5-1-1969

Photosensitivity : an increasing problem

Terry R. Rusthoven

University of Nebraska Medical Center

Follow this and additional works at: http://digitalcommons.unmc.edu/mdtheses

Recommended Citation
PHOTOSENSITIVITY, AN INCREASING PROBLEM

By

Terry R. Rusthoven

A THESIS

Presented to the Faculty of
The College of Medicine in the University of Nebraska
In Partial Fulfillment of Requirements
For the Degree of Doctor of Medicine

Under the Supervision of Dr. C. Wilhelmj
Chairman of Department of Dermatology

Omaha, Nebraska
February 1, 1969
Outline

I. Introduction
   1. Natural sunlight
   2. Suntan
   3. Sunburn
   4. Skin defenses against sunlight
   5. Diseases affected by ultraviolet rays

II. Descriptive Terms
   1. Photoallergy vs. phototoxicity

III. Types of Photosensitivity
   1. Drug sensitivity
   2. Plant sensitivity
   3. Soap sensitivity
   4. Polymorphous light eruption
   5. Persistent light reactors

IV. Patch Testing
   1. Minimal erythema dose
   2. Delayed erythema dose
   3. Office testing
   4. Scotch Tape Provocative Patch Test

V. Drug Photosensitivity
   1. Drugs involved
   2. Mechanisms of reaction
   3. Reactions with sulfa drugs
   4. Reactions with phenothiazines
   5. Reactions with tetracyclines
VI. Soap Sensitivity
   1. Agents involved
   2. Cross sensitization
   3. Histology
   4. Mechanism of reaction

VII. Differential Diagnosis

VIII. Treatment and Prevention
   1. Skin aging
   2. Acute photosensitivity
   3. Prophylaxis
   4. Sun Screen agents

IX. Conclusion
I. Introduction

The "sun worshipper", who spends his summer hours out in the warm, tanning rays of the sun, is fortunate in that his experience with the sun is a pleasant one. For the fair skinned and photo-sensitive people, the sun must be avoided, sometimes through expense or great hardship.

Natural sunlight has a wide spectrum ranging from the blue at 4000 A to the red at 8000 A. Infrared rays are those longer than visible light and ultraviolet rays are those shorter than visible light.

The sunburn range is generally considered to be that between 2500-3200 A. We are fortunate that ordinary window glass cuts out those waves less than 3200 A. However many of the photosensitivity reactions are activated by the longer ultraviolet; that from 3200-3900 A, which is not affected by glass.

When a person gets a suntan, Daniels\(^1\) proposes the following mechanism. In the first step there is darkening of the skin from the oxidation of pigment which is present in the bleached form. The amount of tanning via this step is variable. Second, the ordinarily inactive tyrosinase is activated. The tyrosinase causes an increased production of melanin with its deposition into keratin producing cell. This takes roughly 4-5 days and one's tan reaches its peak in about a week.
The so-called "active" part of sunlight is the ultraviolet spectrum with a range of 400-4000 A. Most rays under 2950 A are filtered by the upper atmosphere. Honeycutt, Dillaha and Jansen² point out that there are three major bands of ultraviolet light which are capable of producing a pigmentation response. The band at 2530 A gives a weak response that fades quickly. The greatest response comes at 2960 A, reaches a maximum in 7-10 days and lasts for several months. The third band is 3400 A and is very inefficient, requiring 1000 times the energy of the 2960 A band. However the pigment response lasts close to a year.

The 2960 A band also produces the greatest erythema response which so often results in sunburn. The mechanism of the erythema response involves vaso-dilatation. This response is greatest in mid-summer, during mid-day, at lower latitudes and also when aided by reflection from white sand and snow. The question of whether ultraviolet light produces its primary injury in epidermis or dermis is as yet not answered. However, following a sunburn there apparently is an increase in mitosis which reaches a peak at 72 hours, with a resultant thickening of the epidermis. This effect may last for 6 weeks.

The main defense of the skin against the effects of the sun is the brown-black melanin pigment. In a well tanned individual or a person with naturally dark skin, the melanin may decrease the effects of ultraviolet light by up to 90%.
This pigment is produced by melanocytes through a series of oxidations of amino acids. The color of one's skin is determined in part by the amount and dispersion of melanin in the epidermis.

There are other minor skin defenses such as the horny surface layer which scatters and absorbs radiation and also urocanic acid which is found in the epidermis and also absorbs some of the ultraviolet rays.

Of course ultraviolet rays are not all bad. They are necessary for the synthesis of vitamin D. Some dermatologic problems are benefited by ultraviolet ray exposure. Among these are the following: acne, psoriasis, pityriasis rosea, keratosis pilaris, atopic dermatitis, seborrheic dermatitis and nummular eczema.

Unfortunately there is also a long list of disorders which are adversely affected by sunlight. These include porphyria, systemic and discoid lupus, xeroderma pigmentosum, lichen planus, recurrent Herpes simplex, keratosis follicularis (Darier's disease), albinism, pellagra, polymorphic light eruptions and actinic keratosis. Even acne and psoriasis occasionally are made worse by ultraviolet exposure. There are also some rare conditions which have an element of photosensitivity. Among these are conditions such as Bloom's Syndrome, Rothmund's and Thomson's Syndrome, Cockayne's Syndrome, lipid proteinosis, pellagrous dermatitis of carcinoid, Hartnup's Syndrome, phenylketonuria and hydroa aest-
ivale. However this paper shall not dwell on these conditions. They have been mentioned for the purpose of completeness only and not in an attempt to broaden the scope of this thesis.

II. "Descriptive Terms"

Since this paper is dealing with photosensitivity, there are several photo-terms which should be defined in a group now rather than singularly as they appear in later pages. Kirshbaum and Beerman ⁴ presented the following:

Photodynamic action - all forms of change which are evoked by the energy of light.

Photochemical reaction - a chemical reaction brought about by the absorption of light.

Photosensitivity - a reaction in which a substance contained in a biological system, and foreign to that system, initiates an observable change by means of its absorption of light.

Photosensitizer - a substance which absorbs light in the biological system that becomes photosensitized.

Photosensitization - an altered state of reactivity of the skin to light brought about by the action of a chemical substance either ingested or applied topically.

There are two forms of photosensitization; phototoxic and photoallergic. Storck ⁵ differentiates between the two
in the following manner. Photoallergy is considered specific and occurs only in persons specifically sensitized. Photoallergy requires an incubation period between the first contact of the drug and light and the formation of antibodies. This is a variable period of days to weeks. In photoallergy a small amount of the chemical is sufficient to cause a reaction when exposed to sunlight. The induction spectrum may be wide in photoallergy ranging from long wave ultraviolet to visible light. The photoallergic reaction itself may present in several forms such as eczema, urticaria or drug exanthems. On the other hand a phototoxic reaction resembles an intensified sunburn. In photoallergy involvement may occur on areas of the skin which are not exposed to light. This phenomena has not been explained. Following photo-patch testing in photoallergy a positive reaction may be ill-defined and eczematoid. Occassionally during photo-patch testing reactions may reappear in previously involved areas.

These criteria are similar to those of Kirshbaum and Beerman who go on to say that a phototoxic mechanism is a non-immunologic state in which the photosensitizing drug molecule absorbs a quanta of light of a specific wavelength. The absorbed energies are then dissipated into biological systems and produce changes; in this case usually a severe sunburn. These changes tend to occur in 24-48 hours. In photoallergic mechanisms, the photosensitizing drug
molecule also absorbs a quanta of light of a specific wavelength but the activated state leads to a photochemical change in the drug itself which then results in the formation of an allergenic response. Baer and Harber\(^6\) add that in photoallergy the phenomena of photocross-sensitization to immunochemically related allergens is seen.

III. Types of Photosensitivity

One of the most common clinical types of photosensitivity is that following the use of internally administered compounds, especially drugs. Among the most common offenders are: sulfonylurea antidiabetic agents, tetracyclines, griseofulvin, sulfonamides, chlorothiazides and phenothiazines. There will be more said about drug reactions later.

Another type of photodermatitis is seen following contact with furocoumarins. The furocoumarins are that group of basic photosensitizers found in several plant families. One family, Umbelliferae, includes parsnips, carrots, celery, yarrow, angelica, fennel, dill and parsley. The other major family is Rutaceae which includes rue, lime and bergamot. Bergamot is used as an oil base of several perfumes. Epstein\(^7\) says that photosensitivity in animals has been known for a long time, especially from buckwheat and clover. He goes on to say that it is surprising that there seems to be not a single authentic case of photosensitivity in humans from ingested food. He feels that it
is possible, perhaps even likely, that food allergy may play a role in some instances of chronic polymorphic light eruptions.

Among the most photo-active furocoumarins are psoralen (unsubstituted furocoumarin), xanthotoxin (8-methoxy-psoralen) and bergapten (5-methoxy-psoralen). Their formulas are seen below:

\[
\begin{align*}
\text{Psoralen} & \quad \text{Xanthotoxin} & \quad \text{Bergapten} \\
\end{align*}
\]

Musajo and Rodighiero\(^8\) feel that the furocoumarins do not act by a photooxidative mechanism as do many other photodynamic substances. With irradiation, the furocoumarins appear to give a reaction of photocycloaddition with the pyrimidine bases (thymine and cytosine) contained in the native DNA.

Sommer and Jillson\(^9\) state that moist skin from water or sweat is a prerequisite before a reaction involving a furocoumarin and sunlight can take place. They describe the reaction as progressing from erythema to edema with vesicles, to bullae formation, and finally an intense residual hyperpigmentation which may last for months. They state that it is often mis-diagnosed as poison-ivy derma-
titis even though the two are grossly dissimilar.

Certain topical agents are commonly incriminated in photosensitivity. The majority of these result in phototoxic rather than photoallergic reactions. The most common example of this category is the various antibacterial agents used in soaps, detergents and cosmetics. In this group are found hexachlorophene, bithional and the various salicylanilides and carbanilides. Also seen is the group of blankophores added to detergents, white paper and textiles to increase brightness. Another topical agent, tar, which is often used for therapy in dermatology, may act as a photosensitizer also. Patients so treated could be justifiably advised to avoid sunlight for a few days. This topic also will be expanded upon later.

Another well defined but poorly understood reaction to light is the polymorphous light eruption. Although there is a good deal of speculation, this reaction is not known to be due to an exogenous photosensitizer. It is usually seen during spring and early summer when the amount of ultraviolet light is increasing rather than at a maximum. This dermatitis tends to be recurrent and involves the exposed areas. It may be a delayed allergic response as the lesions usually appear 24-36 hours following sun exposure and last for 2-4 days. This dermatitis takes several forms including papules, plaques, vesicles or eczema.
The final group of photo-reactions to be presented are those known as the persistent light reactors. Jillson claims that they are a distinct entity, differing markedly from the papular or eczematous forms of polymorphic light eruptions and diagnosis can be made or suspected by history and clinical observation. It is probably true that an undetermined percentage of these people are still coming into contact with their original photosensitizer; in other words some sort of hidden contact. This might be a product containing an amount of the original chemical which is too small to be recognized or the new product might be chemically related to the original substance. However in other definite cases, what started out as a contact photo-dermatitis can evolve into a persistent light reaction. So far it has not been explained why light allergy persists after the photosensitizer has long been avoided. Atopy may be a part of the answer. Most of the persistent light reactions follow a contact dermatitis. Some of the common contactants include: oleoresins of pollens (ragweed oil dermatitis), promethazine cream, antiseptics (tetrachlorosalicylanilide, bithional, tetrabromosalicylanilide and hexachlorophene) and certain sunscreen agents (monoglycerol para-aminobenzoate and digalloyl trioleate). Again, these reactions flare during the spring and present as burning, disfiguring skin disease.

Willis and Kligman describe the persistent light reactor as an inhabitant of the shadows, being so sensitive
that even indirect sunlight has to be scrupulously avoided. They dismiss the early etiological hypotheses such as:
1) the autologous part of the photoallergic molecule, the protein component of the conjugate, becomes independently capable of initiating the reaction; 2) the permanent alteration of groups or clones of cells so as to make them persistently photosensitive; 3) an autosensitization process similar to some cases of cold urticaria; and 4) the inability of the body to metabolize the hapten responsible for the reaction. They feel that their research demonstrated that the exaggerated light sensitivity is due to the persistence of small amounts of bacteriostatic chemicals in the skin for long periods, up to a year or more. In a highly sensitized subject very small amounts of the chemical and long ultraviolet light are sufficient to trigger the reaction.

IV. Patch Testing

When a photosensitivity is suspected, it is becoming quite common to run a patch test in order to substantiate one's clinical impression. Light testing is considered significant if one of the following can be demonstrated. The test may show a reaction to a wavelength which generally has no effect on normal individuals. The amount of energy required to produce an erythema with radiation of 2900-3200 A may be shown to be decreased. The reaction ob-
tained from exposure to sunburn radiation may be different from that which is usually considered as normal sunburn.

When doing tests for light sensitivity two basic concepts are employed. The first is that of the Minimal Erythema Dose (M.E.D.). The M.E.D. is considered to be the least amount of light exposure necessary to produce a barely perceptible erythema of the skin. The second concept is that of the Delayed Erythema Dose (D.E.D.). This becomes important because some of the photoallergic reactions require intense erythema before becoming manifest. The "delayed erythema" does not appear until after the appearance of the normal sunburn erythema. Testing one may require seven to eight times the M.E.D. and then observation for 7-10 days. After the original sunburn fades about the third day, in positive cases a second and more persistent erythema is seen. It is considered photoallergy if an eczematous reaction appears in the erythema.

One of the more prolific writers in the field of photosensitivity is Epstein. He recommends photopatch testing as an office procedure. He feels that all photoallergic reactions can be reproduced with longwave ultraviolet light in the range of 3200 A. The mechanics of photopatch testing will not be presented; however two practical ideas are pertinent. First, when testing for photoallergy and one is concerned with chemicals that may cause a phototoxic
reaction, it becomes necessary to use a weak enough concentration of the agent in question so as to not cause a phototoxic reaction. Second, when at a complete loss as to what may be causing the photo-reaction, he recommends initial testing with several general and common substances. He starts with the following six chemicals: 1) chlorpromazine, 2) promethazine (Phenergren), 3) bithional (which used to be a part of Johnson's First Aid Cream), 4) tribromosalicylanilide (TBS which is found in Lifebuoy and Safeguard soaps), 5) dibromsalon (found in green Lifebuoy soaps), and 6) tetra-chlorsalicylanilide (which was common in older industrial cleansers and Coleo soap). Not to be forgotten is a very thorough history which may point one's efforts in the right direction.

Willis and Kligman \(^{14}\) have recently further advanced the technique of photopatch testing by utilizing the Scotch Tape Provocative Patch Test. They propose that stripping the skin of its horny layer prior to irradiation will make the recognition of photosensitivity much easier. On one's back the horny layer is about 15 cell layers thick and has numerous melanin granules scattered throughout. They point out that removal of this layer increases both the penetration of light and drugs into the living portion of the skin.
V. Drug Photosensitivity

Many drugs have so far been incriminated in photosensitivity and the list is still growing. The enclosed list contains forty-five drugs and chemicals but by the time this thesis is complete it may have grown to double that number. For example, Kobori and Araki\textsuperscript{15} have recently described eleven cases of photosensitivity to sodium cyclohexysulfamate which is an artificial sweetening agent. Lomberg\textsuperscript{16} also discussed sensitivity to the cyclamate compounds and adds saccharin to the list of agents which may induce photosensitivity. He states that the increasing incidence of abnormal reactions to sunlight may be a reflection of the mounting American avidity for both drugs and sunlight.

Baes\textsuperscript{17} presented a case of bullous photosensitivity to the urinary chemotherapeutic agent, nalidixic acid. He felt that the clinical and histological features suggested a phototoxic reaction and that new blisters can be seen up to six weeks after stopping the acid. Miller and Beltrani\textsuperscript{18} add quinethazone (Hydromox) to the list of diuretics implicated in photosensitivity. Hydromox is chemically similar to Diuril and Hydrodiuril. So far only a decreased erythema threshold has been demonstrated after the administration of quinethazone.

The oral contraceptives have also been incriminated. Erickson and Peterka\textsuperscript{19} presented a case of photosensitivity to Enovid E (norethynodrel and mestranol) and the symptoms could also be reproduced by using Oracon (ethinyl estra-
Drugs Commonly Causing Photodermatitis

1. Sulfanilamide and its derivatives
   a. Sulfathiazole
   b. Sulfapyridine
   c. Sulfamerazine
   d. Sulfacetamide
   e. Sulfadiazine
   f. Sulfamethazine
   g. Sulfaguanidine
   h. Gantrisin
   i. Kynex

2. Sulfonylureas
   a. Carbutamide
   b. Tolbutamide (Orinase)
   c. Chlorpropamide (Diabinese)

3. Chlorothiazides
   a. Chlorothiazide (Diuril)
   b. Hydrochlorothiazide (Hydrodiuril)

4. Phenothiazines
   a. Chlorpromazine (Thorazine)
   b. Prochlorperazine (Compazine)
   c. Promazine (Sparine)
   d. Mepazine (Pacatal)
   e. Trimeprazine (Temaril)
   f. Promethazine

5. Antibiotics
   a. Demethylchlortetracycline (Declomycin)
   b. Tetracycline
   c. Chlortetracycline (Aureomycin)
   d. Griseofulvin
6. Psoralen
   a. 8-methoxypsoralen (Methoxsalen, Oxsoralen, 8 MOP)
   b. 5-methoxypsoralen

7. Antihistamine
   a. Benadryl

8. Metals
   a. Gold salts
   b. Silver salts
   c. Arsenicals

9. Barbiturates
   a. Phenobarbital

10. Quinine
    a. Quinidine

11. Estrogen
    a. Estrone
    b. Diethylstilbestrol

12. Cancer Therapeutic Drugs
    a. Triethylene melamine (T.E.M.)
    b. 5-Fluorouracil (5-FU)

13. Miscellaneous
    a. Hematoporphyrin
    b. Para-aminobenzoate (PABA)
    c. Phenylbutazone (Butazolidin)
    d. Procaine group of anesthetics
    e. Riboflavin
    f. Salicylates (ASA)
    g. Stilbamidine
    h. Bithional
    i. Hexachlorophene
dial). Ortho Novum (norethindrone with mestranol) and diethylstilbestrol (1 mgm/day). Apparently estrogen is the active ingredient in the photosensitivity. The lesions appeared as hypopigmented patches on the dorsa of the hands and forearms and within these patches were erythematous papulovesicular eruptions. Since the eruption could be produced with light passing through window glass the ultraviolet rays responsible were greater than 3200 Å.

Epstein and Taylor, by using photodynamic bioassay, have even demonstrated photosensitive compounds in extracts of finished drinking water. These are polycyclic compounds which get into the water from the soil, fallout from polluted air and domestic or industrial pollution of raw water. Water was mentioned in this section because of its common use as an adjunct to therapy with drugs.

Another common drug which can be added to the list is chlordiazepoxide (Librium). Luton and Finchum discussed mild, generalized skin eruptions seen on sun exposed areas and other sites distant to sun exposure which they felt were a result of sensitivity to Librium. They considered this a type of photoallergic reaction.

The mechanisms involved in drug photosensitization are complicated and not fully worked out. Several theories exist. The chart on page 18 from Baer and Harber gives one of the popular conceived mechanisms for phototoxicity.
and photoallergy.

The reactions seen following the use of drugs capable of inducing photosensitivity take many forms. Many are sunburn-like and intensely erythematous. At times there are exaggerated sunburn-like lesions with edema, vesiculation and bullae formation. Other observed forms include eczematous, lichen planus-like, morbilliform and urticarial. Generally it is the phototoxic type reactions which resemble an exaggerated sunburn. Some drugs are capable of causing both phototoxic and photoallergic reactions. Examples of these include the sulfonamides and phenothiazines. The action spectrum of photoallergy tends to fall in the longer wavelengths of ultraviolet as compared to phototoxicity. Often ordinary window glass, which absorbs most of the ultraviolet radiation below 3200 Å, will prevent phototoxic response. They point out that it is not a single point but a range which generally has a peak or span of highest effectiveness.

Some drugs such as the sulfonamides, phenothiazines and tetracyclines have been the object of extensive study in regard to photo-reactions. In part this may be due to their common usage and also because they have been suspected photosensitizers for a long time. For example the first exanthemata resulting from the combination of light and sulfa was described in 1937. The sensitivity resulting from the sulfa compounds may follow either internal or external use. The reaction may become manifest as either eczematous,
PHOTOSENSITIZING DRUG

Absorption of Electromagnetic Energy (Photons)

PHOTOTOXIC

Change in photosensitizer from ground energy state to excited singlet or triplet energy state

Transfer of energy

Formation of free radicals, peroxides, and heat

Alteration in cell membrane, cytoplasm and/or nucleus

Sunburn-type reaction

PHOTOALLERGIC

Oxidative formation of "new" compound (haptene)

Formation of full antigen (Conjugation of haptene with protein)

Antigen engenders formation of cellular or humoral antibodies

Antigen-antibody reaction upon reexposure to drug plus light

cellular damage

Cutaneous reaction of varied morphology

Data from Baer and Harber$^{22}$
exanthematic or urticarial skin changes. By thorough investigation of the histological changes and conditions of exposure to sulfa and light, both phototoxic and photoallergic mechanisms may be demonstrated.

Photosensitivity to phenothiazine derivatives has long been recognized and also may be either of a phototoxic or photoallergic nature and may follow either external or internal contact. The phenothiazines may be distinguished from the sulfas and tetracyclines in part by their rather extensive photocross-reactions among the various derivatives. The more common reactions seen with the phenothiazines include eczematous, erythematocedematous, morbilliform, scarlatiniform and polymorphous exanthemata.

Two of the phenothiazine derivatives which have demonstrated photosensitivity are thioridazine hydrochloride (Mellaril) and chlorpromazine hydrochloride (Thorazine). Satanove and McIntosh discussed phototoxic reactions following high doses of these compounds. They feel that the critical dosage level required to produce a phototoxic reaction with these compounds is approximately 600 mgm/day for Thorazine and between 400-600 mgm/day for Mellaril. Part of the reaction with these compounds is a hyperpigmentation of a slate-grey to purple color. The development of the hyperpigmentation seemed to be related more to the daily dosage level rather than the length of time the drug was used.
Their theory for the production of the pigmentation starts with the absorption of a photon of light by the high concentrations of Thorazine or Mellaril in the skin thus causing these compounds to enter into an excited state. Next would come a transfer of the energy to the tyrosine-tyrosinase system causing an increase in melanin production. The melanin, with its ability to trap free radicals, would then combine with the irradiated drug or its metabolites with the production of an amorphous structure with a purplish color.

The tetracyclines are a commonly used broad spectrum antibiotic and are another drug often implicated in photosensitivity. So far reactions have only followed internal contact with tetracyclines and all reactions have been of a phototoxic nature. Until recently only demethylchlortetracyclines of the tetracycline family had demonstrated photodynamic action. Now Cullen and Catalano claim that all the commonly used tetracyclines may induce photosensitivity. Apparently the capacity to photosensitize lies in the unsaturated resonating ring structure of the tetracycline molecule and this capacity may be augmented by chlorination. They do admit that photosensitivity following the use of tetracycline and oxytetracycline does not occur as frequently as following the use of chlortetracycline and demethylchlorotetracycline.
Verhagin\textsuperscript{26} agrees that several of the tetracyclines, essentially those mentioned above, do cause photosensitivity. He points out that the majority of the reactions are seen in the following: 1) groups treated with high doses, 2) groups with chronic liver disease and retarded breakdown of the drug and 3) young children with low M.E.D. and fair skin. Blank, Cullen and Catalano\textsuperscript{27} took an interesting and appealing experimental approach by giving their subjects oral demethylchlorotetracycline or doxycycline for a week and then taking them on a sea voyage to maximize their sun exposure. They were successful in producing reactions in 9 of 10 on demethylchlorotetracycline and in 2 of 10 on doxycycline. Maibach, Sams and Epstein\textsuperscript{28} also experimentally reproduced tetracycline photosensitivity but only after the erythema producing rays of the sun were excluded by a plastic film and not at all when artificial light sources were used. Their artificial light sources apparently lacked sufficient energy in the 3200 Å range.

VI. Soap Sensitivity

It has been 7 years since Wilkinson\textsuperscript{29} first described photodermatitis due to tetrachlorosalicylanilide which was then an agent of common household soap. Harber, Targovnik and Baer\textsuperscript{30} report that now there are over 200 cases of photosensitivity to halogenated salicylanilides and related compounds in the literature. According to
Harber, Harris and Baer, antimicrobial agents have been employed in soaps for the past 15-20 years. Their purpose being to decrease the bacterial flora of the skin and in so doing decrease the body odor by decreasing the amount of bacterial decomposition of skin surface elements such as lipids and sweat. These antimicrobial agents have generally been hydroxy-halogenated benzene rings which are cross-linked to a halogenated benzene ring which may or may not carry a hydroxyl group. It would seem probable that photosensitivity to these agents existed before 1961 but was not recognized as such. Hjorth and Wilkinson report that 55% of the United States population now uses soaps with antibacterial agents. They also point out that many popular brands of deodorant soaps have switched from tetrachlorosalicylanilide to trichlorocarbanilide with a subsequent decrease in reported cases of sensitivity.

Among the antibacterial agents employed are: dichlorophene, bithional, hexachlorophene, 3,4,4' trichlorocarbanilide (TCC), 3,4',5 tribromosalicylanilide (TBS), and 3,3',4',5 tetrachlorosalicylanilide. As can be seen on page 23, these compounds are structurally quite similar. Freeman and Knox state that cross reactions between salicylanilides and related germacides such as bithional and hexachlorophene are common. Epstein and Enta theorized that if cross-sensitization originates with a potent sensitizer, then less-sensitizing members of the same
Formulas of Several Common Antimicrobial Agents

Dichlorophene

Bithional

Hexachlorophene

3,4,4' Trichlorocarbanilide

3,4',5 Tribromosalicylanilide

3,3',4',5 Tetrachlorosalicylanilide
chemical group are less likely to cross react. However, if a chemical with a low-sensitizing potential causes the original sensitization, then cross-sensitization to the more potent sensitizers of the same group can be expected.

Another problem arising with the antiseptic soaps is presented by Molloy and Moyer. In addition to the contents stated on the package, the soap may contain trace amounts of other chemicals. Thus there would be some difficulty in attributing the source of the photosensitivity on the basis of testing with the soaps alone since an impurity may be the causative agent. Another problem which has been reported when photo-patch testing with soaps is a delayed positive reaction. The reaction may not appear for up to 96 hours which necessitates observation of the site for longer than the usual 24-48 hours.

Ison and Tucker presented a series of 12 cases of typical photosensitive dermatitis from soaps. Their reactions were sharply demarcated, of moderate severity and eczematous. They too noted one case in which the photo-patch test was not positive until 96 hours. The soaps involved were white and colored Lifebuoy, Safeguard and Zest.

Histologically in the acute reaction one sees eczematous epidermal changes with spongiosis and vesicle formation. Edema of the upper dermis and about vessels is common. In the chronic, lichenified lesions there is acanthosis, hyperkeratosis and parakeratosis.
According to Epstein and Enta\textsuperscript{39} the sensitizing agent may penetrate the epidermis via three routes. These are through the follicular area, the sweat ducts or through the unbroken stratum corneum. Previous damage to the skin will increase the occurrence of reactions.

Although the basic mechanism of the photosensitivity to the salicylanilides and related compounds is not fully understood, the theories proposed are for the most part quite similar; at times differing only as to definitions and phrasing. The hypothesis of Harber, Targovnik and Baer\textsuperscript{40} is that the effect of light is to form a highly reactive moiety (free radical halogenated salicylanilide) that combines with cutaneous proteins and forms a nondialyzable salicylanilide protein unit. It is this unit or "photoantigen" to which a minute percentage of the population develops an immunologic response and becomes photoallergic.

Willis and Kligman\textsuperscript{41} feel that photocontact allergy is simply a form of contact allergy in which light transforms the "photosensitizer" into a potent contact allergen. The products of this phototransformation can elicit the reaction in the absence of light. For example, the transformation products of 3,4',5 tribromosalicylanilide (TBS) would be 4',5 dibromosalicylanilide (DBS) and 4' monobromosalicylanilide (MBS). In this case, MBS is the most potent contact allergen.

\section*{VII. Differential Diagnosis}

Before advising your patient to avoid sunlight, one
must consider the other possibilities. Pillsbury and Caro feel that a reasonable differential should include contact dermatitis, drug eruptions, neurodermatitis and erythema multiforme in addition to photosensitivity reaction. Of obvious importance is an adequate history in an attempt to determine if contact has been made with one of the photosensitizing agents. The distribution of the dermatitis is also important. The exposed areas such as the face, "V" of the neck, hands and arms are commonly involved although involvement of sun protected areas has been reported. One should remember that with a contact dermatitis the eyelids are often involved first. Also with contact dermatitis the medial aspect of the arms may be involved rather than the lateral.

VIII. Treatment and Prevention

It is apparent that as we grow older many changes take place in our physical and metabolic stature. These changes are perhaps most obvious in our skin, its appendages and subcutaneous fat.

Daniels notes that many of the changes seen in the aging skin also are produced or aggravated by ionizing radiation or by ultraviolet radiation. Among these changes are thinning and depigmentation of hair, decreased sebum, increased dryness, and thinning and atrophy of the epidermis. The skin develops wrinkles, folds and sags as the dermis
loses its elasticity and becomes thinner. Also seen are dilatation of blood vessels, uneven pigmentation, development of keratoses and small angiomas. It must be remembered that these are for the most part naturally occurring processes. Add to these an element of photosensitivity and you have further alteration of skin homogeneity. For example the dermatitis of photosensitization may result in large amounts of melanin entering the dermis. Prophylactic use of sun screen agents by the population as a whole simply for their cosmetic value is not feasible although protection from the sun is a necessity when photosensitivity is present.

Typically a photocontact dermatitis is treated as any contact dermatitis. The acute stage requires wet compresses and mild lotions. Later corticosteroid ointments may be used. Antihistamines may be of value for urticarial eruptions. Severe cases may necessitate the use of short courses of systemic corticosteroids.

Having accomplished adequate therapy of the acute photosensitivity reaction one needs to consider means for preventing recurrence or progression of the dermatitis. In other words one must either remove the photosensitizing agents or protect the susceptible individual from sunlight. Since removal of the agent is often impossible, (eq., the persistent light reactors, systemic disease) one must then strive for protection. The commonly employed methods include:
1) limiting exposure to sunlight, 2) applying a film which will decrease ultraviolet radiation by opaqueness or absorption and 3) oral medications such as the psoralens and anti-malarials. 45

The combination of 8-methoxypsoralen and ultraviolet light has been shown to result in increased pigmentation and increased thickening of the epidermis, especially the stratum corneum. 46 On the other hand, quinine and similar compounds are able to protect the epidermis by their ability to polarize light. 47

The films mentioned earlier are the anti-sunburn ointments and lotions of which there are three general categories. P-aminobenzoic acid absorbs ultraviolet rays between 2900-3150 Å. The benzophenones absorb all ultraviolet rays. Finally there are the opaque preparations containing zinc or titanium oxide which provide a shield-like effect. There are several solar protective agents on the market. Among the most popular are: 1) UVAL (a benzophenone), 2) A-FIL (menthyl anthranilate and titanium dioxide), 3) RVP (red petrolatum additive free), 4) Solbar (a benzophenone), 5) Sun Dare (2-ethoxyethyl p-methoxycinnamate and alcohol), and 6) Reflecta (a hypo-allergenic). The advertising lines for these compounds are similar and in brief are as follows: 1) prevents sunburn, freckling and aging of the skin due to overexposure to sunlight, 2) protects sunsensitive people against damaging sun rays, 3) pro-
tects against a wide range of the sun's burning rays but permits tanning, 4) absorbs UV rays, 5) prevents burning and permits tanning, and 6) a sun and winter hypo-allergenic protective.

As an adjunct to this thesis on the problem of photosensitivity it was decided to attempt to compare the relative protective ability of these sun-screens. This was done in the following manner. The source of ultraviolet light was natural sunlight during mid-day in August. The site of exposure was previously untanned Caucasian skin of the back and each test site was one square inch. The adjacent skin was protected with adequate drapes. The time of exposure varied from 30-60 minutes depending on when erythema became visible on the control sites. Results were read immediately and the amount of visible erythema was labeled as none, trace, 1+ and 2+. Only a very thin film of the respective agents was applied. Results are seen on page 30.

These results are in no way intended to promote one product over another but merely to point out the varying degrees of protection available to any one person. In a simple comparison such as this there are many factors which cannot be controlled such as individual sensitivity, time of exposure, objectivity of examiner and thickness of film applied. There has been and will be much more elaborate testing done. For example Kooyers has developed
### SUN SCREEN AGENTS

<table>
<thead>
<tr>
<th>CONTROL</th>
<th>SOLBAR</th>
<th>RVP</th>
<th>AFIL</th>
<th>REFLECTA</th>
<th>UVAL</th>
<th>SUN DARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2+</td>
<td>trace</td>
<td>2+</td>
<td>2+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>2</td>
<td>1+</td>
<td>trace</td>
<td>trace</td>
<td>trace</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2+</td>
<td>trace</td>
<td>1+</td>
<td>trace</td>
<td>1+</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>2+</td>
<td>trace</td>
<td>2+</td>
<td>2+</td>
<td>1+</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>2+</td>
<td>trace</td>
<td>trace</td>
<td>1+</td>
<td>2+</td>
<td>1+</td>
</tr>
<tr>
<td>6</td>
<td>2+</td>
<td>1+</td>
<td>2+</td>
<td>2+</td>
<td>1+</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>2+</td>
<td>trace</td>
<td>2+</td>
<td>2+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>8</td>
<td>2+</td>
<td>1+</td>
<td>2+</td>
<td>1+</td>
<td>2+</td>
<td>1+</td>
</tr>
<tr>
<td>9</td>
<td>trace</td>
<td>trace</td>
<td>trace</td>
<td>1+</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>10</td>
<td>2+</td>
<td>trace</td>
<td>2+</td>
<td>1+</td>
<td>1+</td>
<td>trace</td>
</tr>
</tbody>
</table>

Scale of Increasing Erythema

0, trace, 1+, 2+
a method for testing the efficacy of topical sunscreen preparations using photosensitive albino rats. His method involves pretreatment of one hind paw with a sunscreen preparation followed by oral administration of a photosensitizing agent and exposure to direct sunlight. Following the delayed reaction, Kooyers determined that the resulting difference between the treated and untreated hind paw weight was an objective index of the protection afforded by the preparation used.

IX. Conclusion

The purpose of this paper was to present the scope of photosensitivity as an expanding, ever growing problem. The contents were, by necessity, broad. For in this manner the magnitude of this relatively new entity was emphasized.

The amount of material presented under each heading was roughly proportional to the literature available. By far the bulk of the literature to date deals with drug and soap sensitivity.

In an effort at originality, an experimental comparison was made of several popular sunscreen agents. This was not an attempt to determine the best of these compounds but rather to show that the clinical response of the subject varies with the agent used. In other words, one must find the best drug for each patient. What works for one may well be ineffective in the next person.
BIBLIOGRAPHY


25. Cullen, S.I.; and Catalano, P.M.; and Helfman, R.J.: Tetracycline Sun Sensitivity, Arch Derm 93: 77 (Jan) 1966.


