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Current Status of Mammalian and Human Models for Predicting Drug Photosensitivity

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The status of efforts to develop experimental models for drug photosensitivity reactions in small mammals is reviewed. Tests which are practical and also have a high predictive value in determining photosensitivity hazards to man are the goal of this research. The various animal model systems which have been used are evaluated with respect to these goals.

It is widely recognized by both the laity and the scientific community that the introduction of an innumerable number of new chemicals into our environment has been a "double-edged" sword. Although many of these compounds have contributed to improving the "quality of life," others have been associated with hazards. The reported undesirable reactions from chemicals have ranged from the oncogenic effects of diethylstilbesterol in the offspring of pregnant women [1] to the hepatotoxic effects of tetrachlorodibenzo-p-dioxin [2].

The number of adverse responses considered to be drug photosensitivity reactions account for only an exceedingly small percentage of the total undesirable effects from environmental chemicals. However, the rising incidence and severe disability, especially when of the persistent light-reactor type [3], indicate that increased photobiologic research and developmental efforts are required. Predictive tests are an obvious approach to minimize or eliminate those chemicals in which the risk-benefit ratio shows them to be undesirable to society in general, or to an unknowing individual in particular.

Historically, the term "drug photosensitivity" had been widely used in clinical medicine to designate certain adverse reactions associated with the administration of a medication to a patient who was subsequently exposed to sunlight. Although it was originally limited to therapeutic agents, its current usage has been widely expanded and now includes a large group of chemicals found in cosmetics, food preservatives, household cleaners, fragrances, industrial products and by-products, and agricultural items [4].

This report represents a brief overview of the current status in the development of more effective drug photosensitivity models with predictive value. It stresses laboratory mammalian models and human photosensitivity test systems.

HISTORICAL

Eighty years ago, Raab described a photosensitivity model characterized by loss of motility of the cilia of paramecia when these organisms were exposed to an acridine dye and light. Exposure to the dye or light alone evoked no reaction [5]. This was not only the start of modern photobiology, but also a classic demonstration of the adverse type of response referred to today as "drug photosensitivity." Numerous classifications of drug photosensitivity occurring in man have been noted. Table I is a composite [6, 7]. Other unrecognized forms may also exist but have not been sufficiently recognized as distinct entities. The 2 major mechanisms that are involved in the pathogenesis of drug photosensitivity reactions are "phototoxic" and "photoimmunologic." The current status of testing or assaying photosensitivity associated with these 2 mechanisms will be assessed. Chemicals reported to cause phototoxic and photoallergic reactions in man are listed in Tables II & III. Mechanisms and chemicals involved in other types of drug-induced photosensitivity (drug-induced porphyria, lupus, and pellagra) have previously been reviewed [6].

DRUG INDUCED PHOTOTOXICITY

Phototoxic reactions are the most frequent and best understood type of drug photosensitivity reaction. They can occur in 100% of the population on first exposure. Using appropriate experimental conditions, a dose-response curve can be demonstrated with the incidence of phototoxicity reaction being related to the concentration of the photosensitizer and the intensity of the appropriate wavelength of light. Similarities and differences between phototoxic and photoallergic reactions are summarized in Table IV.

Biochemical and biologic techniques for studying phototoxic drug reactions have been of major value in elaborating the basic photochemical and biophysical principles of photobiology, but at present offer inadequate predictive models for man.

Biochemical

The development of a simple and effective *in vitro* laboratory test of predictive value for drug photosensitivity of the phototoxic type remains an ideal goal [38]. Recent studies by Schorthorst, Suurmond, and deLuster [39] describing biochemical alterations in amino acids, glutathione, and unsaturated fatty acid indicate promise. Unfortunately, these tests presently do not meet the desired predictive standards.

Single Cell Systems

Models reported useful for assaying phototoxicity of compounds have included cell cultures [40] red blood cells [41], paramecia, fungi and viral systems. However, all of these test systems produce data which fail to correlate well with the occurrence of photosensitivity reactions in man to the same agents. On a subcellular level the specific receptor site for phototoxic damage has been shown to involve various cellular constituents including the nucleus [42], cytoplasmic organelles [43], as well as the cell membrane [44, 45]. These too although of basic science interest are of limited clinical value. Both cellular and subcellular models have been reviewed by Spikes [46], Morikawa et al [47] and Harber, Baer, and Bickers [48]. The common denominator in all these assays has been the detection of a biologic or chemical alteration in the system associated with the introduction of a phototoxic agent followed by light exposure. However, not one of the systems described has had the complete success required for a predictive model to assess the photosensitizing potential of these chemicals in man. Some of the systems have produced false-positive responses while others have failed to detect commonly encountered phototoxic agents. These inadequacies are due to numerous factors, including: (a) failure to account for variations in the percutaneous absorption of potential photosensitizers; (b) failure to account for variations in gastrointestinal absorption, cutaneous storage, and excretion of different photosensitizers; (c) failure

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TABLE I. *Photosensitivity reactions to drugs*

Reaction	Example	Theoretical mechanism
Drug phototoxicity	Psoralen	DNA binding
Drug photoallergy	Halogenated salicylanilides	Delayed hypersensitivity
Drug-induced porphyria	Hexachlorbenzene	Hepatic prophyrinogenesis
Drug-induced lupus	Hydralazine	Slow acetylator phenotype; DNA binding
Drug-induced pellagra	Isonicotinic acid	Altered tryptophan metabolism
Depigmentation	P-tertiary-butyl phenol	Unknown

TABLE II. *Chemicals inducing phototoxicity in man*

Chemical	Reference
Aminobenzoic acid derivatives	8
Anthraquinone dyes	9
Chlorothiazides	10
Chlorpromazine	11
Coal tar derivatives	12,13
Anthracene	
Acridine	
Phenanthrene	
Pyrene	
Nalidixic acid	14
Phenothiazine	15
Protriptyline	16
Psoralens	17,18,19
Sulfanilamide	20,21
Tetracyclines	22,23,24

TABLE III. *Chemicals reported to induce photoallergic reactions in man*

Chemical	Reference
Aminobenzoic acids	25
Bithionol	26,27
Chlorpromazine (thorazine)	28
Chlorpropamide (diabinese)	29
Fentichlor	30
Halogenated salicylanilides	31
Jadit	32
6-Methylcoumarin	33
Musk ambrette	34
Promethazine (phenergan)	35
Sulfonilamide	36
Thiazides	37

to account for hepatic and cutaneous metabolic alteration of potential photosensitizers; (d) failure to account for inactivation of the photosensitizer by other body constituents.

Consequently, it is appropriate that this report emphasizes mammalian systems as they more closely approximate conditions in humans. The relative strengths and weakness of these predictive mammalian model will be noted. However, even with the use of these systems, which have been shown to have a higher predictive value, there still remains inherent limitations when the phototoxicity data derived from animals is applied to the actual environment conditions encountered by humans.

EXPERIMENTAL MAMMALIAN ANIMAL MODELS DEMONSTRATING PHOTOTOXICITY

Phototoxicity has been demonstrated with relative ease in numerous mammalian animal models including mice, rats, rabbits, swine, and guinea pigs. Table V lists several animal models which have been successfully used to induce phototoxic reactions. Each has relative advantages and disadvantages as noted below.

Mice

Drug phototoxicity studies by Rothe and Jacobus [49] as well as those of Ison and Blank [50] have shown the feasibility of using Swiss Webster albino mice. Ison and Blank have demonstrated the superiority of an assay based on intraperitoneal injections of phototoxic agents to mice as compared a fungal culture model.

Topical application of photosensitizers and irradiation of swiss albino mouse ears has also been assayed. The major advantage of this procedure is that in contrast to the back, depilation is unnecessary. Hairless mice studies have recently been used [47]; However, their major photobiologic use has been in oncogenic studies such as the carcinogenic effects of ultraviolet light with or without the topical application of retinoids. In addition edema of the tail of mice has been used as a measure of phototoxicity [51].

Advantages: Mice are relatively inexpensive and easy to house and handle. Phototoxic assays can be made on the basis of edema, erythema, and necrosis observed on the ears and tail [51]. When hairless mice are used, no depilating procedures are required.

Disadvantages: The thinness of the mouse epidermis as compared to man results in a larger percentage of UVB radiation reaching the basal cell layer, connective tissue, and vasculature. This increases the potential for false-positive reactions. In addition, false-positive reactions can be obtained following minimal trauma to affected sites as compared to other experimental animals such as the guinea pig. It is also more difficult to evaluate and assess erythema in mice than guinea pigs. Even

TABLE IV. *Mechanisms of drug-induced photosensitivity: Comparison of phototoxic and photoallergic reactions in test models*

Reaction	Phototoxic	Photoallergic
Incidence	Usually relatively high (theoretically 100%)	Usually lower
Reaction possible on first exposure	Yes	No
Incubation period necessary after first exposure	No	Yes
Can persistent light reaction develop	No	Yes
Cross-reactions to structurally related agents	No	Frequent
Passive transfer	No	Possible
Lymphocyte stimulation test	No	Possible
Macrophage migration inhibition test	No	Possible

TABLE V. *Mammalian models effective in demonstrating phototoxicity*

Mammal	Example of photosensitizer	Selected references
Mouse (whole body)	Demethyltetracycline	(50,47)
(ear)	Chlorpromazine	(51)
(hairless)	O-dimethylamino benzoic acid	(7)
Rats	Psoralen	(47)
Rabbit	Psoralen	(47,58)
Pig (miniature)	Psoralen	(53)
Guinea pig (back)	Psoralen	(54)
(ears)	Demethylchlortetracycline	(56)

though Ison and Blank reported successful induction of photosensitization with most of the common phototoxic agents using intraperitoneal injections as a test system; the chlorothiazides proved to be an exception.

Rats

Rats have been used to assay photosensitivity to topical agents and to assay changes in porphyrin synthesis which may relate to photosensitivity.

The phototoxic model in rats is similar to the one recently described in mice [51] and also measures tail edema. It involves the assay of the phototoxic reaction of the rat tail which is excised then weighed wet, and again after drying. This value is compared to a control animal that is treated identically except that the animal is unirradiated.

Advantages: A dose-response curve representing phototoxic inflammation can be quantitatively expressed in terms of edema for any one photosensitizing agent.

Disadvantages: Difficult to make comparisons between different photosensitizers based on edema response.

The rat can also be used as a sensitive biologic assay to measure porphyrin synthesis by quantitating urinary excretion of porphyrins. The indirect induction technique involves systemic administration of nonphotosensitizing agents per se such as hexachlorobenzene [52].

Advantages: Rats are exquisitely sensitive and ideally suited for hepatic enzyme induction studies [52]. Agents such as allylisopropylacetamide, dicarbethoxy-dihydrocollidine, and griseofulvin administered as part of the diet can serve as effective models for studying induction of porphyrins. It is this increased rate of synthesis of normal heme metabolites that in selected instances, results in photosensitivity in man. This subject has been reviewed in depth by De Matteis [52].

Disadvantages: Use of the rat as an *in vivo* model is relatively expensive and also poses animal handling problems. The actual sensitivity of the enzyme induction potential of drugs is too great, and the experimental data does not closely correlate with findings in man. Another disadvantage is that for photobiologic studies in rat skin, it is often necessary to depilate the animals, a procedure which adds a non physiologic trauma and is difficult.

Rabbits

Data by Morikawa indicate rabbits should be of considerable value in screening for phototoxicity of topically applied photosensitizers [47]. These male albino animals weighing 2.5–3.0 kg have been used in relatively few published photobiologic studies. Depilated skin on the back of the animal serves as the test site.

Advantages: Rabbits appear to develop phototoxic reactions more readily and respond with greater erythema than do guinea pigs [47]. Far superior to mice and rats in terms of sensitivity and ease in assaying erythema.

Disadvantages: These are relatively large and expensive animals. Facilities to house large numbers pose a problem as compared to mice, rats, and guinea pigs.

Miniature Swine

These animals have been used in relatively few published studies [53] but appear promising. The phototoxic agents studied have been topically applied to the restrained animals.

Advantages: Skin thickness, closely approximate man. Urbach, (personal communication) feels that studies using miniature pigs for assaying phototoxic damage to the vasculature in the cutis are valuable for investigating the response to 8-methoxypsoralen and similar agents.

Disadvantages: Large and expensive. Require specialized animal facilities, and more personnel for experimental procedures.

Guinea Pigs

These are probably the most widely used small laboratory mammal for studying topical phototoxicity agents [54–58]. Noninbred albino animals are commonly used. These are usually of the Hartley strain.

Advantages: Investigators often prefer guinea pigs as they are relatively docile, widely available, and have a good erythema response to ultraviolet type B radiation. Data correlates well with man for vast majority of topical agents. Erythema is clearly visible as compared to mice and miniature swine.

Disadvantages: must be depilated, thinner epidermis than man, poor animal for inducing tumors following repetitive drug photosensitivity reactions. Cost for purchase and housings expensive as compared to mice.

Extensive studies designed to investigate species variation in drug photosensitivity responses have been limited. One of the most comprehensive of these concerned species differences in phototoxic responses and was reported by Morikawa [47]. 8-methoxypsoralen (8-MOP) was used as a reference standard of comparison as noted in Table VI. Morikawa et al noted that the threshold and magnitude of phototoxic reaction to 8-MOP in decreasing order was: miniature swine, hairless mouse, guinea pig, rat and rabbit. They also reported that the hair cycle was found to influence the phototoxic reaction in rabbit skin. More sensitivity to phototoxic agents was noted during telogen than anagen phase [47].

A comparison of 21 well-known photosensitizers was also made by Morikawa in rabbits and guinea pigs. Data indicated that both qualitatively and quantitatively rabbits were more sensitive than guinea pigs in assaying for phototoxicity.

EXPERIMENTAL HUMAN MODELS FOR DEMONSTRATING PHOTOTOXICITY

Photosensitivity assays in man for predicting the phototoxic potential of chemicals has been comprehensively reviewed by Maibach and Marzulli [59]. In general these studies can be done with relative ease on the lower lumbar area of volunteers, and if only small body areas are exposed do not pose an undue hazard. However, before human studies are instituted as a precautionary measure toxicity and phototoxicity studies in animals are advised. Table VII lists selected types of human assays. Each has relative advantages and disadvantages as noted below.

Scotch Tape "Stripping"

This so-called "maximization test" has shown application to both phototoxic and photoallergic compounds [60, 61]. A xenon

TABLE VI. *Evaluation of species difference in phototoxic reaction to 8-methoxypsoralen [47]*

Species	Phototoxic reaction to 8-MOP		
	0.0025%	0.001%	0.005%
Rabbit [a]	10/00	8/10	3/10
[b]	8/10	1/10	0/10
Rat[a]	10/10	9/10	2/10
Mouse[a]	0/10	0/10	0/10
Hairless Mouse	1/6	0/6	0/6
Guinea Pig	10/10	2/10	0/10
Miniature Swine	0/5	0/5	0/5

Phototoxic reaction to 8-methoxypsoralen (8-MOP) was read at 48 hr. The hair cycle was at the telogen[a] and anagen[b] phase (Morikawa).

TABLE VII. *Assay of phototoxic agents in human models [58]*

Technique	Example of photosensitizer	Reference
Scotch tape stripping	Eosin	60, 61
Intradermal injection	Chlorothiazides	62
Clinical test ("boat ride")	Tetracyclines	63, 64

lamp is the usual light source and relatively physiologic amounts of drug are used.

Advantages: The instrument used for irradiation studies (Solar simulator) emits ultraviolet light similar to sunlight. As part of a photobiologic unit it has been used to demonstrate a broad range of phototoxic agents in man and animals.

Disadvantages: The cellophane "stripping" was an ineffective procedure for demonstrating phototoxicity to sulfonilamide, tetracycline, and chlorothiazide [60]; the system is also hard to standardize and may cause pain. The trauma of the procedure predisposes to localized bacterial infection.

Intradermal Injection of Photosensitizer

The lower back of volunteers receives an intradermal injection of 0.1 ml aliquots of the photosensitizer in saline solution or suspension delivered with a 27-gauge needle. This is followed in 10 to 30 min by UVA or UVB radiation.

Advantages: This system has relative ease of use, wide application, and good correlation with actual clinical experience. This technique is similar to that used by S. Epstein to classically demonstrate phototoxicity to sulfanilamide. There is slight pain.

Disadvantages: Unable to demonstrate phototoxicity to tolbutamide and chlordiazepoxide [62]. Material must be incorporated into liquid vehicle at proper pH with no primary irritant properties.

Clinical Test

Direct application to skin of topical phototoxic agents has been standardized using lumbar and scrotal tissue [59, 63] with known types and amounts of light.

A more direct and reliable method has been the modified usage test as reported by Frost [63]. This clinical model was used for assaying phototoxicity to methacycline as compared to demethylchlortetracycline and a placebo using natural sunlight as a light source [64]. The test consisted of a double-blind evaluation of erythema 1 day after 50 volunteers had participated in 6-hr boatride under intense Florida sunlight. The scores of the test material were thus compared to a known photosensitizer and a placebo.

Advantages: Most accurately duplicates actual exposure conditions in which photosensitivity might occur. In actuality is a "usage" test.

Disadvantages: A relatively large number of volunteers necessary. It is difficult to control or duplicate actual test condition in terms of temperature and amount of light exposure.

PHOTOALLERGIC REACTIONS

Drug photosensitivity can also be mediated by a photoimmunologic mechanism. The role of light is restricted to photochemically altering the hapten or causing its combination with "carrier" protein. Following formation of this "photoantigen," it is believed to be processed by macrophages and then to come in contact with T-cell lymphocytes as in an "ordinary" delayed-hypersensitivity immunologic response. The complete photoantigen is recognized on subsequent exposure when "sensitized" T-cell lymphocytes are present. An immunological response is then initiated which results in erythema in laboratory animals and a papulovesicular, eczematous response in man. This hypothesis has been supported by *in vitro* and animal studies. The photoadducts of tetrachlorosalicylanilide and Jadit (4-chloro-2-hydroxybenzoic acid-N-n-butylamide) in combination with protein were tested for elicitation of immunologic responses in *in vitro* systems and have been found to give positive test results [66, 67]. Passive transfer of photosensitivity to tetrachlorosalicylanilide using peritoneal mononuclear from photosensitized guinea pigs, has been demonstrated [68, 69].

Although many photosensitizing compounds have been cited in the clinical literature as mediated by a photoimmunologic mechanism (Table III) only a few of these have been verified in experimental models. The most comprehensive data concerning photoallergy to halogenated salicylanilides and its derivatives being induced in laboratory animals was that of Morikawa et al [47]. Classic examples of clinical reports include chlorpromazine [70], bithionol [71], Jadit [72], and promethazine [73].

EXPERIMENTAL ANIMAL MODELS DEMONSTRATING PHOTOALLERGY

The successful induction of experimental photoallergic contact dermatitis in guinea pigs was first reported by Schwarz and Schwarz-Speck [74] in 1957 with sulfanilamide. Following this Vinson and Borselli induced contact photoallergic reactions with tetrachlorosalicylanilide [75] which has been confirmed by several other groups [47, 68, 69, 76–78]. More recently contact photoallergy to musk ambrette [79] and 6-methylcoumarin [80] have been induced.

The guinea pig has been the only experimental animal used to demonstrate photosensitivity of the delayed-hypersensitivity type in all of the reported animal studies. Hartley strain albino guinea pigs (375–425 gm) are ideal. Whenever possible animals are kept in individual cages. However, if it is necessary to have 2 or more animals housed together, females appear to be preferable as there is likely to be less scratching of phototest sites.

Table VIII lists the techniques of inducing contact photoallergy in guinea pig models. Following induction and a suitable incubation period, elicitation has always been accomplished with topical application of the photosensitizer followed by ultraviolet A radiation. Each model has relative advantages and disadvantages as noted below.

INDUCTION TECHNIQUES

The typical induction procedure consists of the topical application of a relatively high concentration (10 to 100 times more than the lowest eliciting concentration) of the photosensitizer followed by irradiation. This induction procedure solely involves the nuchal region. Elicitation is restricted to the depilated surface of the back and is repeated 3–5 times during a 7 day period.

UVB Irradiation

This model first introduced by Vinson and Borselli [75] has undergone numerous modifications and is an excellent one for inducing photosensitivity to halogenated salicylanilides and its derivatives. It employs the use of both UVA and UVB radiation during the induction phase.

Advantages: Widely established model that has been duplicated in several laboratories [47, 68, 69, 76–78].

Disadvantages: Ineffective in inducing photoallergy to methyl coumarin and musk ambrette. Eyes of the investigator must be protected (goggles), against corneal burns from UVB exposure.

TABLE VIII. *Techniques used to increase index of photoallergic contact dermatitis in guinea pigs*

Nuchal[a] technique	Example of photosensitizer	Reference
Ultraviolet radiation (Type B)	Halogenated salicylanilides	47,68,76,77,78
Sodium lauryl sulfate	Halogenated salicylanilides	81
Skin "stripping" with cellophane tape	Musk ambrette	79
Stripping plus intradermal injection of Freund's adjuvant	Musk ambrette Methyl coumarin	80

[a] These procedures preceed irradiation of topically applied chemical with ultraviolet (Type A) radiation.

Sodium Lauryl Sulfate

This system introduced by Horio offers promise and should be further evaluated [81]. The induction procedure consists of the topical application of a 20% aqueous solution of sodium lauryl sulfate to the nuchal area. One hour later the photosensitizer is applied to the same site and immediately followed by UVA radiation. This procedure is repeated 5–10 times during a 10-day period.

Advantages: Appears simple and effective. Good index of photosensitization to halogenated salicylanilides and bithionol.

Disadvantages: Limited reports of usage by photobiologists.

Skin "Stripping" with Cellophane Tape

The induction procedure consists of the repeated application of cellophane "Scotch" tape to the nuchal site until "glistening" is noted. The photosensitizer is then applied after which the site is irradiated with UVA. The procedure is repeated 3 to 5 times during a 7-day period. The rationale of stripping may involve increased percutaneous absorption of photosensitizer, but the effectiveness of the model may also be related to an inflammatory response.

Advantages: Appears analogous to maximization test in man. Was successful for induction of musk ambrette photosensitivity in guinea pigs [79].

Disadvantages: Ineffective in inducing photoallergy to methylcoumarin, difficult to standardize. Thick crust often forms on nuchal induction site.

Intradermal Injection of Freund's Adjuvant

The induction procedure consists of the intradermal injection of Freund's adjuvant into the corners of the depilated and "stripped" nuchal area. The photosensitizer is then topically applied and removed with acetone 30 min later. Following this, the site is irradiated with UVA. The procedure is repeated 5 times during a 10-day period although Freund's adjuvant is employed only the first time. Preliminary studies indicate this may be the method of choice [80]. Reservations regard the possibility that this system may be an overly sensitive model.

Advantage: Easy to use and standardize. Has high index of photosensitization.

Disadvantage: May be overly sensitive; has not been sufficiently assessed for false positives. Excellent for inducing photoallergic reactions to halogenated salicylanilides, musk ambrette, and methyl coumarin [80].

EXPERIMENTAL HUMAN MODELS FOR DEMONSTRATING PHOTOALLERGY

In 1968 Willis and Kligman [82, 83] reported the experimental induction of photoallergic contact sensitization to halogenated salicylanilides and related chemicals in human volunteers. This system has been widely reproduced. Unfortunately, it has been associated with the induction of persistent light reactors and really should not be used if a suitable animal model can be substituted [82, 83].

REFERENCES

1. Robboy SJ, Kaufman RH, Prat J, Welch WR, Gaffey T, Scully RE, Richart R, Fenoglio CM, Virata R, Tilley B: Pathologic findings in young women enrolled in the National Cooperative Diethylstilbestrol Adenosis (DESAD) Project. Obstet Gynec 53:309–317, 1979
2. Pitot HC, Goldswarthy R, Campbell HR, Poland J: Quantitative evaluation of the promotion by 2,3,7,8-tetrachlorodibenzo-p-dioxin of the hepatocarcinogenesis from diethylnitrosamine. J Cancer Res 40:3616–3620, 1980
3. Fisher AA: Contact photodermatitis Contact Dermatitis. Philadelphia, Lea and Febiger, 1973, pp 197–214
4. Harber LC, Levine GM: Photosensitivity dermatitis from household products. GP 39:95–100, May, 1969
5. Raab O: Ueber die Wiekung fluorescirender Stoffe auf Infusorien. Z Biologie, 39–43, 524, 1900
6. Harber LC, Baer RL: Pathogenic mechanisms of drug-induced photosensitivity. J Invest Dermatol 58:327–342, 1972
7. Emmett EA: Phototoxicity from exogenous agents. Photochem Photobiol 30:429–436, 1979
8. Hjorth N, Moeller H: Phototoxic textile dermatitis. Arch Dermatol 112:1445–1447, 1976
9. Gardiner JD, Dicksen A, MacLeod TM, Frain-Bell W: The investigation of photocontact dermatitis in a dye manufacturing process. Br J Dermatol 86:264–271, 1972
10. Sams WM Jr, Epstein JH: The experimental production of drug phototoxicity in guinea pigs. I. Using sunlight. J Invest Dermatol 48:89–94, 1967
11. Epstein JH, Brunsting LA, Peterson MC, Schwarz BE: Study of photosensitivity occurring with chlorpromazine therapy. J Invest Dermatol 28:329–338, 1957
12. Crow KD, Alexander E, Buck WHL, Johnson BE, Magnus IA, Porter AD: Photosensitivity due to pitch. Br J Dermatol 73:220–232, 1961
13. Foerster HR, Schwartz L: Industrial dermatitis and melanosis due to photosensitization. Arch Dermatol 39:55–68, 1939
14. Ramsay CA, Obreshkova E: Photosensitivity from nalidixic acid. Br J Dermatol 91:523–528, 1974
15. De Eds F, Wilson RH, Thomas JO: Photosensitization by phenothiazene. JAMA 114:2095–2097, 1940
16. Kochevar IE, Lamola AA: Chlorpromazine and protriptyline phototoxicity: Photosensitized, oxygen independent red cell lysis. Photochem Photobiol 29:791–796, 1979
17. Pathak MA, Fitzpatrick TB: Photosensitivity caused by drugs. Radiation Drug Therapy 6:1–6, 1972
18. Harber LC, Harris H, Leider M, Baer RL: Berloque (Berlock) Dermatitis. Arch Dermatol 90:572–576, 1964
19. Forbes PD, Urbach F, Davies RE: Phototoxicity testing of fragrance raw materials. Fd Cosmet Toxicol 15:55–62, 1977
20. Epstein J: Photoallergy and primary photosensitivity to sulfanilamide. J Invest Dermatol 2:43–51, 1939
21. Buckhardt W: Untersuchungen uber die photoaktivitateiniger sulfonamide. Dermatologica 83:63–69, 1941
22. Morris WE: Photosensitivity due to tetracycline derivatives. JAMA 172:1155–1156, 1960
23. Falk MS: Light sensitivity due to demethylchlortetracycline. JAMA 172:1156–1157, 1960
24. Harber LC, Tromovitch TA, Baer RL: Studies on photosensitivity due to demethylchlortetracycline. J Invest Dermatol 37:189–193, 1961
25. Mathias CGB, Maibach HI, Epstein J: Allergic contact photodermatitis to Para-aminobenzoic acid. Arch Dermatol 114:1665, 1978
26. O'Quinn S, Kennedy CB, Isbell KH: Contact photodermatitis due to bithionol and related compounds. JAMA 199:125–128, 1967
27. Jillson OF, Baughman RD: Contact photodermatitis from bithionol. Arch Dermatol 88:409–418, 1963
28. Epstein JH, Brunsting LA: Topical application of chlorpromazine: Its effect on the erythema response to ultraviolet light. J Invest Dermatol 30:91–94, 1958
29. Hitselberger JF, Fosnaugh RP: Photosensitivity due to chlorpropamide. JAMA 180:62–63, 1962
30. Burry JM: Photoallergies to fentichlor and multifungin. Arch Dermatol 95:287–291, 1967
31. Wilkinson DS: Photodermatitis due to tetrachlorosalicylanilide. Br J Dermatol 73:213–219, 1961
32. Burry JM, Hunter GA: Photocontact dermatitis from Jadit. Br J Dermatol 82:224–229, 1970
33. Kaidbey KH, Kligman AM: Photocontact allergy to 6-methylcoumarin. Contact Dermatol 4:277–282, 1978
34. Raugi GJ, Storrs FS, Larsen WG: Photoallergic contact dermatitis to men's perfume. Contact Dermatol 5:251–260, 1979
35. Sidi E, Hincky M, Gervais A: Allergic sensitization and photosensitization to Phenergan cream. J Invest Dermatol 24:345–352, 1955
36. Peterkin GA: Skin eruptions due to the local application of sulphonamides. Br J Dermatol 57:1–9, 1945
37. Harber LC, Lashinsky AM, Baer RL: Skin manifestations of photosensitivity due to chlorthiazide and hydrochlorothiazide. J Invest Dermatol 33:83–84, 1959
38. Harber LC, Kochevar IE, Shalita AR: Mechanisms of photosensitization to drugs in man, Photomedicine. Edited by J Parrish, in press, Plenum Press
39. Schothorst AA, Suurmond D, deLuster A: A biochemical screening test for the photosensitizing potential of drugs and disinfectants. Photochem Photobiol 29:531–537, 1979
40. Freeman RG: Interaction of phototoxic compounds with cells in tissue culture. Arch Dermatol 102:521–526, 1970
41. Kahn Q, Fleischaker B, I: Red blood cell hemolysis by photosensitizing compounds. J Invest Dermatol 56:85–90, 1971
42. Musajo L, Rodghiero G: Studies on the photocyclo-addition reactions between skin photosensitizing fuorcoumarins and nucleic acids. Photochem Photobiol 11:27–31, 1970
43. Allison AC, Magnus IA, Young MR: Role of lysosomes and of cell membrane in photosensitization. Nature 209:874–878, 1966
44. Fleischer AS, Harber LC, Cool JS, et al: Mechanism of in vitro photohemolysis in erythropoietic protoporphyrin. J Invest Der-

matol 46:505–509, 1966
45. Schothorst AA, Van Stevenick J, Went LN, Suurmond D: Protoporphyrin-induced photohemolysis in protoporphyria and in normal red blood cells. Clin Chim Acta 28:41–40, 1970
46. Spikes JD: Photodynamic action. Photophysiology, vol. 3. Edited by Giese. New York, Academic Press, 1968
47. Morikawa F, Nakayams Y, Fukada M, Hamono M, Yokoyama Y, Nagura T, Ishihara M, Toda K: Techniques for evaluation of phototoxicity and photoallergy in laboratory animals and man, Sunlight and Man. Edited by TB Fitzpatrick, MA Pathak, LC Harber, M Seiji, A Kukita. Tokyo, Tokyo University Press, 1974, pp 529–557
48. Harber LC, Baer RL, Bickers DR: Techniques of evaluation of phototoxicity and photoallergy in biologic systems, including man, with particular emphasis on immunologic aspects, Sunlight and Man. Edited by TB Fitzpatrick, MA Pathak, LC Harber, M Seiji, A Kukita. Tokyo, Tokyo University Press, 1974, pp 518–528
49. Rothe WE, Jacobus DP: Laboratory evaluation of the phototoxic potency of quinoline methanols J Med Chem 11:366–371, 1968
50. Ison A, Blank H: Testing drug phototoxicity in mice. J Invest Dermatol 49:508–511, 1967
51. Ljunggren B, Moeller H: Phenathiazine phototoxicity: An experimental study in chlorpromazine and its metabolites. J Invest Dermatol 68:313–317, 1977
52. DeMatteis F: Disturbances of liver porphyrin metabolism caused by drugs. Pharmacol Rev 19:523–557, 1967
53. Bay W, Gleiser CA, Dukes TW, Brown RS: Experimental production and evaluation of drug-induced phototoxicity in swine. Toxicol Appl Pharmacol 17:538–547, 1970
54. Pathak MA, Kramer DM, Fitzpatrick TB: Photobiology and photochemistry of furocoumarins (psoralens), Sunlight and Man: Normal and Abnormal PhotoBiologic Responses. Edited by TB Fitzpatrick, MA Pathak, LC Harber, M Seiji, A Kikuta. Tokyo, University of Tokyo Press, 1974, pp 131–141
55. Levine GM, Harber LC: The effects of humidity on the phototoxic response to 8-methoxypsoralen in guinea pigs. Acta Dermato Venerol (Stockh) 49:82–86, 1969
56. Sams W: The experimental production of drug phototoxicity in guinea pigs. Arch Dermatol 94:773–777, 1966
57. Schwarz J, Schwarz-Speck M: Experimentelle untersuchungen zur frage der photoallergic der sulfonamide. Dermatologica 114:232–243, 1957
58. Morikawa F: Correlation between contact photosensitivity data obtained from man and laboratory animals. Jap J Dermatol Ser A 82:794–801, 1972
59. Maibach HI, Marzulli FN: Phototoxicity (photoirritation) from topical agents, Animal Models in Dermatology. Edited by H Maibach. Churchill Livingstone, Edinburgh, London, and New York, 1975, pp 84–89
60. Kligman A, Breit R: Identity of phototoxic drugs by human assay. J Invest Dermatol 51:90–99, 1968
61. Burdick K: Phototoxicity of Shalimar perfume. Arch Dermatol 93: 424–425, 1966
62. Kaidbey KH, Kligman AM: Identification of systemic phototoxic drugs by human intradermal assay. J Invest Dermatol 70:272–274, 1978
63. Marzulli FN: Perfume phototoxicity. J Soc Cos Chem 21:685–715, 1970
64. Frost P, Weinstein GD, Gomez EC: Methacycline and demechlocycline in relation to sunlight. JAMA 216:2, 326–329, 1971
65. Herman PS, Sams WM Jr: Requirement for carrier protein in salicylanilide sensitivity: The migration inhibition test in contact photoallergy. J Lab Clin Med 77:572–579, 1971
66. Herman PS, Sams WM Jr: Immunologic investigation, Soap Photodermatitis. Springfield, IL, Charles C. Thomas, 1972
67. Jung EG, Hornke J, Hajdu P: Photoallergic durch 4-Chlor-2-hydroxybenzoesauer-N=butylamid. Arch Klin Exp Dermatol 233: 287–295, 1968
68. Harber LC, Targovnik SE, Baer RL: Contact photosensitivity to halogenated salicylanilides: In man and guinea pigs. Arch Dermatol 96:646–656, 1967
69. Harber LC, Baer RL: Mechanisms of drug photosensitivity reactions. Toxicol Appl Pharmacol 3:58–67, 1969
70. Epstein S: Chlorpromazine Photosensitivity. Arch Dermatol 98: 354–363, 1968
71. Jillson OF, Baughman RD: Contact photodermatitis from bithionol. Arch Dermatol 88:409–418, 1963
72. Fregert S, Moller H: Photo cross-sensitization among halogenhydroxybenzoic acid derivatives. J Invest Dermatol 43:271–274, 1964
73. Sidi E, Hincky M, Gervais A: Allergic sensitization and photosensitization to Phenergen cream. J Invest Dermatol 24:345–352, 1955
74. Schwarz K, Schwarz-Speck M: Experimentelle Untersuchunger zur Frage der Photoallergic der Sulfonamide. Dermatologica 114: 232–243, 1957
75. Vinson LJ, Borselli VF: A guinea pig assay of the photosensitizing potential of topical germicides. J Soc Chem 17:123–130, 1966
76. Herman PS, Sams WM Jr: Requirement for carrier protein in salicylanilide sensitivity: The migration-inhibition test in contact photoallergy. J Lab Clin Med 77:572–579, 1971
77. Griffith J, Carter RD: Patterns of photoreactivity and cross reactivity in persons sensitive to TCSA. Toxicol Appl Pharmacol 12: 304–309, 1968
78. Cripps DJ, Enta T: Absorption and action spectra studies on bithionol and halogenated salicylanilide photosensitivity. Br J Dermatol 82:230–242, 1970
79. Kochevar IE, Zalar GL, Einbinder J, Harber LC: Assay of contact photosensitivity to musk ambrette in guinea pigs. J Invest Dermatol 73:144–146, 1979
80. Ichikawa H, Armstrong RB, Harber LC: Photoallergic contact dermatitis in guinea pigs: Improved induction technique using Freund's complete adjuvant. J Invest Dermatol, submitted for publication
81. Horio T: The induction of photocontact sensitivity in guinea pigs without UVB radiation. J Invest Dermatol 67:591–593, 1976
82. Willis I, Kligman AM: The mechanism of photoallergic contact dermatitis. J Invest Dermatol 51:378–384, 1968
83. Willis I, Kligman AM: The mechanism of the persistent light reactor. J Invest Dermatol 51:385–394, 1968