 15	5% PABA + padimate O + 3% oxybenzone	Milky lotion	15–20	8–10	Excellent	Good
Clinique 19	Phenylbenzimidazole-5-sulfonic acid +	Milky lotion	15–19	7–8	Good	Fair
Sundown 15	7% padimate O + 5% octylsalicylate + 4% oxybenzone	Milky lotion	15–20	10–11	Excellent	Good
PABA ester sunscreens						
Block Out	3.3% isoamyl-*p*-*N*,*N*-dimethyl-aminobenzoate (padimate A)	Lotion/gel	6–8	6	Good	Fair
Pabafilm	3.3% isoamyl-*p*-*N*,*N*-dimethyl-aminobenzoate (padimate A)	Lotion/gel	6–8	4–6	Good	Fair
Sundown	3.3% isoamyl-*p*-*N*,*N*-dimethyl-aminobenzoate (padimate A)	Lotion	8–10	4–6	Good	Fair
Original Eclipse	3.5% padimate A + 3.0% octyldimethyl PABA	Lotion	8–10	4–6	Fair	Fair
Aztec	5.0% homomenthyl salicylate + 2.5% amyl-*p*-dimethylamino-benzoate	Lotion	6–8	4	Fair	Poor
Sea & Ski	3.3% octyldimethyl PABA	Cream	7–8	4	Fair	Poor
Non-PABA sunscreens						
Piz Buin-8*	5% ethyl-hexyl-*p*-methoxycinnamate +	Cream	15–20	10–12	Excellent	Good
Ti Screen	3% 2-hydroxy-4-methoxybenzophenone + 4% 2-phenyl-benzimidazole sulfonic acid	Cream	16–22	10–12	Excellent	Good
Piz Buin-8*	5% ethylhexyl-*p*-methoxycinnamate +	Milky lotion	20–22	10–12	Excellent	Good
Ti Screen	3% 2-hydroxy-4-methoxybenzophenone	Milky lotion	16–20	10–12	Excellent	Good
Piz Buin-4*	4.5% ethylhexyl-*p*-methoxycinnamate	Milky lotion	10–12	4–6	Fair	Poor
Uval	10% 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid	Milky lotion	10–12	4	Poor	Poor
Coppertone-4	8% homomenthylsalicylate	Lotion	3.5–4	2	Poor	Poor
Physical sunscreens						
A-Fil	Titanium dioxide + zinc oxide	Cream	6–8	4–6	Good	Fair
RV Paque	+ talc, kaolin, iron oxide, or	Cream	6–8	3–4	Good	Fair
Shadow	red veterinary petroleum	Cream	4–6	2–4	Good	Fair
Reflecta		Cream	6–8	4–6	Good	Fair
Covermark		Cream	6–8	4–6	Good	Fair
Clinique		Cream	6–8	4–6	Good	Fair

*Not available in the United States.

(Ref. #133)

Table 20 lists water and sweat resistance sunscreens, and sunscreens that are not water resistant.

Table 20

Water- and Sweat-Resistant Sunscreens

United States	Europe
Supershade-15	Piz Buin Creme
Elizabeth Arden-15	Piz Buin Lotion-8
MMM-What-A-Tan-15	Ellen Betrix Sun Creme-8
Piz Buin-12	
PreSun-15	
Sundown-15	
Sundown-8	
Ti-Screen-15	

Sunscreens That Are Not Water Resistant

United States	Europe
Estee Lauder-15	Delial-20
Ultra Vera	Ambre Solaire-8
PreSun-15	Nivea-12
UVAL	Marbert Sun Creme-8
Solbar	Lancaster High Altitude-8
PABAFILM	
Blockout	
Sea & Ski	
Sunbrella	

(Ref. #133)

In general those sunscreens which are formulated in a milky lotion or cream vehicle tend to be more resistant to sweating and water immersion. PABA or PABA ester sunscreens are most effective when applied 45 minutes to one hour prior to exposure to the sun. All sunscreens should be reapplied after swimming or sweating. Patients with photo-induced diseases should use products with the greatest substantivity and highest SPF's available.

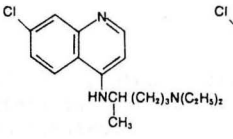
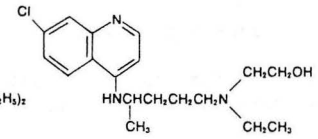
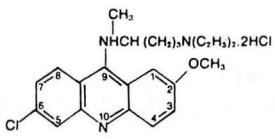
B. SYSTEMIC PHOTOPROTECTION.

Unfortunately, there is no ideal form of systemic photoprotection. Carotenoids such as beta-carotene are of some value in the porphyrias, particularly erythropoietic protoporphyria. This compound has been discussed earlier in this protocol.

The aminoquinoline anti-malarial drugs, including chloroquine (Aralen), hydroxychloroquine (Plaquenil) and quinacrine (Atabrine) have been empirically observed to be of benefit in several photosensitivity states (lupus erythematosus, polymorphous light eruption, solar urticaria, porphyria cutanea tarda). PCT patients have benefitted from these drugs in large part because of their ability to complex and promote the urinary excretion of porphyrins. However the mechanism by which these drugs suppress the manifestations of these other photosensitive states is not at all clear. The major limiting factor in the use of antimalarials is their toxicity which is outlined in Table 21.

Table 21

The synthetic antimalarial drugs

	Chloroquine (Aralen, Nivaquine)	Hydroxychloroquine (Plaquenil)	Quinacrine (Atabrine, Mepacrine)
Structural formula			
Daily maintenance dose	250 mg	200 mg	100 mg
Cinchonism	+	+	+
Ocular side effects:			
Keratopathy	+	+	+
Retinopathy	++	+	−
Neuromuscular:			
Toxic psychosis, fits	+	+	+
Neuropathy, myopathy	+	+	−
Hematologic:			
Agranulocytosis	+	+	+
Hemolysis (in G6PD-deficient patients)	+	+	+
Aplastic anemia	−	−	+
Gastrointestinal:			
Nausea, vomiting, diarrhea	+	+	+
Toxic hepatitis	−	−	+
Cutaneous:			
Exfoliative dermatitis	+	+	++
Lichenoid eruption	+	+	++
Exacerbation of psoriasis	+	+	+
Precipitation of porphyrias	+	+	−
Yellowing of sclerae, skin	−	−	+
Macular hyperpigmentation	+	+	+
Depigmentation of hair	+	+	−
Other rashes	+	+	+

(Ref. #3)

The most important of these side effects is the potential for ocular toxicity. Corneal deposits and retinopathy can occur. The corneal deposits are of little consequence since they rarely affect vision and are reversible upon cessation of the drug. The retinopathic effect of these drugs can be more serious. A number of cases of complete blindness were reported several decades ago when chloroquine was used in high daily doses (1 gm or greater per day) for the

treatment of rheumatoid arthritis and lupus erythematosus. However since the lower daily dose regimens (250 mg of chloroquine, 200-400 mg of hydroxychloroquine) have become popular over the past 15 years the frequency of chloroquine induced retinopathy has decreased considerably (134). In addition, it has been recognized that hydroxychloroquine has a lower potential for retinal toxicity than chloroquine (135).

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Some Drugs That May Cause Photosensitivity

ACNE MEDICATIONS
- Tretinoin (Retin-A)

ANTICANCER DRUGS
- Dacarbazine (DTIC-Dome)
- Fluorouracil (Fluoroplex; and others)
- Methotrexate (Mexate; and others)
- Vinblastine (Velban)

ANTIDEPRESSANTS
- Amitriptyline (Elavil; and others)
- Desipramine (Norpramin; Pertofrane)
- Doxepin (Adapin; Sinequan)
- Imipramine (Tofranil; and others)
- Nortriptyline (Aventyl; Pamelor)
- Protriptyline (Vivactil)
- Trimipramine (Surmontil)

ANTIHISTAMINES
- Cyproheptadine (Periactin)
- Diphenhydramine (Benadryl; and others)

ANTIMICROBIALS
- *Demeclocycline (Declomycin; and others)
- Doxycycline (Vibramycin; and others)
- Griseofulvin (Fulvicin-U/F; and others)
- Methacycline (Rondomycin)
- *Nalidixic acid (NegGram; and others)
- Oxytetracyclines (Terramycin; and others)
- Sulfacytine (Renoquid)
- Sulfamethazine (Neotrizine; and others)
- Sulfamethizole (Thiosulfil; and others)
- Sulfamethoxazole (Gantanol; and others)
- Sulfamethoxazole-trimethoprim (Bactrim; Septra)
- Sulfasalazine (Azulfidine; and others)
- Sulfathiazole
- Sulfisoxazole (Gantrisin; and others)
- Tetracyclines (Achromycin; Minocin)

*Reactions occur frequently.

ANTIPSYCHOTIC DRUGS
- Chlorpromazine (Thorazine; and others)
- Fluphenazine (Permitil; Prolixin)
- Haloperidol (Haldol)
- Perphenazine (Trilafon)
- Piperacetazine (Quide)
- Prochlorperazine (Compazine; and others)
- Promethazine (Phenergan; and others)
- Thioridazine (Mellaril)
- Trifluoperazine (Stelazine; and others)
- Triflupromazine (Vesprin)
- Trimeprazine (Temaril)

DIURETICS
- Bendroflumethiazide (Naturetin; and others)
- Benzthiazide (Exna; and others)
- Chlorothiazide (Diuril; and others)
- Cyclothiazide (Anhydron)
- Furosemide (Lasix)
- Hydrochlorothiazide (HydroDIURIL; and others)
- Hydroflumethiazide (Diucardin; and others)
- Methyclothiazide (Aquatensen; Enduron)
- Metolazone (Diulo; Zaroxolyn)
- Polythiazide (Renese)
- Quinethazone (Hydromox)
- Trichlormethiazide (Metahydrin; and others)
- Thiazides (Diuril; HydroDIURIL)

HYPOGLYCEMICS
- Acetohexamide (Dymelor)
- Chlorpropamide (Diabinese; Insulase)
- Tolazamide (Tolinase)
- Tolbutamide (Orinase; and others)