Vol XVII No 2 5 February 1966

Journal of the Society of Cosmetic Chemists

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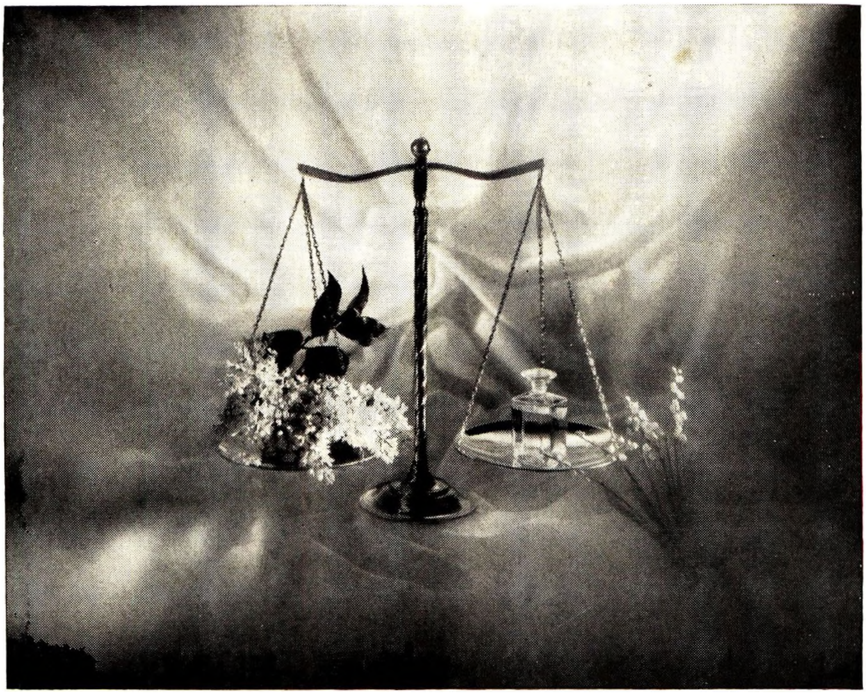

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Journal of the Society of Cosmetic Chemists

VOLUME XVII • NUMBER 2

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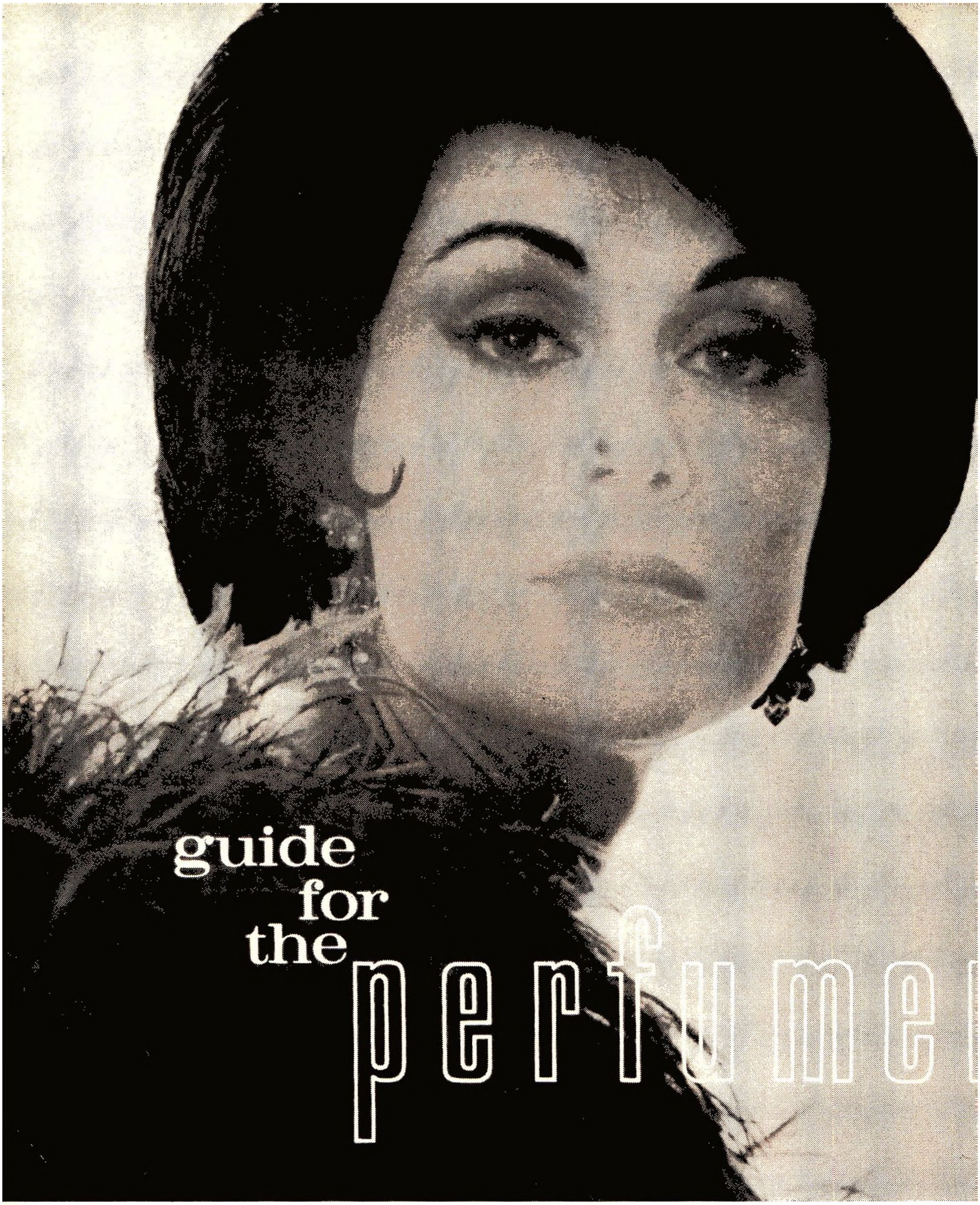

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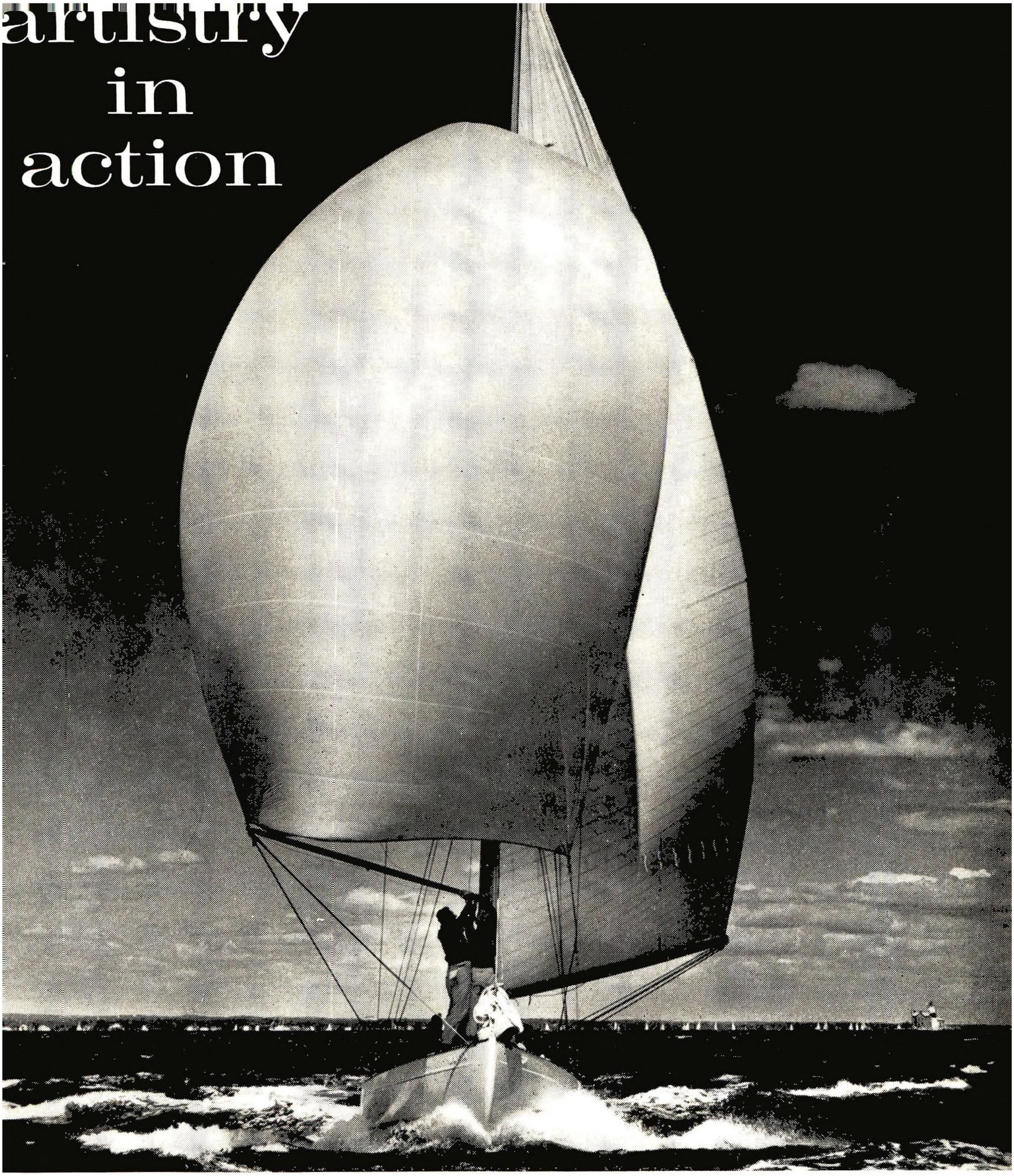
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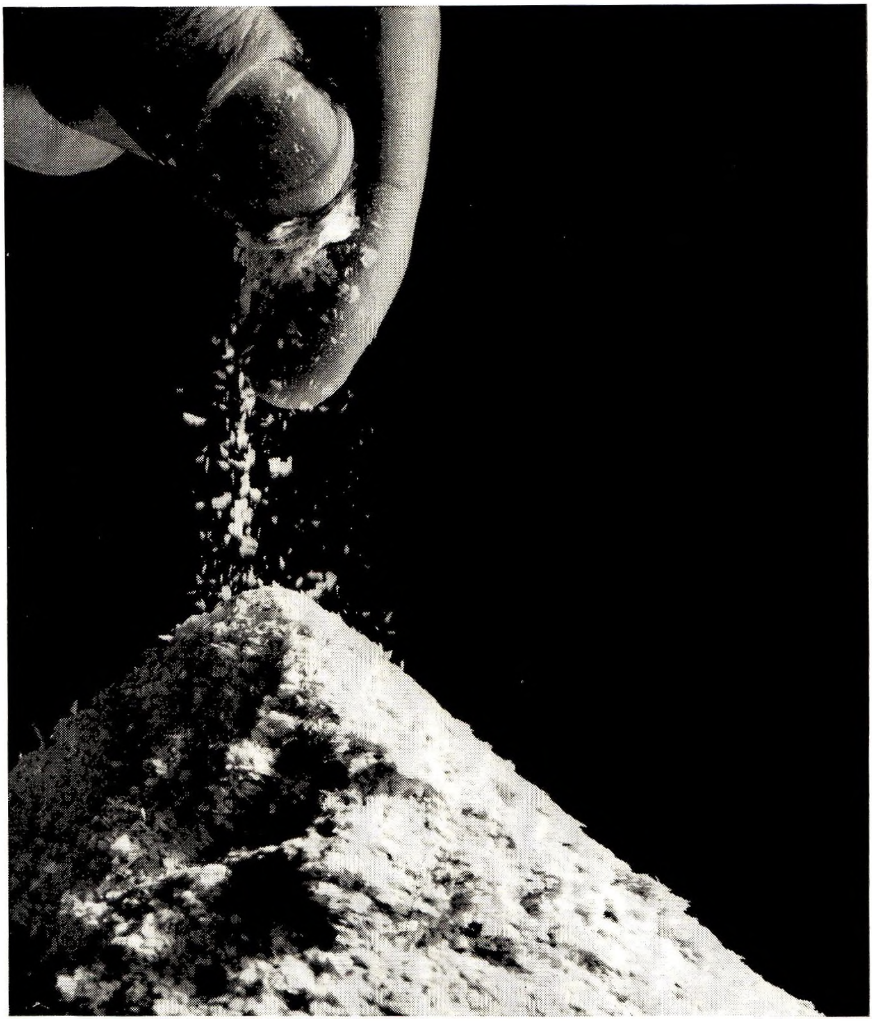

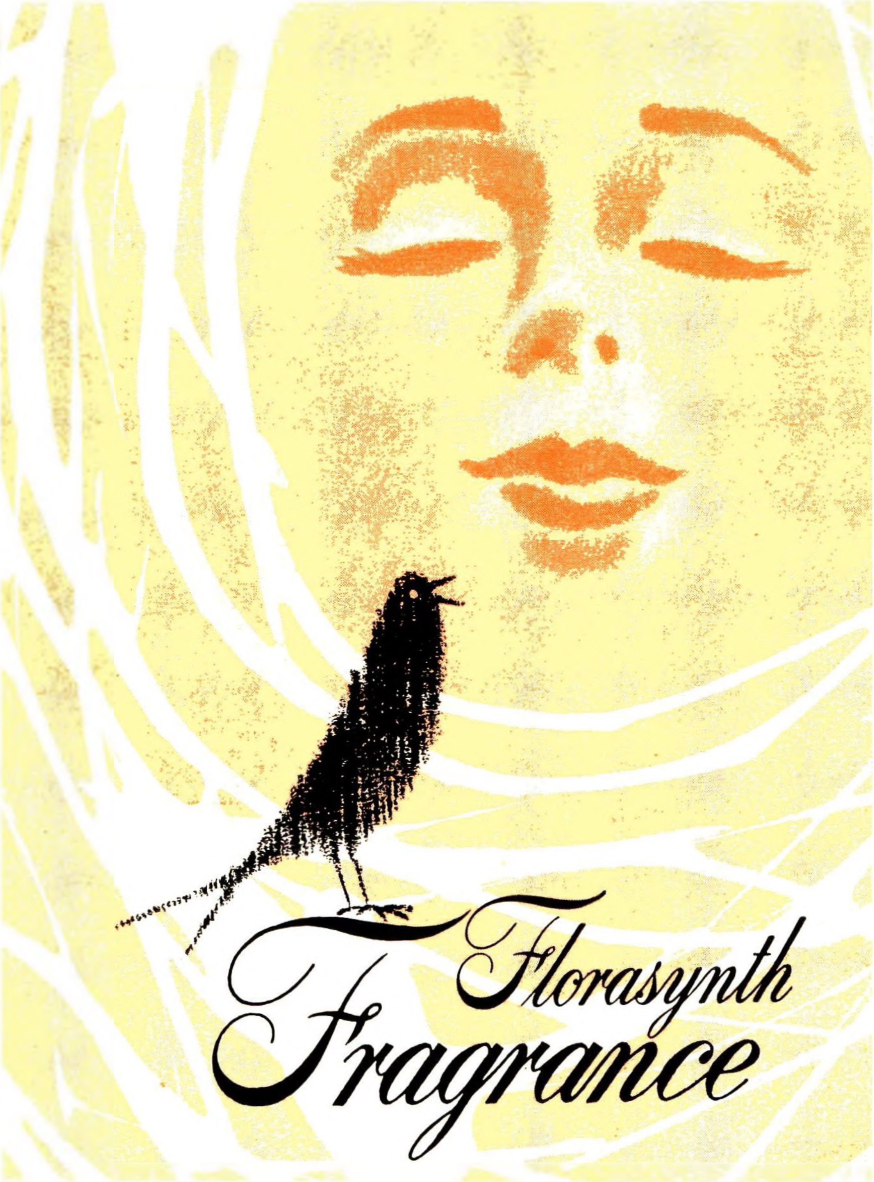
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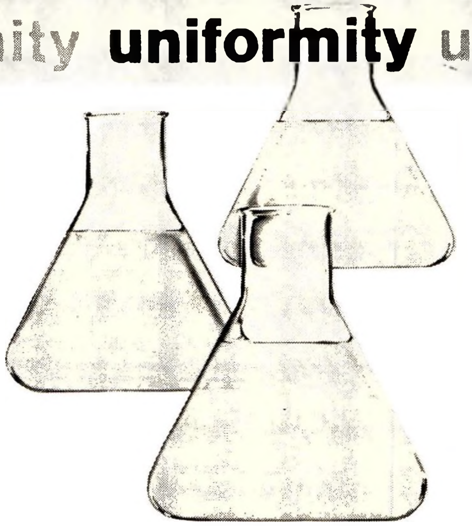

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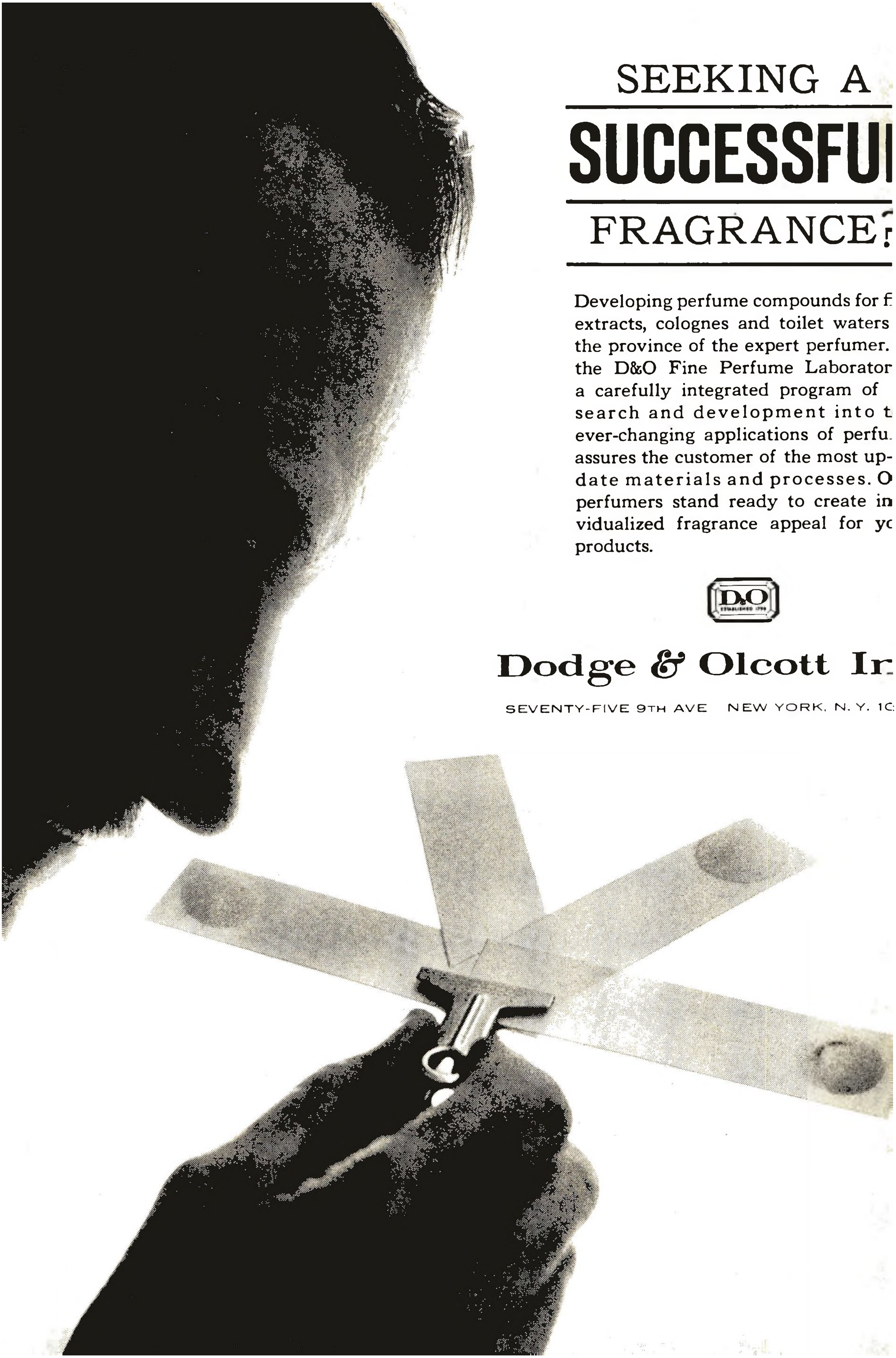

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Aqueous topical adhesives II. Spray-on bandage: Winthrop E. Lange and Victor S. Fang. *Journal of the Society of Cosmetic Chemists* **17,** 115 (1966).

Synopsis—The research and development of protective films for cosmetic and dermatological uses have been of interest to many groups in recent years. Many of these preparations in pressurized packaging are known as "spray-on bandages." They usually deposit film on the skin which cannot be readily washed off. Thus the development of a preparation containing water-washable resins was considered advantageous.

A combination of polyvinyl alcohol with either polyvinyl acetate or acrylic resins produced aerosol concentrates with good stability and film-forming properties. Incorporation of the concentrates into quick-breaking foam formulations gave products with good stability and bandage properties. The products when sprayed on the skin dried to transparent, tack-free films in approximately 10 minutes.

A guinea pig assay of the photosensitizing potential of topical germicides: Leonard J. Vinson and Vincent F. Borselli. *Journal of the Society of Cosmetic Chemists* **17,** 123 (1966).

Synopsis—In recent years there has been increasing use of germicides in soaps, detergents, and cosmetic products to provide significant benefits in the control of odor and minor secondary infections. Even though these agents are carefully screened for safety and effectiveness, an occasional one which reaches the mass market is found to be a marginal sensitizer that escaped detection in animal tests and limited human panel studies.

A guinea pig assay procedure is described which measures the photosensitizing potential of topical germicides. Data are presented relating the photosensitizing and cross photosensitizing activities of commercial germicides, *viz.*, bisphenolics, halogenated salicylanilides, and halogenated carbanilides. Tetrachlorosalicylanilide and, to a lesser degree, bithionol are observed to be photosensitizers. The significance of these findings and results on other germicides in predicting the acceptability of a topical agent in soaps and cosmetics is discussed.

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Annual Report of the President

PAUL W. JEWEL

1965

This is my annual report to the Society regarding the activities of the President and the Officers and Directors during the year 1965.

Being the 20th President represented something of a milestone in the history of the Society. This was the first time that a president was chosen from the Far West; this was the first time that each of the Elected Officers came from the four separate chapters of the Society.

The difficulties inherent in attempting to administer this organization from Los Angeles when the bulk of the members and the head office of the Society are located in the New York area should be apparent. Also, this year the 11th Annual Seminar was held in Los Angeles, thus adding to the problem.

However, the smoothly organized group which constitutes this Society, combined with the complete cooperation of all of the Officers, Directors, Committee Chairmen, and Committee Members, made it possible for me to discharge the duties of President with comparative ease.

I have always been impressed with the idea that the most effective way in which the prestige of this organization could be enhanced was continually to upgrade, as far as possible, the scientific papers presented at our meetings.

Accordingly, I appointed Win Lange to act as Program Chairman for the main meetings and Bob Conner for the Seminar. These two were instructed to put into effect the policy of having only papers of unquestioned scientific value, definitely publishable, for all meetings of the Society.

The results I leave to your critical appraisal. It is my opinion that the program presented at the December 1 Meeting of the Society has been the best we have had. I am sure my successor, Bill Mueller will continue this policy.

This report would not be complete without a special kudo for the Seminar Committee. This was, by all odds, the most dedicated, efficient, and hard-working group of men and women I have ever seen; Ken Walker as General Chairman, Clive Ross as Entertainment Chairman, Harold Jackson as Honorary Chairman, and last but not least Marie Carroll, Executive Secretary of the California Chapter, who handled all of the arrangements with the hotel. Without Marie the Seminar would certainly have cost more and might have resulted in a sizable deficit instead of very nearly breaking even.

Everybody, without exception, who attended the 11th Annual Seminar has reported that it was the best ever, and they all expressed the hope that the Annual Seminar might be held in Los Angeles again soon. The California Chapter certainly proved to be excellent hosts.

This year the Publications Committee again chose the recipient of the IFF Award. This is $1000 contributed by International Flavors and Fragrances, Inc., for the best paper published in the United States edition of THE JOURNAL OF THE SOCIETY OF COSMETIC CHEMISTS. The award was given to J. Facq, D. L. Kirk, and G. A. Rebell for a paper entitled: "A Simple Replica Technique for the Observation of Human Skin." Everybody agrees that Marty Rieger and his group made a wise choice. This is in addition to the enormous amount of work they do in the publication of our JOURNAL.

The Literature Award, also consisting of $1000, was presented to William Griffin and Paul Becher, not for any one paper but for their numerous contributions to cosmetic emulsion technology over a period of many years. The Literature Review Committee, which chooses the recipient of this award, has a very difficult task to perform. It is the duty of its members to review all of the world's literature in order to select one paper which they deem worthy of receiving the award. The thanks of the Society go to Willard Somerville, Bob Goldemberg, and their associates.

Paul Lauffer and his Metal Award Committee chose Sophie Plechner to be the recipient of the Medal Award for this year. She was selected for her excellent work in the field of antiperspirants as well as her outstanding contribution to the Society and especially to women in the Society. This choice merits the approval of all of the members. The committee could hardly have done better. The formal presentation of the award was made at the banquet, December 1, 1965.

Each year a considerable number of members are delinquent in their dues. The by-laws of the Society provide that these delinquents must be arbitrarily dropped from membership at an appointed time. This year I asked the Chapter Chairmen to interview personally each of these members to ascertain if he really wanted to give up his membership. The result was that a great number decided to pay their dues and remain in the Society rather than be dropped. A little personal attention by individual members would help also. If you know someone who has not paid his dues or who does not attend meetings regularly, talk to him and try to find out what is wrong. You might thus help keep a member in the Society rather than let him be dropped.

Milton Schwarz and his Membership Committee increased our members by 78 net after resignations and drops. We passed the 1000 mark in active membership for the first time this year.

Three awards were made by the Chapter Awards Committee this year. For the New York Chapter the award went to Thomas F. McNamara for a paper entitled; "Skin Substantivity as a Criterion in the Evaluation of Antimicrobials." For the Northeastern Chapter to Martin G. Brookins for a paper entitled: "The Action of Hair Sprays on Hair." For the Midwest Chapter to Karl Laden for a paper entitled: "A Comparative Chemical Study of Dandruff Flakes, Skin Scrapings, and Callus." Each of these awards carries a prize of $250 to the author. I am sorry to report that the California Chapter did not submit a paper for consideration this year.

The International Affairs Committee under the leadership of Lester Conrad is busily taking care of our International obligations, among which are the plans for the International Congress at Paris in 1966.

Jesse Starkman as Chairman of the Education Committee has prepared a model Syllabus for use in courses in Cosmetic Science, and already several universities are considering giving such courses. It is to be hoped that the day will come when degrees will be given in this field.

The Arrangements Committee under Shaw Mudge has managed our meeting requirements efficiently and well. Next year we will move from the Biltmore to the Americana, a change which will meet with universal approval.

The committees not specifically mentioned here are not left out because their work has not been done but because the nature of their activities is such that they rarely make the front pages of the newspapers.

Jim Baker has been preparing the by-laws for a reprinting, and hopefully we will have an up-to-date edition in the very near future.

The Nominating Committee prepared a very good slate of candidates for your consideration. After the votes were counted it was found that Henry Maso will be your President-Elect, Harry Isacoff will continue as Secretary, Bob Swaine as Treasurer, and the Directors for 1966 will be Maison G. de Navarre, James W. Jenkins, Richard K. Lehne, and Martin Rieger. William Mueller will, of course, automatically become President. With this group of officers and directors the Society will be in good hands.

In accordance with the by-laws Article III, Section 3, a general meeting of the Society was held December 1 immediately after the final paper of the morning session.

According to the report of our Treasurer, Bob Swaine, we spent less money in 1965 than our income, so we are in good sound financial condition.

During the year I worked very closely with Bill Mueller, then President-Elect, who is now becoming your President. He has known of all policy decisions, and all correspondence has been copied to him. This, however, was no one-way street. His advice and counsel on several occasions was most helpful to me. I am sure that 1966 will show him to be very effective. He will make an outstanding president.

Finally I would like to thank all of the Officers, Directors, Committee Chairmen, and Committee Members as well as the General Membership for their help in making it possible for me to function as President of this Society. Everybody went way out above and beyond the call of duty to do the best job he could do. Believe me, I am very grateful.

The Seventeenth Medal Award

December 1, 1965

Hotel Biltmore, New York City

Dr. Sophie Louise Plechner, Associate Research Director of Carter Products, was honored by the Society of Cosmetic Chemists for her scientific achievements and for her services to the Society. Dr. Plechner received the Medal of the Society during its annual Dinner Dance.

Mr. James H. Baker acted as toastmaster and Mr. Robert Kramer was the eulogist. Dr. Paul W. Jewel, as President of the Society, presented the Medal with the following citation:

Award to

Sophie L. Plechner for Outstanding Contribution
to the Art and Science of Cosmetics.

Sophie Louise Plechner

EULOGY BY ROBERT A. KRAMER*

My fellow members and friends of the Society of Cosmetic Chemists:

This evening we are recognizing an unusual woman for her contributions to the art and science of cosmetics. That grand lady is none other than our charming colleague, Dr. Sophie Louise Plechner. We do honor to Dr. Plechner for the more than three decades she has spent in fostering the growth of cosmetic science.

Like Jack Benny, our honored guest is an ageless 39. She was born Sophie Louise Coppersmith and has spent her entire life in New Jersey. At the age of 20, she graduated with honors from the New Jersey College for Women at Rutgers University on a Newark High School Alumni Scholarship. Sophie majored in mathematics but turned to chemistry when she decided to improve her marks in that subject, with the result that she became both a good mathematician and an excellent chemist.

Then came three years of teaching chemistry, algebra, and geometry in New Jersey high schools, following which she earned her Master's Degree in 1927 and Doctorate in 1929 at Columbia University.

Her college ties with Rutgers have always remained strong. She was a director of her College Alumnae from 1939 through 1947; its treasurer from 1947 to 1953; and vice president from 1953 to 1958. Her contributions through her alumni work brought her an Award for Alumnae Service from Douglass College in 1948.

The year 1929 was an historic one for Sophie. After receiving her doctor's degree from Columbia University, she joined Bristol-Myers as a cosmetic research chemist, then culminated this glorious year of 1929 by marrying Walter W. Plechner on that memorable October 26th, the day of the stock market crash. Still keeping in step with renowned events, her son, Richard, was born when Roosevelt was first elected in November of 1932. He and his loving wife, Eleanor, are with us this evening, and it is they who have made Sophie a grandmother three times over during the past ten years.

The only time we delve into the personal background of a member of the Society of Cosmetic Chemists is on occasions such as this banquet

---

* Evans Chemetics, Inc., New York, N. Y. 10017

Dr. Sophie L. Plechner (l.) after receiving the Society's Medal from Dr. Paul Jewel (r.), President of the Society

when we honor one of our colleagues. It is not likely that many of you know that Sophie's husband, Walter, was also a Ph.D.; a chemical engineer; an Assistant Research Director of the National Lead Company; and a Colonel in the U. S. Army, First Division, Headquarters Staff, during World War II. Colonel Plechner was killed in action in North Africa in March, 1943.

Following this tragedy in her life, Sophie returned to our industry in 1943 by joining Carter Products, Inc., now called Carter-Wallace, Inc., where she is now an Associate Director of Research.

Sophie was selected for the Medal Award of our Society because of her long record of achievement and publications covering a broad spectrum of cosmetic and related sciences. After her thesis at Columbia University on "Properties of the Amylase of Aspergillus Oryzae or Taka

Diastase" she wrote a handbook on "Food, Drugs and Cosmetics" for Consumers Research. Following that she wrote a bulletin on "Trichophytosis," better known as "Athlete's Foot."

While Sophie has over-all scientific knowledge of our industry, it is in the field of antiperspirants and deodorants that she excels. When the editors of the book, "Cosmetic Science & Technology," were searching for someone to write the chapters on antiperspirants, there was only one person they could select; that was our dear friend, Sophie.

Just to indicate to you one of the advances she has made on the frontier of cosmetic science, I shall read to you an example of an area covered by her work, on which four patents were issued jointly to her and Dr. Frank M. Berger of Carter-Wallace, Inc.: Combinations of astringent salts as new active ingredients in antiperspirant preparations containing aluminum sulfate, sodium zirconium lactate and a long series of titanyl mono- and di-lactates.

In Sophie, we have a very serious and quiet person whose mere presence brings out the best in any group. Her fellow scientists have the greatest respect for her ability, which accounts for her outstanding reputation in our field. In every type of operation, in her matchless and orderly manner, Sophie made scientific contributions to the many committees on which she served, never seeking or expecting a reward but always being willing to serve when there was something of importance to be done. Thus, the Toilet Goods Association selected her for its Scientific Advisory Committee in 1947, and she became, in 1954, the first woman to serve as the Chairman of its Scientific Section.

The Society of Cosmetic Chemists recognized her outstanding work by having her serve on one committee after another, electing her a Director in 1957 through 1959 and then selecting her in 1961 as its first and only woman President.

The Toilet Goods Association and the Society of Cosmetic Chemists will long remember her outstanding ability, her sincere desire to cooperate, and her willingness to take on and complete any task assigned to her.

Sophie loves to travel and expressed this love by going on all four of our European tours and the recent one to Mexico. These trips have made her our best goodwill ambassador and endeared her to our many friends in the cosmetic industry, both here and abroad.

Her personal courage, her warmth, her respect for others, her kindness to many in the Society, give us a sincere feeling of gratitude for all she has done for us. All of her personal attributes and her scientific contributions have helped to elevate the science of cosmetics and have been an inspiration to both the men and the women scientists in our field.

Our Society is honored in giving its Medal Award to such a gracious lady and wonderful scientist.

CALIFORNIA CHAPTER OFFICERS FOR 1966
Left to right: Harold R. Jackson, Past (1965) Chairman; Dr. Paul W. Jewel, Past (1965) National Chairman; Dr. Joseph Michaelson, Chairman; Horst A. Ehrhardt, Chairman-Elect; Richard F. Sommers, Secretary; Benjamin Kapp, Treasurer

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Treasurer	John Paredes, Onyx Chemical Company
Secretary	Chet Moculeski, Clintwood Chemical Company

MIDWEST CHAPTER OFFICERS FOR 1966

National President Congratulating Midwest Chapter Officers for 1966. *Left to right (seated):* Bill Mueller, National President, 1966; Morris J. Root, Chairman, Midwest Chapter. *Standing:* Chester F. Moculeski, Secretary; John J. Paredes, Treasurer. *Absent from picture:* Jesse Starkman, Chairman-Elect

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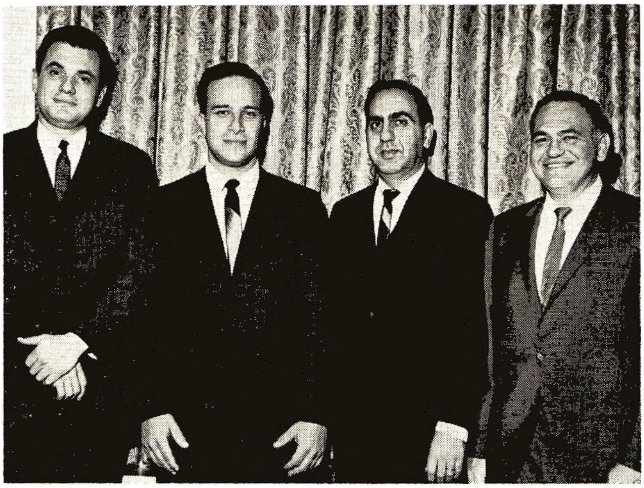

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Left to right: George Fioto, Chairman-Elect; Mitchell L. Schlossman, Chairman; Vincent DeGennaro, Secretary; Stanley Brechner, Treasurer

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February 2, 1966	Shelbourne Hotel, New York Dr. Robert Auerbach—"The Epidermis—Recent Advances."
March 2, 1966	Statler-Hilton Hotel, New York Dr. J. H. Shulman, Columbia University—"Surface Energy of the Amorphous State in Correlation to Membrane Permeability and Adhesion."
April 13, 1966	Robin Hood Inn, Clifton, New Jersey Dr. Bernard Idson, Dome Chemical Company—"Dermatological Agents."

Translations Available

English translations of the following papers may be obtained by writing to Mr. Robert A. Kramer, Evans Chemicals, Inc., 250 East Forty-third Street, New York, New York 10017.

"Studies of the Phenomenon of Permanent Waving of Human Hair," by Dr. Hans Freytag.

"Alteration of Hair Keratin by Cosmetic Processing and Natural Environmental Influences," by Dr. Peter Berth and Dr. Gunter Reese.

"New Information about the Morphological Structure of the Hair," by Dr. Rudolf Randebrock.

"The Application of the Analytical Methods of Sulfur Chemistry to Permanently Waved Hair," by Prof. Dr.-Ing. Helmut Zahn, Dr. Tarsilla Gerthsen, and Dipl.-Chem. Marie-Luise Kehren.

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Photosensitivity*

MILTON M. CAHN, M.D.†

Synopsis—This paper deals with the effects of the sun's rays upon human skin. The rays of the sun may act merely as a trigger to precipitate local skin and systemic disease or they may combine with photosensitizing materials in the skin to produce local reactions. A basic classification is presented and an attempt made to clarify the classification according to the diseases produced by ultraviolet light. Some recently developed therapeutic agents are excellent drugs but have been responsible for photosensitivity reactions. It is sometimes possible by examining the chemical formulas to predict a possible photosensitizing agent and perhaps to modify the structure slightly to eliminate its photosensitizing potentials.

There has been an apparent increase in the incidence of abnormal skin reactions to sunlight. These abnormal reactions have varied from mild and minor skin involvement, to severe and even fatal systemic disease. Following the pioneer work by Epstein (1), Blum (2), and Lamb (3) whose interest early focused on this field, there has been a vast amount of basic research and clinical investigation resulting in a voluminous but sometimes confusing welter of published articles on the subject.

Exposure of the skin to sunlight produces many patterns of reaction, and numerous attempts have been made to classify these reactions. The simplest classifications propose that skin lesions may be produced by ultraviolet light of wavelengths shorter than 3200 A, i.e., radiations which induce the sunburn of normal skin; or second, skin lesions may be due to abnormal photosensitizing substances in the skin and may be produced by wavelengths *outside* of the sunburn spectrum, i.e., above 3200 A (2).

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* Based on a presentation before the New York Chapter of the Society of Cosmetic Chemists, September 8, 1965.

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An attempt is made below to present a step by step analysis and clinical classification of the photosensitivities in accordance with the following scheme:

Reactions to Sunlight

- I. Normal reaction (sunburn)
- II. Hypersensitivity reactions
    - A. Nonspecific hypersensitivity (*e.g.*, lupus erythematosus)
    - B. True photosensitivity
        - 1. Phototoxicity, quantitative hypersensitivity
        - 2. Photoallergy, qualitative hypersensitivity (altered reactivity)

NORMAL REACTION TO SUNLIGHT

The normal photobiologic response of the skin, when exposed to ultraviolet light of a specific wavelength, is erythema ("sunburn"). This must be stressed, since sunburn is sometimes thought to be analogous to a thermal (infrared) burn, but they are not the same. The terms "sunburn spectrum" and "sunburn radiation" are used to describe those ultraviolet light wavelengths which produce erythema in normal human skin. The appearance of minimal perceptible erythema is the most accurate method for determining the erythemic response and is graphically represented by a curve (Fig. 1), known as the "action spectrum curve for erythema." There is a maximum at about 2500 A, falling to a minimum at 2800 A, reaching a very sharp maximum at 2967 A, then falling sharply and nearly reaching zero at 3200 A. Ordinary window glass prevents transmission of wave lengths below 3200 A and, therefore, will prevent sunburn. Frequently, the wavelengths transmitted to the earth are not shorter than 3200 A, and in this case sunlight has no sunburn producing power.

An approximate average curve for the spectral distribution of sunlight is shown in Fig. 2 ("S"). The wavelength distribution is between 2900 and 18,500 A. The intensity and spectral distribution of sunlight varies with the season of the year and with varying atmospheric conditions, including water vapor, smoke, and clouds. The sun's rays are most intense in late spring and early summer when the sun is at its zenith (summer solstice). At this time the sun is directly overhead and its rays are perpendicular to the earth's surface, thus traveling their shortest distance to earth, with the least filtering effect of the atmosphere. It is during this season, naturally, that most skin reactions are observed.

As expected, the normal reaction of the skin to sunlight in the sunburn spectrum varies with the intensity and length of time of exposure. Finally, some individual factors are involved: Thus, dark skinned races react less to sunlight than light skinned people. Blondes are more susceptible to the action of the sun's rays than brunettes. There is also a variation in individual tolerance to sunlight, due to unknown factors.

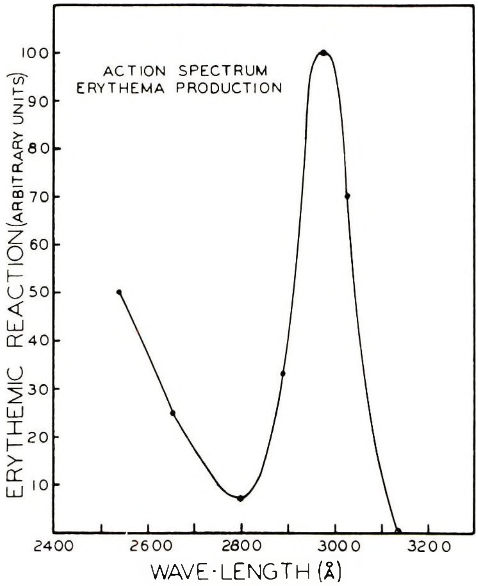

Figure 1. Action spectrum for erythema [after Blum (2)]

With the above factors in mind, one may then observe certain biologic effects.

(a) *Production of erythema:* The degree of erythema and the latent period before its appearance vary according to the intensity and duration of the irradiation. Excessive irradiation may result in blistering of the skin. At 2536 A, maximal reddening ordinarily occurs in about six hours and may last for a few days. At 2967 A, maximal reddening usually occurs in twenty-four hours and persists longer.

(b) *Pigmentation:* Pigmentation is usually observed much later than erythema. The degree and rate of pigmentation vary with the amount of radiation. The primary changes that lead to pigmentation are the same as those which cause erythema, and the wavelengths that result in pigmentation correspond to those that cause erythema; however, wavelengths longer than those of the sunburn spectrum will also cause skin darkening. This process is identical with the darkening of dead pigmented skin brought about by heat or by ultraviolet radiation and is probably due to the oxidation of pigment already present in a colorless reduced state. It is thus a reversible process, quite independent of the formation of new pigment. This darkening effect represents a relatively large amount of the observed tanning produced by sunlight because of the greater proportion of longer wave lengths present in sunlight. This process occurs in the spectral region from 3200 to 4400 A, with maximum at 3400 A.

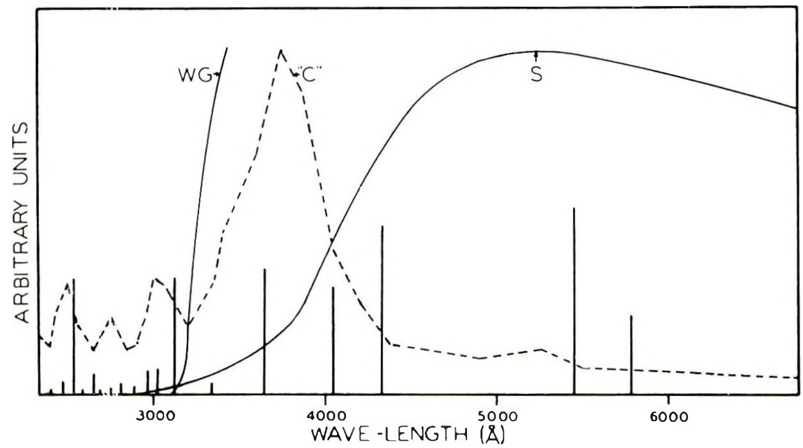

Figure 2. Spectral distribution of light; S-sunlight at sea level [after Blum (2)]

(c) *Bactericidal effects:* The action spectrum for the killing of unicellular organisms is 1850 to 2500 A. Cold quartz ultraviolet light falls within this range.

(d) *Antirachitic action:* This process depends upon the synthesis of Vitamin D or other antirachitic substances from precursors and occurs in a spectral range between 2600–3200 A.

HYPERSENSITIVITY REACTIONS

Non-Specific Hypersensitivity

Nonspecific hypersensitivity is that form in which sunlight may be a factor in producing or precipitating the disease in a *particular* patient but is not an essential element for the production of this disease in all patients. Examples are:

1. Herpes simplex: There is no question that the virus of herpes simplex can be "activated," or skin resistance diminished, by sunlight exposure, following which a typical crop of vesicles appear.

2. Degeneration of collagen and elastic tissues of the skin: In skin repeatedly exposed to sunlight, degeneration of collagen and elastic tissue fibers may occur. Such changes are seen in persons of *any* age who are exposed to the elements (so-called "sailor's and farmer's skin"). The skin changes manifest themselves clinically in thinning and atrophy of subcutaneous fat, so that the skin becomes dry, inelastic, wrinkled, and furrowed and assumes a dull brownish-yellow hue.

3. Chronic sunburn with or without keratoses: Repeated sunlight exposure may cause a permanent dilatation of the minute blood vessels of the corium and a chronic reddening. In chronically sunburned patients, senile (actinic) keratoses may develop. These are precancerous lesions, the precursors of prickle cell cancers, and occur most frequently on the face and dorsa of the hands. There have been several reported cases of generalized tumor-like keratoses in the exposed areas due to sunlight (4). These tumors remain benign, although histologically they resemble grade I squamous cell epithelioma, and may even disappear spontaneously if sun exposure is avoided.

4. Epithelioma: Prolonged exposure to sunlight may stimulate the production of malignant tumors of the skin. The great majority of skin cancers occur on the exposed surface of the face and hands. There is strong evidence that the exciting wavelengths for the production of skin cancers are in the region of the sunburn spectrum.

5. Lupus erythematosus: Sunlight in some individuals may sometimes precipitate local or systemic disease. The history of sun-exposure preceding the development of discoid lupus erythematosus or systemic lupus erythematosus is well known. Dissemination of lupus erythematosus has been observed following exposure of only a small patch of skin to the hot quartz ultraviolet light. A patient was observed who suddenly developed photosensitivity of the skin of a type resembling systemic lupus erythematosus morphologically and pathologically; this patient had bronchogenic carcinoma. Another patient had a cutaneous reaction to sunlight limited to the exposed portions of his body and resembling acute contact dermatitis—he had adenocarcinoma of the stomach. This relationship between visceral carcinoma and sudden onset of photosensitivity reactions of the skin is not too common.

In all the above examples sunlight is a factor in producing a disease process in certain subjects. Yet sunlight is not a factor in producing these same diseases in all patients.

True Photosensitivity Reactions

Here sunlight is the essential element in the pathogenesis of the disease process. Without sunlight the disease could not occur.

1. Phototoxicity is a quantitative hypersensitivity—an intensification of the normal sunburn response. The erythemic response of the skin is heightened so that the skin reacts to smaller than normal doses of ultraviolet light.

This reaction requires (a) the presence of the photosensitizing chemical in the epidermis and (b) a source of ultraviolet light which contains rays which are absorbed by the particular photosensitizing chemical. This process is manifested by erythema, edema, and—if the reaction is intense enough—vesiculation, limited to the sunlight exposed areas; it results from exposures that normally would cause little or no reaction. The photosensitizing chemical may be administered topically, orally, or parenterally.

Among the orally or parenterally administered agents are certain tranquilizers (*e.g.*, chlorpromazine), thiazide, and related sulfonamide diuretics, the oral hypoglycemic agents (chlorpropamide, tolbutamide), sulfonamide antibacterial agents, antibiotics (demethylchlortetracycline hydrochloride), antifungal agents (griseofulvin), antihistamines (promethazine hydrochloride), and miscellaneous agents (quinidine, gold, barbiturates, furocoumarins).

Shelley (5) points out that chlorpromazine and its host of later congeners are simple derivatives of phenothiazine, and hence all produce predictable photosensitivity reactions. This list includes Thorazine, Vesprin, Compazine, Sparine, Temaril, Trilafon, Dartal, and Pacatal, as well as the related antihistaminics, Phenergan, Theruhistin, and Pyrrolazote. It is interesting that many cross-sensitivities have been demonstrated between compounds in this grouping. Particular note has been made that Phenergan sensitizes topically but usually not when given systemically. These dye (methylene blue) derivatives, then, all show the common potential of photosensitization. The thread of continuity goes back to the original dye photosensitivity reactions to eosin observed in 1900 (2).

Of the newer sulfonamide derivatives, the diuretics and oral hypoglycemic sulfonamides are capable of producing an appreciable number of photosensitivity reactions.

In some instances, chemically related compounds, such as the local anesthetics (procaine group), hair dye components, such as *p*-phenylene diamine, and the drug and sunscreen, *p*-aminobenzoic acid, will induce photosensitivity reactions. Moreover, the same patient, because of cross-sensitivity mechanisms, may show photosensitization to all of these. Derivatives are also potentially active, as for example, monoglycerol *p*-aminobenzoate (5).

Demethylchlortetracycline (Declomycin), a member of the tetracycline family, produces reactions in as high as 25% of users exposed to sunlight. In a clinical study by Cahn and Levy (6), 600 mg. daily resulted in an incidence of 15–25% phototoxicity; 450 mg. daily resulted in 3% reaction, while 300 mg. resulted in 0–1% reaction. This observation is important since in phototoxic reactions the chemical not only must be present in the skin but must be present in *adequate* concentration, for even great amounts of sunlight would not produce phototoxicity in patients having less than threshold concentration of drug.

Of paramount interest to the cosmetic chemist is the *effect of certain topical agents* in producing photosensitivity. If the agent is of plant origin, a variety of names may be found in the literature to confuse the issue, such as "perfume" dermatitis, Berloque dermatitis, meadow grass dermatitis, phytophotodermatitis, fig dermatitis, and dermatitis bullosa striata pratensis. The photosensitizers are furocoumarins, of which there are more than 20 naturally occurring derivatives (5). These substances are used in many perfumes and colognes and, after being exposed to sunlight on the skin, may initiate the development of patchy areas of redness and blistering, with subsequent scaling and hyperpigmentation. The eruption usually appears about the face and neck, symmetrically distributed. Photosensitization is caused by radiation between 3100 and 3700 A (7).

Promethazine hydrochloride (Phenergan) may cause photosensitization when topically applied or ingested (8). Coal tar has long been noted for its photosensitizing properties when applied to the skin. The ability of coal tar to photosensitize is of appreciable consequence in industrial medicine. Workers coming into contact with the crude tar or its distillates frequently develop varying degrees of reaction on the affected skin surfaces, with a marked tendency to develop hyperpigmentation. This sensitizing principle is used in the Goeckerman treatment of psoriasis, employing coal tar and an ultraviolet lamp or natural sunlight. The sensitizing range is 3900 to 5000 A.

Sunscreens may act as photosensitizers in man, and it has been proven that monoglycerol *p*-aminobenzoate could be a contact photosensitizer (9). Other reports have followed, describing the esters of *p*-aminobenzoic acid as photosensitizers. Later, it was noted that the sunscreening preparation digallolyl trioleate could sensitize the skin to ultraviolet light (10). Recently, a persistent light reactor was found to have positive photopatch tests to both of these agents (11).

Certain antiseptics may produce photosensitivity reactions. Four well-known bactericidal agents are tetrachlorosalicylanilide (TCSA), bithionol, tribromosalicylanilide (TBS), and hexachlorophene. Contact and contact photodermatitis from TCSA has occurred in hundreds of individuals (12).

Recently, the bactericidal agent bithionol used in a number of soaps, shampoos, cosmetics, and acne preparations was found to be a contact photosensitizer. TBS is rarely a primary contact photosensitizer, and as yet hexachlorophene has not been proved to be a primary contact photosensitizer. However, cross-sensitization may exist between all of these antiseptic agents (12–15).

2. *Photoallergy* represents a qualitatively altered reaction to specific bands of light, as a rule in the sunburn spectrum. These imply an antigen-antibody reaction, therefore an incubation period. Certain drugs (ingested) may cause an eczematous, urticarial, or papular response after exposure to sunlight, for example, sulfonamides, gold, and quinidine and some phenothiazine derivatives. There is also a class of patients who have chronic polymorphous light eruption, a disease characterized by papular and plaque-like dermatitis of exposed parts of the body, occurring each spring and summer after exposure of sunlight and resembling lupus erythematosus clinically (16).

What is the role of porphyrins in sensitizing the skin to sunlight? Photosensitization by the porphyrins is produced by wavelengths of light between 3000–4500 A principally and to a lesser extent by visible radiations extending to about wavelength 6500 A. Except in the disease porphyria, either the erythropoietic or the hepatic type, it has not been shown that the porphyrins have a role in any of the other skin diseases associated with sunlight sensitivity.

Mechanism of Photosensitizers

Photosensitizers act by virtue of *photodynamic* action—a term used to describe the interaction of light and a photosensitizer in the presence of oxygen, causing a destructive photochemical reaction.

Four criteria must be met. First, the compound must be present in the *living epidermal cell* and must have gotten there by virtue of absorption either parenterally or by topical application.

Secondly, the compound must be of specific nature. In a study of contact dermatitis the authors showed that, in a subject previously sensitized to a phenothiazine derivative containing a chlorine atom in the ring, positive skin reactions were elicited by patch testing only with compounds having a chlorine in the 2-position. Other atoms or radicals gave negative reactions. The structure of the side chain did not seem to be a critical factor in causing contact (allergic) sensitization. In this case exposure to strong mid-day sunlight did not bring out any latent reactions and did not seem to affect the severity of the skin reaction (17).

The experimental data suggest a possible structure-activity relationship, which may be a factor in the development of allergic skin reactions following contact with certain phenothiazine derivatives. Furthermore, sensitization of this type may be related to other side reactions the manifestations of which strongly suggest an allergic basis for this reaction. Other investigators found no reactions with other phenothiazine derivatives lacking the chlorine atom (Diparcol and Parsidol) in patients who had positive patch tests to chlorpromazine (18).

It has recently been shown that subjects could be cross-photosensitized to all of the halogenated salicylanilides tested except tribromosalicylanilide. It appears, therefore, that TBS is not a cross-photosensitizer, although with the chlorine analog cross-photosensitization does occur (19).

Demethylchlortetracycline induces photosensitivity of the phototoxic type in approximately 20% of ambulatory patients receiving ordinary therapeutic doses (6). It is of considerable interest why demethylchlortetracycline possesses such a marked capacity to photosensitize while the other three congeners are much less capable of inducing such a reaction (20). The frequent association of light sensitivity reactions with drugs containing a free chlorine radical has been pointed out (21); however, chlortetracycline also possesses such a radical, and photosensitization reactions to it have been distinctly uncommon. Thus attention is focused on the substitution of a hydrogen for a methyl group at the R_1 position. This alters one of the central rings at the meso position and suggests a possible analogy with compounds which have an anthracene-like structure and whose photosensitizing capacity can be increased by change of one or more of the meso or para atoms of the central ring (22).

The precise molecular specificity is shown by the effect that structural alteration has on the erythemal activity of furocoumarins and makes the difference between an inert and active compound (5).

Thirdly, light of an effective (proper) wavelength, and in adequate quantity, must reach the skin. Hence source, exposure time, atmospheric conditions, thickness of stratum corneum, and melanin content all may cause differences in quantity of light reaching the epidermal cell. The specific band of light which elicits the photosensitivity reaction is the *action spectrum.* Each photosensitizer has its own specific *absorption spectrum,* which usually matches the action spectrum but not always. The only radiant energy capable of producing photodynamic action is the ultraviolet or visible. Some examples are: Fluorescent dyes (3900–7900 A); sulfonamides, chlorpromazine, demethylchlortetracycline (2900–3100 A); 8 methoxypsoralen (2700–3200 A).

Finally, oxygen is necessary (2, 5).

Diagnosis is complicated because one has to decide whether a particular reaction is photoxic or photoallergic. As Baer and Harber point out, the morphological characteristics of the eruption and a knowledge of the incidence of the adverse reaction and the concentration of the drug necessary to evoke it are often crucially important in arriving at a decision. Also, tests used in making a diagnosis of drug-induced photosensitivity are usually based on reproducing the lesions under controlled conditions with known types and amounts of artificial light (23).

Treatment for acute phases of photodermatitis is similar to that used in treating other dermatoses (24); usually rapid improvement occurs if the photosensitizing agent and sunlight in the responsible wavelength spectrum are avoided.

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Society of Cosmetic Chemists 1966 Meetings

The Society of Cosmetic Chemists will hold the following meetings in 1966:

Date	*Meeting*	*Location*	*Program*
May 10, 1966	Semiannual	Americana Hotel, New York, N.Y.	To be announced later
Sept. 20, 1966 Sept. 21, 1966	Seminar	Americana Hotel, New York, N. Y.	Pediatric Cosmetics Geriatric Cosmetics Perfume Psychology Cosmetic Safety Testing
Nov. 30, 1966	Semiannual and medal award dinner-dance	Americana Hotel, New York, N.Y.	To be announced later

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Employment Contracts

EUGENE M. BOND*

Presented May 4, 1965, New York City

Synopsis—The problem of employment contracts is examined from the point of view of legal and moral obligations on the part of employees and employers. Aspects of nondisclosure of trade secrets and of covenants not to work for a competitor after termination of employment are discussed in greater detail.

Those who have never been troubled with employment contracts may doubt the need for concern with this subject. Recent developments in this field of law have been rapidly taking place as a result of increased litigation, and today, no one can be sure that he will not, sooner or later, be confronted with the problem. As a result of this increased litigation, the law dealing with employment contracts has been transposed from a dormant issue to one very active and turbulent.

Some of the recent revival of interest in employment contracts and concern for the resulting legal consequences may be attributed to various articles on the subject in popular technical (1) and trade publications (2). Management and technical personnel are now more aware of some of the delicate problems which may arise out of employment contracts. However, caution must be urged in the prevalent practice of advancing simple answers to involved questions, especially to questions dealing with personalities and emotions, by simply applying general rules of law to particular factual situations. Therefore, although reference may be made to specific court cases to establish certain points of law, it must be realized at the outset that these cases are not the last word on the law, as a great many exceptions to the established rules are known to exist.

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The first question to be considered in any general analysis of employment contracts is: What constitutes an employment contract? Generally, it is well known that any agreement between at least two parties, upon sufficient consideration in which the minds of the parties meet and concur, establishes a contract. When the agreement prescribes an employer-employee relationship, an employment contract is established.

Employment contracts require no particular form and, surprising to many individuals, the related legal obligations may take effect even in the absence of a formal contract or other written expression of confidence (3). If legal obligations may take effect in the absence of any formal contract, why do we have employment contracts, and are they necessary? Every employee, unless exempted by his employer, has a definite legal and certainly a moral obligation to preserve and protect all information concerning the business affairs or technical disclosures of the employer. Since it is recognized that no formal expression is necessary to establish an employment contract, we may next consider what purpose is to be derived from the use of formal contracts.

First of all, it may be recognized that formal employment contracts are used primarily to enlarge the legal obligations of the employee to the employer. The employer further benefits by issuance of an actual notice in writing of the obligations to be expected of the employee. With the increasing mobility of personnel into and out of competing organizations and of the movement of employees specializing in highly limited and extremely sensitive areas, it is necessary for a business organization to safeguard itself against loss of confidential information and to avoid also creating an embarrassing situation relative to competitive organizations.

The precipitated effect of a disclosure of confidential information to a competitor upon the image of an adverse employee may be readily appreciated. Seldom, however, is it appreciated until after the fall that even the image of the employer may be damaged in a sincere attempt to prevent dissemination of confidential information by legal recourse against an adverse employee. Should the employer receive sufficient publicity for his efforts, it is likely that even the recruiting of new employees may become more difficult. After all, what employee wants to be "married to the company" after reading a press report that a "multimillion dollar corporation filed suit against a former employee?" Certainly, the damage of adverse publicity is an important factor which must be considered by both the employee and by the employer before transgressing the involved rights and duties of employment contracts.

The employee may also derive benefits from employment contracts. By knowing the boundaries of the incurred obligations to his employer, the employee may then recognize the area in which he may operate without conflict. The gray area between these two extreme boundaries of recognition and obligation, however, presents the difficult area where individual judgment becomes involved in resolving potential conflict of interest problems.

It is not difficult to understand the reason for using formal employment contracts, especially since people entrusted with confidential information may be found to be vulnerable. There is nothing special in the makeup of an individual that should cause him to make off with information committed to his management, nor is there anything special in the constitution of an individual that causes him to act such that he yields under the pressure of temptation. Individuals who are not influenced by monetary pressure may be influenced by flattery. Those impervious to flattery may be warped and biased by social inclinations. One way or another, every individual may become vulnerable. Resultantly, employment contracts are used to establish, at the outset, the rights and duties of an employee as well as those of the employer.

There has been renewed interest on the part of many companies with regard to the particular form of employment contract which is used. The reason for this renewed interest in employment contracts is probably due to the great competition which now exists between companies for skilled personnel. The more advanced corporations have now shortened their employment contracts by use of simple language in place of legalistic "whereas" clauses. The total effect of the change in form of the agreement has been from something that looks like a complex legal document to a clear, simple, and friendly letter which is executed in duplicate.

Almost every individual, at one time or another, has been asked to sign an employment contract. Few individuals, however, actually read these contracts, and even fewer individuals actually understand their content. The difficulty with this state of affairs probably resides within the corporate personnel department, where the new employee is often merely asked to sign a series of papers without any great explanation as to what the papers involve. The real surprise and understanding of employment contracts positively arises when the sensitively placed employee decides to terminate his employment with one employer and thereupon advises the employer of his intention to work for a competitor within the same area of sensitivity. It is necessary then to consider the question: What are the component parts of an employment contract?

All contracts, including employment contracts, necessarily require as a legal prerequisite that consideration be present as one of the significant requirements to establish the contract. In part, the consideration phrase of an employment contract typically reads as follows:

> In consideration of my employment with the XYZ Corporation and of the salary or wages paid for my services in the course of such employment . . .

The "employment" or the "hiring of the employee" is generally specified as such and these formal words are usually sufficient to establish consideration to sustain an employment contract between the employer and the employee. Many contracts for employment, however, go further and include with the "consideration" continuation of the employment and payment of an unspecified compensation in the form of a wage or salary.

Neatly set forth beneath the consideration clause there usually appears the "I agree" clauses. Three basic clauses or covenants are found in almost all employment contracts, and these clauses usually present little or no problem between the employer and employee. The clauses obligate the employee to (a) keep, maintain, and make available complete and up-to-date records, (b) assign all new inventions and improvements of inventions, whether patentable or not, within the company's sphere of interest, and (c) cooperate and execute all necessary papers relating to the employee's inventions.

The clauses which cause the greatest concern and difficulty in employment contracts are those relating to (d) nondisclosure of trade secrets by the employee outside the company both during and after the period of employment, and (e) the covenant not to work in the same area for a competitor during a fixed number of years after termination of the employment. Use of these latter two clauses is considered justified by the courts so long as the clauses do not unreasonably restrain the employee's right to earn a livelihood. Those clauses which unreasonably restrain or limit the employee's right to earn a livelihood will be struck down by the courts as contrary to public policy.

It is quite certain in the law that any employment contract which goes beyond a reasonable degree to embrace anything and everything that an employee saw or learned during the period of his employment will be struck down by the courts. For example, unreasonable covenants have been held to be unenforceable by injunction under New Jersey law as established in the leading case of Sternberg *vs.* O'Brien (4). Although discussion of the unenforceability of the agreement in the case is dictum, the reasoning behind the decision has been repeatedly followed in New Jersey (5).

The development of the law of employment contracts has resulted from an attempt by the courts over the years to balance two conflicting elements essential to our society. There is a strong policy favoring free competition, for an employee is entitled to use the skill and knowledge of his trade or profession which he has learned or developed in the course of any employment for the benefit of himself and the public, provided he does not violate a contractual or fiduciary obligation in doing so. On the other hand, in order to promote the orderly progress of science and the useful arts, the law provides certain protections as safeguards against breaches in employee incurred obligations. Among these protections are the patent and copyright statutes and the law of torts prohibiting unfair competition. The law protecting trade secrets is another related protection afforded by the law.

An examination of the holdings of the common law dealing with employment contracts will suggest the presence of a persistent distaste for all contracts in restraint of trade. Nevertheless, the courts usually upheld the validity of covenants by an employee not to compete with his former employer upon termination of the employment as well as the validity of covenants of a vendor of a business not to compete with the vendee. Obviously, an employee is more apt than a vendor to be coerced into an oppressive agreement, and therefore the courts were more apt to construe strictly the terms and provisions of a covenant ancillary to an employment contract.

The more recent court holdings have considered the after-employment or holdover clauses of an employment contract with a view toward what is considered to be the reasonableness of the provisions after examination of all the pertinent facts. Overriding these basic policies are the more practical guidelines of time and area limitations, although most employment contracts do not contain specified area limitations.

During the period of employment, the employee is bound by the nondisclosure clause and may not reveal any confidential information entrusted to his confidence, even though such information is not specifically considered or classified by the employer as a trade secret. When, however, the employee's services are terminated, his rights of disclosure are usually restricted to information which is in fact considered by the courts to constitute a trade secret. The ban, therefore, against disclosure of trade secrets during employment is much stricter than is the ban against disclosure of trade secrets after employment has ceased.

An accurate definition of what constitutes a trade secret is difficult to formulate, although the Restatement of Torts (6) seems to present as accurate a definition as is available. The Restatement describes a trade secret as follows:

> A trade secret may consist of any formula, pattern, device or compilation of information which is used in one's business, and which gives him an opportunity to obtain an advantage over competitors who do not know or use it. It may be a formula for a chemical compound, a process of manufacturing, treating or preserving materials, a pattern for a machine or other device, or a list of customers.

The more precise question of whether or not a trade secret exists and, if there is, whether the owner of the secret will be protected against its unlawful disclosure has been considered in numerous cases (7) and has also been greatly analyzed by text writers (8). The legal principles are not in great dispute either in the case law or that of the text writers, but it is the application of the legal principles to the particular set of facts on which the decision must turn which presents great difficulty.

The Restatement (9) sets forth some elements useful for consideration in determining whether a trade secret, in fact, exists. These elements include:

(a) The extent to which the information is known outside of his business;
(b) The extent to which it is known by employees and others involved in his business;
(c) The extent of measures taken by him to guard the secrecy of the information;
(d) The value of the information to him and to his competitors;
(e) The amount of effort or money expended by him in developing the information;
(f) The ease or difficulty with which the information could be properly acquired or duplicated by others.

Much of what has been stated so far has been concerned primarily with the employer-employee relationship during the period of employment. Now we come to the time in an employee's life when, after attending a professional or social meeting and seeing or hearing of all the available opportunities he may qualify for, he decides to leave for another position.

Prior to departure, the technically sensitive employee should be reminded by the employer of his contractual obligations not to disclose confidential information or trade secrets to his new employer. Some corporations have even gone so far as to establish a standard exit interview with all employees to be certain that the departure procedure is properly and effectively handled.

Depending on the circumstances or reasons of the employee's termination which may vary within the spectrum from involuntary departure to voluntary termination, it is not surprising to visualize that the termination may cause the ex-employee to brood on real or fancied unfair treatment, to recall that he was paid less for creating some highly successful product than a salesman who sold the product, and to seek the seemingly easy road of using trade secrets of one employer as a basis for establishing his new position with a subsequent employer. Under such circumstances, what action can be taken by a former employer when the ex-employee loaded with trade secrets leaves to work for a competitor but is not officially hired? Since it is apparent that no contract of employment is valid which withdraws from an employee the right to earn a living, the employer's hands are usually tied in such situations. An exception exists, however, when the employee is going from a position in which his complete time was spent in a highly confidential capacity to a precisely similar position with a competitor who desires the trade secrets to increase his competitive position in the industry. Probably the leading case in which the employer was successful in preventing an employee from working with a competitor is that of Eastman Kodak Co. *vs*. Powers Film Products, Inc. (10). In this case, Powers Film Products located its plant in Rochester, N. Y., and sought to employ one of Eastman's film processors. Eastman thereupon brought suit seeking an injunction against the employee from working with Powers Film Products. The Court upheld the employment contract between Eastman and the employee and issued an injunction restraining him from disclosing trade secrets and from entering into the employment of Powers. Interesting enough, the Eastman contract contained a holdover clause which limited employment with a competitor for a period of two years after termination of the employment in any part of the United States except the Territory of Alaska. The year of the decision was 1919!

What action may be taken by a former employer after the controversial employee has been hired by the new employer? Several recent cases have considered this question, among which are included the well-publicized cases of E. I. du Pont de Nemours & Co. *vs.* American Potash & Chemical Corp. *et al.*, (11) and of B. F. Goodrich Co. *vs.* Wohlgemuth (12). In both of these cases, the employee continued to work for the new employer, although injunctions were issued by the courts enjoining the employee from improperly disclosing any trade secrets of the former employer.*

What about the new employer and his obligations when hiring an ex-employee who is loaded with confidential information? First of all, it is highly advisable that the old employer place the new employer on written notice that the employee in question may have knowledge of confidential information or trade secrets. Once so notified, the new employer must exercise good faith in seeing that the information remains undisclosed. Generalities present difficulties, but once it is determined that trade secrets are in fact involved and that these secrets may be disclosed to the new employer, the new employer becomes involved in a very awkward position and should advise his new employee that he is not interested in any confidential information of the former employer. Preferably, the new employee should be employed in a capacity different than that of his past employment to increase the certainty of non-disclosure. Although this is good advice in theory, it has little practical value, especially with less reputable concerns which usually hire an employee on the basis of his knowledge of confidential matters.

Disclosure of trade secrets obtained during the course of employment by employees is a cause of increasing concern. What once first appeared as a very limited geographical problem has now expanded into one of world-wide importance. Some of the causes of the concern are obvious and may be directly attributable to the great annual expenditure on research and development. Even legislators are becoming more aware of the problem of protecting trade secrets such as in New York (13) where certain acts of an employee are now considered grand larceny in the second degree and punishable by a prescribed term in prison. Both present and projected future attempts to resolve and control unauthorized disclosure of trade secrets, however, will continue to be complex, since the employer's legitimate interests must be balanced with the correlative interests of the employee. Such a balance of interests is further

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* For a more detailed discussion of these cases and the problems involved, attention is directed to Ref. (1).

compounded by the natural and continuing interest of the public which requires workable employee-employer relationships as well as individual freedom from unreasonable contractual restraints. So long as technological change requires increased specialization by employees, the problems of employment contracts and adverse employees will inevitably become more acute. The number of controversies, however, may be limited by informed employers and employees who honestly seek to avoid conflicts over employment contracts.

(Received September 11, 1965)

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Water Vapor Sorption and Suction Potential of Starch Grains

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H. VON CZETSCH LINDENWALD, Ph.D.*

Synopsis—The influence of water vapor sorption on the particle characteristics of potato, corn, and wheat starch is evaluated critically. The suction potential of the starch grains in a packed column is studied in both the presence and the absence of colloidal silica. The results of these experiments lead to the conclusion that the suction potential and the rate of linear diffusion are closely related to the amount of silica dispersed in the powder bed.

INTRODUCTION

In different industries, particular attention has been given to vapor sorption and its influence on the properties of particulate materials (1–4). Millet and Parisot (5) reported that the frictional and wear phenomena of graphite and carbon are related to their surface sorption properties. Ulmann (6) reported that the type of water present in potato starch, either in bound or adsorbed state, can be studied by the slow reduction in weight by means of infrared radiation. Dumonskii and Nekrgach (7) found a quantitative correlation between the amount of combined water and the heat of wetting evolved from starches. In a previous communication (8) it was shown that the bulk volume, frictional properties, and size distribution of cornstarch were markedly influenced by humidity. The intimate mixing of cornstarch with 0.5% hydrophobic silica reduced the interparticle friction to a definite value which remained constant at all degrees of humidity.

The purpose of the present study is to evaluate the process of water vapor sorption and the suction potential in different starches, with the

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aim of obtaining a basic understanding of the action of starch as a tablet disintegrant and to provide further information about the influence of Aerosil®* as an additive.

RESULTS AND DISCUSSION

Materials

Corn, wheat, and potato starches were selected for this study. These were dried at 100°C to constant weight. As an additive, Aerosil® (colloidal silicic acid or hydrophilic silica) was used experimentally.

Water Vapor Sorption

Accurately weighed samples (approximately 1 g. each) of dried starch were placed in a humidity oven†, adjusted to 95% relative humidity and 35°C. The samples were quickly weighed every twenty-four hours, until the equilibrium moisture content was attained. The water sorption in each sample has been calculated in gram per cent. Larger quantities were treated in the same way in order to investigate the packing, frictional, and swelling properties of the moist material.

(a) The packing characteristics were studied by mechanical tapping. The tapping experiment was carried out with 25 g. of the material. The bulk volume at the close packing arrangement was measured for both dry starch and starch at equilibrium moisture content (95% relative humidity and 35°C).

(b) The rheological properties were studied by the angle of repose. The coefficient of interparticle friction was taken as a measure of the frictional properties for the dried and wet material.

(c) The swelling properties were studied by comparing particle size distribution in both dry and wet conditions. The particle size distribution was determined by the microscopic count technique. The relative change in the mean volume diameter was taken as a measure of the swelling capacity.

The experimental details of the mechanical tapping, angle of repose measurement, and microscopic count technique are described in a previous communication (8) but are repeated below:

Mechanical tapping: The tapping experiment (9) was carried out as follows: Twenty-five grams of starch, having a loose packed volume,

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* Aerosil is colloidal silica manufactured by Degussa, A.G., Frankfurt/M (Germany).

† Gallenkamp, London (England).

was filled carefully in a fine stream into a 100 ml. glass measuring cylinder, avoiding any movement which could promote close packing. After observing the initial volume, the cylinder was mechanically tapped, using the standard sieve shaker,* until no change in volume was observed. The final volume represents the volume at the close packing arrangement (bulk volume in cc./25 g. of starch).

Angle of repose: The method was mentioned by Neumann (1), Train (10), Grosby (11) and Tawashi (12) and consists of pouring the powder through a funnel onto a horizontal sheet of graph paper until the top of the heap so formed reached the tip of the funnel. The diameter of the base of the heap was read and the angle of repose calculated from:

$$\tan \theta = \frac{H}{R}$$

where:

$\tan \theta$ = coefficient of interparticle friction
H = height of the funnel tip from the graph paper (20 mm.)
R = radius of the circular base in mm.
θ = angle of repose

Each experiment was repeated three times, and the average was calculated.

Microscopical counting technique: The method was described in detail by Tawashi (13). A projection microscope was used for these determinations. The particle size range was divided into intervals. The number of particles in each size interval was counted in ten microscopical fields. The average number was calculated, and from the number frequency the volume distribution was determined. The mean volume diameter was computed on the basis of the volume distribution.

The experimental results are shown in Table I and Fig. 1. Table I summarizes the changes which occur when dry starch is kept at 35°C and 95% relative humidity until the equilibrium moisture content is reached. These changes are increase in bulk volume and variable increases in frictional and swelling properties.

Although the increase in bulk volume in the three different starches is nearly equal (almost 100%), there is a remarkable difference in the relative changes in the frictional and swelling properties. Generally speaking, a thin layer of water condenses on the outside of the particle in a moist atmosphere. This layer favors adhesion between the in-

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TABLE I

Particle Characteristics under the Influence of Humidity (95% R.H.—35°C)

	Packing Characteristics		Frictional Properties		Particle Size		
Type of Starch	Bulk Volume	% Change	Coefficient of Friction	% Change	D_r	% Change	% Water Uptake
Potato							
Dry	27	94.3	0.800	66.6	59.2	124.09	38.2
Wet	41		1.333		69.24		
Corn							
Dry	39	84.6	0.851	28.6	14.5	91.27	28.8
Wet	72		1.094		18.0		
Wheat							
Dry	38	87.3	1.000	17.6	23.4	17.9	31.1
Wet	72		1.176		24.6		

TABLE II

Variables Related to the Suction Potential of Starches (Using 5 g. of the Material)

Type of Starch	Bulk Volume	Volume of Entrapped Air (cm.^{3})	Final Pressure Increase (mm.)	Time of Water Rise (min.)	Expansion of Powder Bed (mm.)
Potato	5.25	2.15	132	90	29
Corn	7.5	4.45	134	120	1
Wheat	7	3.9	102	540	. . .

dividual particles. The water layer, being easily deformable, will result in the reduction of the total surface energy (14); consequently, the bulk volume is expected to diminish. The expected decrease in the bulk volume should be in the order corn > wheat > potato, according to the grain size.

Experimentally, approximately the same increase in bulk volume is observed in the three investigated starches. In order to explain this abnormal behavior, one must assume that the increase in bulk volume is the net result of two interacting components: *i*, decrease in the bulk volume due to adhesion of the individual particles and consequent diminishing of the void fraction, and *ii*, a large increase in bulk volume as a result of swelling, in addition to the tendency toward aggregate formation. The latter certainly outweighs the former. The increase in bulk volume during aggregation is due to the air contained in the gaps between the particles, in addition to the entrapped air produced by the arches and bridges between the aggregates themselves. The extent of this increase is also dependent on the shape of aggregates, Cumulative distribution curves shown in Fig. 1 (cf. also Table I) indicate that the swelling tendency of potato starch is much more pronounced than that of corn and wheat, the latter exhibiting the least swelling capacity. In potato starch, the apparent increase in volume is 94%, and the absolute increase in particle volume is 124%; the difference is due to particle adhesion. In the case of cornstarch, the absolute increase in particle volume by swelling is approximately equal to the apparent increase in bulk volume. Therefore, the effect of adhesion is nullified by aggregate formation. The absolute increase in particle volume of wheat starch (17%) would not be the only explanation for the doubling of bulk volume. There should be another factor initiating the increase in bulk volume; this factor is probably the formation of aggregates with high apparent volume.

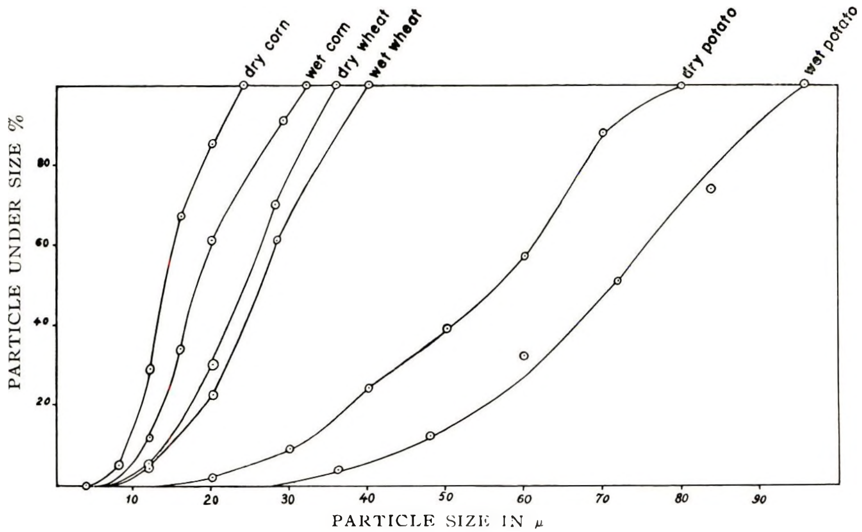

Figure 1. Particle size distribution of starches in the dry and wet condition

Regarding the variation in frictional properties, it is known that the interparticle friction depends on the particle shape, size, size distribution, and surface roughness. At high humidity, a condensed water film deposits on the individual particles and causes the following changes: *i*, adhesion and decreased surface energy of the system, and *ii*, resistance to flow and sliding induced by higher interparticle friction.

A comparison of the relative changes produced by humidity in the investigated starches indicates that potato starch suffers a significant

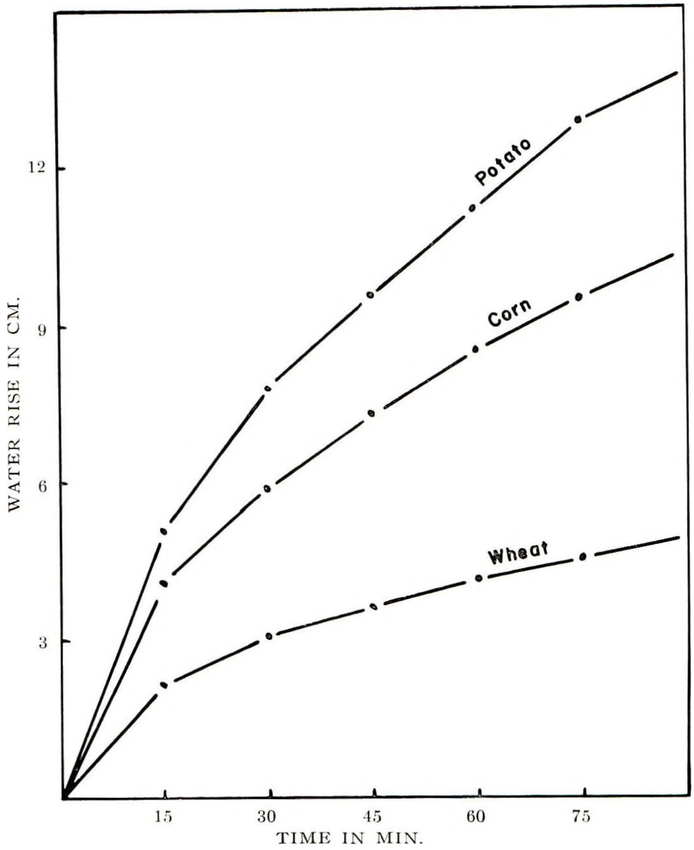

Figure 2. Water rise as a function of time

decrease in its flow properties (66%), while corn and wheat starches are less affected (28.6 and 17.6%, respectively). This can be explained on the basis of particle aggregation. The degree of aggregate formation in these experiments is in the order wheat > corn > potato. Since size enlargement by aggregation is known to improve the free running properties of powders, it can be assumed that, in the presence of humidity, the stickiness produced by water vapor will be partially counteracted by the degree of aggregation. This finding is of practical importance in selecting a starch as an ingredient in dusting powders. Wheat starch is preferred to corn and potato in this respect.

Diffusion Rate and Suction Potential

Five grams of starch was packed in a glass tube (9 mm. diameter) closed at one end with filter paper and open at the other end. The powder bed was mechanically tapped, using a standard sieve shaker* until the minimum bulk volume was reached. The tube was immersed in a beaker containing distilled water so that the surface of the water just touched the filter paper. The water rise in the powder bed was measured at successive time intervals. The hydraulic pressure was also measured at the same time intervals by means of a water manometer connected with the free end of the tube. The results are given in Table II and Figs. 2 and 3.

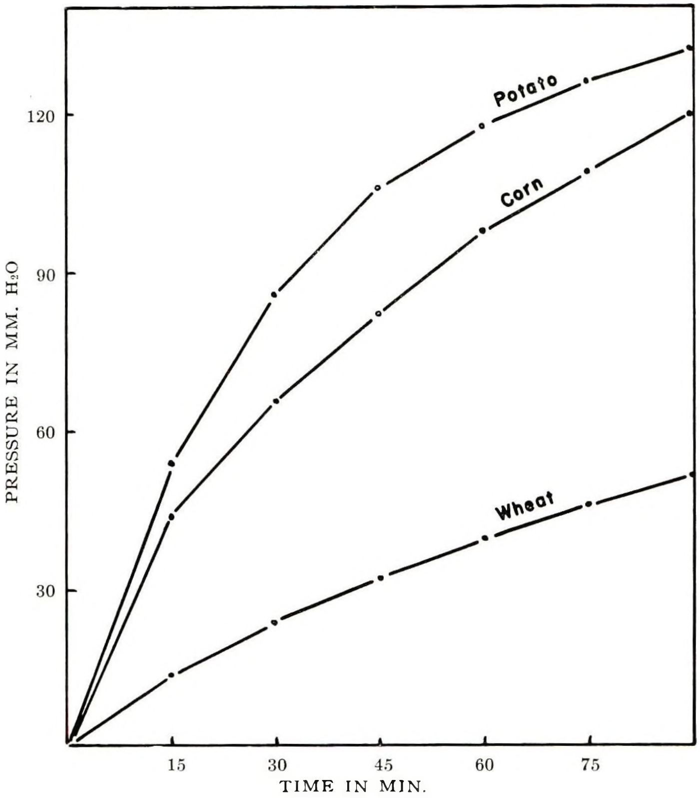

Figure 3. Hydraulic pressure as a function of time

Figure 2 represents the water rise or the linear diffusion in the powder bed as a function of time, while Fig. 3 denotes the hydraulic pressure produced as a function of time. These figures indicate that the linear diffusion rate and the pressure exerted are in the order potato > corn > wheat.

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It is a well-known phenomenon that liquids can diffuse against gravity in a powder bed under the influence of capillary suction. The diffusion takes place in the free space between the particles. The free space is assumed to consist of a series of tortuous channels. The linear diffusion rate in the powder bed will depend on the diameter of the pores, viscosity of the fluid, and contact angle (15). Several studies (16, 17) have been conducted on the flow of liquids through granular beds and packed columns. Most of these studies were concerned with model substances of uniform size and with definite geometrical shape. In this study, the problem is more complicated since it involves materials which differ in particle size, shape, and pore size, as well as the changes which take place during the flow of liquid (e.g., swelling and possible shape deformation). Therefore, a quantitative theory for the flow of water in packed columns of starch grains cannot be developed at this time.

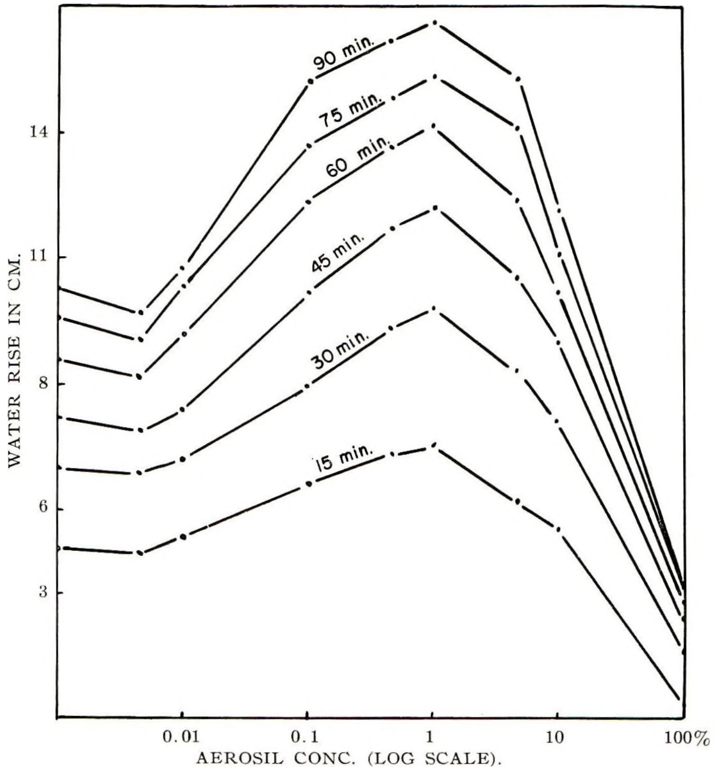

Figure 4. Influence of Aerosil on the suction rate of corn starch

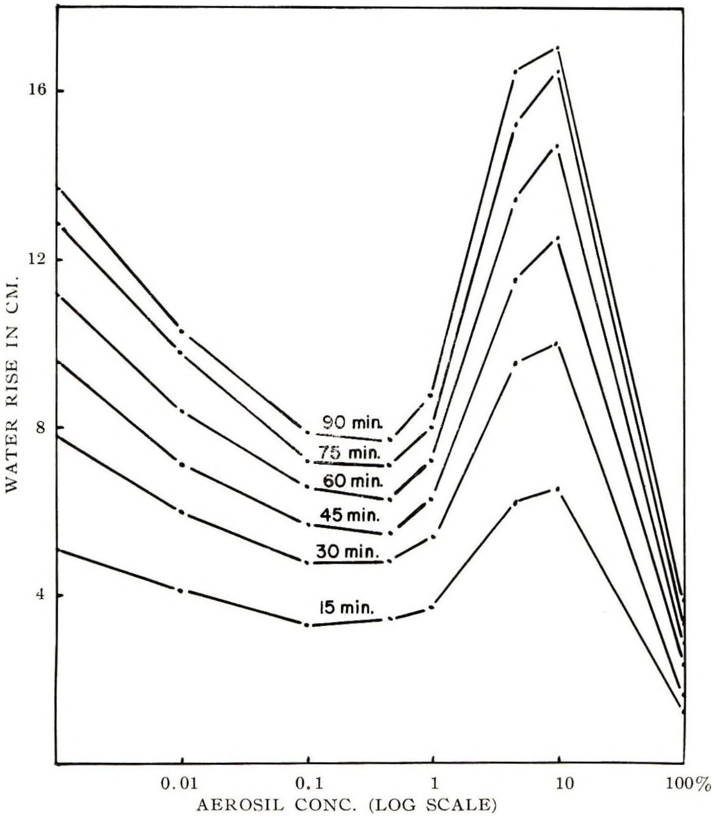

Figure 5. Influence of Aerosil on the suction rate of potato starch

In the case of potato starch the higher rate of linear diffusion could not be explained on the basis of the pore size alone. There are some other factors that should be considered, such as the nature of the starch grains (e.g., wettability), particle size distribution, and particle shape, as well as the swelling capacity during the diffusion process. The pressure exerted at any moment can be taken as the net result of three interacting forces:

(1) The displacement of entrapped air by water as a result of capillary suction.
(2) The swelling of starch grains due to water sorption.
(3) The shrinkage of the powder bed due to wetting and particle-particle adhesion.

Table II indicates that a potato starch powder bed possesses the least amount of entrapped air (2.5 cc./g.). However, it has nearly the same final pressure as corn starch, which has 7.5 cc. entrapped air/5 g. of powder. Wheat starch has a final pressure which is less than that of corn and potato. This means that the final pressure obtained in the case of wheat and corn is mainly due to the entrapped air, while the swelling capacity is nearly compensated by shrinkage of the powder bed. In potato starch the final pressure obtained is due to the evident swelling capacity of the grains, which is greater than the negative force of shrinkage and the relatively small amount of entrapped air.

Influence of Aerosil on the Rate of Linear Diffusion

The diffusion rate experiment has been repeated on each starch after the addition of gradually increasing amounts of Aerosil (from 0.005 to 100%). Intimate mixing of Aerosil with starch was achieved in a Turbula shaking mixer.* The results, given in Figs. 4, 5, and 6, represent the linear diffusion rate plotted against the Aerosil concentration at different time intervals. The graphical representation indicates that the addition of finely divided silica effects a remarkable change in the linear flow rate in the powder bed. The action of Aerosil on the linear diffusion rate is demonstrated by two peaks or two critical concentrations. The first concentration represents a minimum diffusion rate, and the second represents a maximum diffusion rate. This behavior can be explained on the following basis:

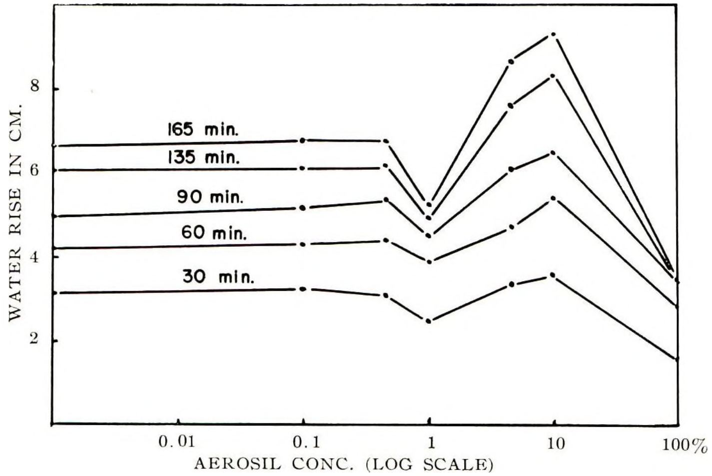

Figure 6. Influence of Aerosil on suction rate of wheat starch

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* W. A. Bachofen, Basel.

The addition of small amounts of Aerosil produces rearrangement and new orientation of the starch grains. The very fine Aerosil particles separate the starch grains from one another, and this results in relatively wide voids. Since the size of the voids is partially responsible for the suction potential, the smaller the void the higher the suction potential. Therefore, the suction will be suppressed, and the first critical concentration will correspond to the amount of Aerosil producing the smallest suction potential for the packed column.

The addition of more Aerosil starts to fill the voids between the particles in the powder bed. The effective pore size gradually diminishes, favoring an increase in suction potential. The maximum rate of linear flow is obtained at the second critical concentration where the minimum pore size is reached. Further addition of Aerosil above the second critical value produces an expansion in the powder bed. The system is then assumed to consist of a matrix of Aerosil in which the starch grains are dispersed. The effective pore size increases greatly with the expansion in the powder bed. Thus suction potential and rate of linear diffusion will be seriously affected.

On the basis of these basic experiments it is possible to modify the water permeability and capillary suction in a powder bed by appropriate addition of Aerosil. This finding is of practical importance in tablet disintegration since the suction potential and rate of permeability, coupled with the swelling capacity, are the main factors responsible for the disintegration time. The proper choice of a starch with suitable swelling capacity and the correct content of Aerosil in tablet formulations might explain the short disintegration time obtained with such tablets.

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Aqueous Topical Adhesives II. Spray-on Bandage

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Presented December 2, 1964, New York City

Synopsis—The research and development of protective films for cosmetic and dermatological uses have been of interest to many groups in recent years. Many of these preparations in pressurized packaging are known as "spray-on bandages." They usually deposit film on the skin which cannot be readily washed off. Thus the development of a preparation containing water-washable resins was considered advantageous.

A combination of polyvinyl alcohol with either polyvinyl acetate or acrylic resins produced aerosol concentrates with good stability and film-forming properties. Incorporation of the concentrates into quick-breaking foam formulations gave products with good stability and bandage properties. The products when sprayed on the skin dried to transparent, tack-free films in approximately 10 minutes.

INTRODUCTION

The research and development of medicated films for cosmetic and dermatological uses have been topics of great interest in recent years. Many of these preparations in pressurized packaging are known as "spray-on bandages." They are generally two-phase aerosols containing plain or medicated resin dressings, an organic solvent, and a propellant. Although these products have been widely accepted because of their convenience, they have some shortcomings. They usually deposit a film on the skin which cannot be washed off. The organic solvent systems prevent the incorporation of drugs which are soluble only in water.

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* Massachusetts College of Pharmacy, Boston, Mass.

Because of their film-forming property, the water-soluble resins have been satisfactorily employed in cosmetic formulations. The use of water-soluble resins for protective films has been investigated by several workers. Sperandio and co-workers have prepared an ointment base (1) and a film-forming base (2, 3) with polyvinyl alcohol as the water-soluble plastic. Preparations containing water-soluble resins as skin protectants in film-forming bases were reported in Part I (4) of this series. It was the purpose of this investigation to develop a spray-on bandage with water-soluble resins as the main ingredient and water as the solvent. It is probable that such a product would be better in some respects than the conventional type of spray-on bandages which use organic solvent systems.

EXPERIMENTAL

The starting point for the development of a spray-on bandage was the formulation of the aerosol concentrate. The major ingredient in the concentrate is the resinous film-forming agent. Several resins were investigated with different plasticizers. The basic formula for the concentrate was as follows:

Resins	
Plasticizers	
Solvent system	
Benzoic acid	0.05%
Sodium nitrate	0.05
Antifoam	0.1
Nonionic surfactant	0.2
Distilled water	

With water as the solvent in the concentrate the need for a preservative against mold growth and an inhibitor of corrosion of the metal container were required. A surface active agent to prevent gelling of the resins and a defoaming agent were also added to all formulations.

The concentrate preparations were evaluated for two qualities: The stability of the preparation and the properties of the film formed. The stability tests included viscosity measurements, color, odor, emulsion creaming, and mold growth. The period of observation lasted 9–10 months. The film properties were evaluated by studying the drying time of the film, the tackiness of the film, the film strength, the resistance of the film to water, and the ease with which the film could be moved. To determine the film properties the concentrate was applied directly on either the back of the hand or on Petri dishes. Despite the subjective nature of the tests, sufficient differences were noted to allow for differentiation of the preparations.

In the following discussion of the preparations, the procedure and results are considered in reference to individual resins.

Polyvinyl Alcohols

The film-forming properties and preparation of aqueous solutions of polyvinyl alcohols are discussed in detail in technical bulletins and in Part I (4). From the experimental data obtained from the preparation of thirty polyvinyl alcohol concentrates the following was observed:

1. Polyvinyl alcohol rapidly combines with polyethylene glycol to form a gel.
2. Glycerin and sorbitol delay the drying time.
3. Propylene glycol increases the film strength.
4. Triethanolamine markedly increases the viscosity of the concentrate.
5. Formaldehyde solution USP was the best plasticizer. It has no effect on viscosity, shortens the drying time of the film, improves film strength, and prolongs adhering time. Optimum concentration of formaldehyde as a plasticizer for polyvinyl alcohol was 1.6–3.2% (v/v) of the resin concentration.

As no free formaldehyde could be detected in the formulations, it was considered to be bound with the polyvinyl alcohol. However, despite the low concentration used and the absence of free formaldehyde, it is realized that the material has potential sensitizing properties and should be carefully tested.

Polyvinyl Acetate

Unlike polyvinyl alcohol, polyvinyl acetate is not water soluble. Commercial products, such as Gelva®* aqueous emulsions, are available which form clear continuous films at room temperature. Gelva emulsions containing 54.5% of solids were readily diluted with water but were not stable for extended periods of time.

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* Gelva, a product of Shawinigan Resins Corporation, Springfield, Mass.

Polyvinylpyrrolidone and Copolymers

Polyvinylpyrrolidone (PVP) was too soluble in water to prepare films with water resistance. The PVP/vinyl acetate copolymers had less water solubility but still produced films with low water resistance. It was also noted that, in many cases, the tackiness of a PVP film was increased by plasticizers.

Polyvinyl Methyl Ether aud Copolymer

The low molecular weight grades of polyvinyl methyl ether produced very sticky solutions with water. Therefore they were not suitable for the preparation of a film-forming concentrate. Polyvinyl methyl ether maleic anhydride copolymers, Gantrez AN®,* have good adhesive properties. However, films prepared with Gantrez AN alone were brittle, and those prepared with plasticizers were tacky and lacked strength sufficient to meet bandage requirements.

Acrylic Polymers

Acrylic polymers include polyacrylic acid, polymethacrylic acid, their salts, and copolymers of acrylic acid and methacrylic acid with other monomers. One specific feature of these resins is that the viscosity of their water solutions is affected by the pH, the degree of ionization of the resins, the kind and amount of counterion, the concentration of the polymer in solution, and the molecular arrangement of the resins. Rhoplex®† resins thicken when the pH is increased and produce films which are generally sticky. The excellent strength and water-resistance of the film prepared from acrylic polymers indicate a good prospect for further study of concentrates containing some of these materials. The odors of these materials can be partially masked by the use of various cover odors.

Ethylene Oxide Polymers

The very high molecular weight (20,000 to 7,000,000) ethylene oxide polymers, Polyox,®‡ are a fairly new class of synthetic water-soluble resins. Strong agitation during the preparation of aqueous solutions

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* Gantrez AN, a product of General Aniline and Film Corporation, New York, N. Y.

† Rhoplex, a product of the Rohm and Haas Company, Philadelphia, Pa.

‡ Polyox, a product of Union Carbide Chemicals Corporation, New York, N. Y.

TABLE I

Summary of Aerosol Concentrate Evaluations

Resin	Strength	Flexibility	Adherence (hrs.)	Tackiness	Water Resistance
Polyvinyl alcohol	Fair	Good	1–5	None	Poor
Polyvinyl acetate	Fair	Fair	>24	None	Good
Polyvinylpyrrolidone	Poor	Poor	15–24	Tacky or brittle	Poor
Polyvinylpyrrolidone/vinyl acetate	Poor	Poor	15–24	None	Poor
Polyvinyl methyl ether/maleic anhydride	Poor	Poor	>24	Tacky	Good
Acrylic polymer	Good	Excellent	>24	Tacky	Good
Ethylene oxide polymer	Poor	Good	15–20	None	Poor
Polyvinyl alcohol/acrylic polymer	Good	Excellent	>24	Slightly	Excellent
Polyvinyl acetate/acrylic polymer	Good	Good	>24	None	Excellent

TABLE II

Formulations of Concentrates Containing Acrylic Polymers and Polyvinyl Alcohol or Polyvinyl Acetate[a]

	Acrylic Polymers[b]		Polyvinyl Alcohol (Elvanol 51-05)[c]	Polyvinyl Acetate (54.5% Gelva TS-71)[b]	Plasticizer (Formaldehyde)
Formula No.	46% Rhoplex B-5	38% Rhoplex B-85			
74-1	85 ml.	10 ml.	5.7 g.	...	2.3 ml.
76-2	85 ml.	10 ml.	11.4 g.	...	4.6 ml.
79-3	85 ml.	10 ml.	...	21 ml.	2.3 ml.
81-4	85 ml.	10 ml.	...	30 ml.	5.0 ml.

[a] Sufficient solvent was added to make 142 ml.

[b] For identification of commercial products, see text.

[c] Elvanol, a product of E. I. du Pont, Wilmington, Delaware.

may cause cleavage of the linear polymer. A slow permanent loss of viscosity occurred, and a white precipitate developed on aging of concentrates prepared with these resins.

The evaluation results of films obtained from various water-soluble resins are summarized in Table I. The viscosities and the drying times of the preparations do not appear, as they are dependent upon the concentration of the resins and can usually be controlled. From this table it is apparent that a concentrate prepared with a single resin cannot meet all of the requirements of a spray-on bandage, but mixtures of either polyvinyl alcohol with acrylic polymer or of polyvinyl acetate with acrylic polymer gave concentrates with most of the desirable characteristics. Examples of these formulations are given in Table II. In general, the preparation of these formulations was best accomplished by first warming the aqueous solvent system to 60°C and adding the polyvinyl alcohol powder slowly with gentle stirring. The solution was cooled, and the plasticizer was added. The mixture was then added in small portions with thorough mixing to the Rhoplex emulsion system. The defoaming agents in the aerosol product, to be described later, were added last.

TABLE III

Formulation and Evaluation of Spray-on Bandages[a]

Aerosol No.	10-1	13-2	14-3	15-4	16-5
Concentrate formula No.	74-1	74-1	81-4	81-4	81-4
(% by wt.)	38.5%	38.5%	54%	43.8%	41.8%
Ethyl alcohol (% by wt.)	31.1%	31.1%	36%	26%	28%
Pluronic L-61	...	10 drops	...	10 drops	10 drops
Chloroform (% by wt.)	1.4%	1.4%	...	...	...
Octyl alcohol	10 drops	...	...	...	...
Propellants 12/114	20:80	20:80	57:43	20:80	20:80
(% by wt.)	30%	30%	10%	30%	30%
Spray character	Quick-breaking foam	Quick-breaking foam	Stream	Unstable foam	Quick-breaking foam
Film drying time	10 min.	10 min.	10 min.	15 min.	10 min.
Stability	Good	Good	Poor	Good	Poor

[a] The development of aerosols in this study involved the use of plastic-coated glass containers of 80 ml. capacity with Precision standard valves with a foam head. Aerosols were pressure-filled.

Formulation and Evaluation of Aerosols

Since all satisfactory concentrates were o/w emulsions, the expected aerosol was destined to be a foam spray, preferably a quick-breaking foam spray. Thus, modifications of the basic concentrate formulation were necessary with the addition of foam breaking agents.

Aqueous alcohol aerosol foams have been extensively studied in recent years (5). For a spray bandage it was not desirable to have a high concentration of alcohol as it would enhance penetration of the material through the skin and would irritate mucous membranes or abraded skin. Other agents used to increase foam breaking were chloroform, octyl alcohol, and nonionic surface active agents, such as the Pluronics®.* Examples of formulations of spray-on bandages and their evaluation are given in Table III.

One of the serious drawbacks of a quick-breaking foam spray was the excessive amount of material present on application. Too much spray delayed the drying time of the bandage, for the outer layer of spray dried fast, and the film formed delayed further drying beneath it. Too much spray also caused a problem in holding the concentrate to the desired sprayed area after the foam broke. This necessitated experimentation with various propellants and valves. Some of the packaging changes which were investigated included the use of a dip-tube of narrow inside diameter, a modified foam head on the valve, and a mechanical breakup valve. None of these changes from a Precision standard valve† provided the desired spray pattern. These changes in the aerosol package are still under investigation.

Animal Testing of Spray-on Bandage

A limited number of rabbit skin tests on normal and abraded skin of aerosol No. 13-2 were carried out. The spray-on bandage did not show any irritation or toxic reaction. There was no significant difference in healing time of abraded skin with or without the bandage. It was also noted that neutral or acidic drugs such as phenylmercuric nitrate, allantoin, or bacitracin were compatible with the bandage formulation.

SUMMARY

The development of a spray-on bandage with water-soluble resins has been attempted. The main drawback of such a product was the relatively long drying time of the film under the conditions of spray control employed. The best aerosols developed in this study are described in Table III. Formulations containing a mixture of polyvinyl alcohol and either polyvinyl acetate or acrylic resins were found to produce the best film-forming concentrate.

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* Pluronic, a product of Wyandotte Chemicals Corporation, Wyandotte, Mich.

† Precision Valve Corporation, Yonkers, N. Y.

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A Guinea Pig Assay of the Photosensitizing Potential of Topical Germicides

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Presented September 8, 1965, New York Chapter

Synopsis—In recent years there has been increasing use of germicides in soaps, detergents, and cosmetic products to provide significant benefits in the control of odor and minor secondary infections. Even though these agents are carefully screened for safety and effectiveness, an occasional one which reaches the mass market is found to be a marginal sensitizer that escaped detection in animal tests and limited human panel studies.

A guinea pig assay procedure is described which measures the photosensitizing potential of topical germicides. Data are presented relating the photosensitizing and cross photosensitizing activities of commercial germicides, *viz.*, bisphenolics, halogenated salicylanilides, and halogenated carbanilides. Tetrachlorosalicylanilide and, to a lesser degree, bithionol are observed to be photosensitizers. The significance of these findings and results on other germicides in predicting the acceptability of a topical agent in soaps and cosmetics is discussed.

INTRODUCTION

Photodermatitis is a phenomenon that has been known for many years. As far back as 1897, Stowers (1) described a case of skin eruption due to exposure to sunlight after contact with wild parsnips. Dermatitis in some individuals following use of eau de Cologne and exposure to sunlight was found to be due to certain essential oils—oil of bergamot being chiefly responsible. Klaber (2) coined the name phytophotodermatitis for the skin condition resulting from contact with certain

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* Lever Brothers Co., Research Center, Edgewater, N. J.

plants or their extracts followed by sun exposure. Some of the plants implicated in addition to wild parsnips are carrots, pink rot celery, persian lime, fig, buttercup, lady slippers, and many others. More recently, certain drugs and cosmetic ingredients have been reported to have photosensitizing effects on some individuals. Included are the sulfonamides, coal tar and derivatives, psoralens, and the phenothiazine drugs. Among the cosmetic ingredients implicated are lipstick dyes and sun-screening agents. Price gave an excellent review of photocontact dermatitis (3). Certain germicides have been reported to be photosensitizers, and one in particular, tetrachlorosalicylanilide, has received considerable notoriety (4–7). Unlike therapeutic agents, where a certain amount of risk may be justified to achieve cure, agents such as germicides for use in cosmetic and soap products must be carefully and thoroughly screened so as to avoid undesirable skin reactions. However, to find useful agents that provide effectiveness with safety for 100 per cent of the population is quite impossible when one considers the wide range in the biologic response of man.

Many factors are involved in trying to predict how skin will react to a topical agent. Some of the principal ones are:

1. Toxicity of the material.
2. Its allergic potency.
3. Concentration of the active ingredient.
4. Frequency and duration of use.
5. Nature of vehicle employed.
6. Environmental factors—temperature, relative humidity, and sunlight.
7. Sensitivity of the individual—genetic factor.

The problem of ascertaining the irritation potential of most agents, both primary irritants and sensitizers, is not a formidable one. Standard toxicological procedures which have proved useful are described in the FDA sponsored book on methods for safety evaluation of chemicals (8). Agents capable of inducing skin reactions in 1 in 100 or even 1 in 1000 subjects are readily detected in such tests, but it becomes increasingly difficult to predict the irritation or sensitization potential of a preparation causing skin reaction in 1 in 10,000 or even 1 in 100,000. This is particularly true for topical agents having weak photosensitizing properties. It is this particular type of agent that concerns those who are responsible for passing on the safety of soaps and cosmetics that are used by millions of people. A photosensitizing response occurring in more than 1 in 10,000 is not acceptable from a safety or business point of view. An incidence of 1 in 100,000 or less is the desirable goal for such products.

This report will be limited to a discussion of topical germicides for use in soaps and cosmetic products and to a description of a new laboratory procedure for assessing photosensitizing potential of topical agents on guinea pigs.

Topical Germicides

Topical germicides to be fully acceptable for use in soaps and cosmetics must have the following properties:

1. Effectiveness against skin bacteria at low concentrations.
2. Substantivity to skin.
3. Compatibility with vehicles.
4. Stability to light and heat.
5. Activity in presence of soil.
6. Safety—not a primary irritant, sensitizer, or photosensitizer.

The following topical germicides have received the greatest attention:

1. 2,2′-methylenebis (3,4,6-trichlorophenol) (Hexachlorophene)
2. 3,4′,5-Tribromosalicylanilide (TBS)
3. 3,4,4′-trichlorocarbanilide (TCC)
4. 2,2′-thiobis (4,6-dichlorophenol) (Bithionol)
5. 3,3′,4′,5-tetrachlorosalicylanilide (TCSA)

Tetrachlorosalicylanilide (TCSA), a germicide used in soaps, has been reported both in England and the United States to be a photosensitizer and has been promptly withdrawn from the market. This is an example of a biological agent that has passed conventional toxicological screening tests but was found to cause adverse skin reactions in some consumers after market introduction of soap containing TCSA. Bithionol has experienced similar difficulties but to a lesser degree and affecting a much smaller segment of the population. Jillson and Baughman (9, 10) reported on the photosensitizing action of bithionol on subjects characterized as persistent light reactors (PLR). Both TCSA- and bithionol-sensitized subjects were reported to be cross photosensitized, in some instances, to germicides like hexachlorophene and certain polybrominated salicylanilides.

In view of these unexpected incidents of photosensitization by some germicides, it has become very evident that an animal assay procedure to screen out weak photosensitizers would be a valuable aid in the continuing search for safe and effective topical agents for use in soaps and cosmetics. Such a procedure has been developed.

The guinea pig is the animal of choice for studying sensitization phenomena, and it has proved to be useful for checking out potential photosensitizers. The key to this procedure is to apply the test agent under "abuse" conditions. Solvents are used that have the effect of altering the skin defenses, thus making the guinea pig more vulnerable to the action of irritants. Three major skin defenses that provide protection against environmental stress, both physical and chemical, are (a) the skin barrier in the stratum corneum; (b) the water binding capacity of the stratum corneum; and (c) the buffering capacity of the skin. It is believed that the normal subject is capable of effectively combating weak irritants that come in contact with the skin, but the hypersensitive person is prone to react to low-order irritants because of poor skin defenses. The test procedure to be described is, therefore, based on the concept that the test animal should be exposed to the topical agent under conditions of stress that undermine the skin defenses. This is accomplished by administering the test material in organic solvents known to reduce barrier efficiency, water binding capacity, and buffering capacity.

Procedure Employed for Determining Photosensitization Potential of Topical Agents on Guinea Pig Skin

This test is comprised of two stages with an optional third stage.

1st Stage

Young adult guinea pigs, usually six to a group, are shaven with electric clippers on the upper dorsal area (cervical region). To this site is applied 0.05 ml. of a 2% solution of the test agent in absolute alcohol. This is repeated daily for a total of five applications. After each application the guinea pigs are ultraviolet-irradiated for 15 minutes, employing a Sun Lamp (GE or Westinghouse) from a distance of 18 in. The animals for this exposure are contained in a box with dimensions $15\frac{1}{2} \times 13\frac{1}{2}$ and 8 in. high. Skin readings for evidence of erythema are made 24 hours after each application as follows:

0 = no erythema
1 = pink erythema
2 = red erythema
3 = erythema and trauma

No erythema is evident in the first stage except for strong photosensitizers when erythema may appear after the third application.

2nd Stage

After a rest period of 7–10 days, during which time the treated skin is restored to normal appearance, one or two challenge applications of 0.05 ml. of a 0.1% solution of the test agent in olive oil is applied. Ultraviolet irradiation is administered for 15 minutes, and on the following day skin readings are taken. A relatively strong photosensitizer will give readings of 2 and 3. If the erythema is marginal, it is desirable to repeat the challenge with the test agent in the vehicle for which it is intended, such as soap.

3rd Stage (Optional)

Guinea pigs photosensitized to a test agent are shaven in the flank areas and treated with 0.1–0.2% of the test agent in an 8% soap solution once daily for a total of three applications. The solutions are applied by means of gauze patches (6 ply) kept in contact with the skin for 1 hour. The guinea pigs are immobilized on a board by means of tape. Ultraviolet irradiation for 15 minutes follows each application. Skin readings are taken 24 hours after each treatment. Erythema development indicates photosensitization. A control soap solution without the test agent is applied on the opposite flank. When slight erythema develops on the control side, the test side must show a more intense erythema to establish photosensitization.

RESULTS

Photosensitization data are given in Table I in a typical experiment in which the photosensitizing action of TCSA is compared with that shown by several other halogenated salicylanilides. Of particular interest is the negative response obtained for 3,4′,5-tribromosalicylanilide (TBS).* This agent has been widely used in soaps and detergents for more than eight years. The chlorinated salicylanilides cause more photosensitizing reaction than the brominated analogs.

In a study of the cross photosensitizing potential of germicides, TCSA-photosensitized guinea pigs, after a suitable period to allow the

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* Temasept II, manufactured by Fine Organics, Lodi, N. J.

skin to return to normal appearance, were shaven again in the neck region and treated with 0.05 ml. of 0.1% test agent in olive oil, followed by u.v.-irradiation, as described previously. The next day, skin readings were taken. Cross photosensitization data are given in Table II for hexachlorophene, bithionol, TCC, and TBS. Also presented in the way of comparison are data on sensitization potential (Landsteiner-Jacobs procedure) and photosensitization. It can be observed that bithionol and, to a lesser degree, hexachlorophene showed some cross photosensitizing action when studied on TCSA-sensitized guinea pigs. TBS and TCC were without effect in this cross photosensitization study.

TABLE I

Relative Photosensitizing Effects of TCSA and Other Halogenated Salicylanides (Guinea Pig Skin Readings)[a]

Substituents on Salicylanilide Ring	2% in Absolute Alcohol, 1st Stage (days)					0.2% in Olive Oil Challenge		0.5% in 8% Soap Solution Re-challenge (days)		
	1	2	3	4	5	1	2	1	2	3
3,3'4',5-Tetrachloro	0	0	0	2	2	2	3	1	2	2–3
3',4',5-Trichloro	0	0	0	1	1	2	2	1	2	2–3
3',4'-Dichloro-5-bromo	0	0	0	0	sl.	1	1	0–sl.	sl.	1
3,5-Dibromo-3',4'-dichlor	0	0	0	0	sl.	0	0	0–sl.	1	1–2
3,4',5-Tribromo-3'-methyl	0	0	0	0	0	0	sl.	0–sl.	sl.–1	1–2
3,4',5-Tribromo	0	0	0	0	0	0	sl.	0	0	0

[a] *Skin readings:* 0 = no erythema, sl. = patchy pink, 1 = pink erythema, 2 = red erythema, and 3 = erythema and trauma.

TABLE II

Sensitizing and Photosensitizing Potential of Topical Germicides

	Skin Response		
	Sensitizing Potential (Landsteiner-Jacobs Test)	Photosensitizing Potential	
		Guinea Pigs with No History of Photosensitization	Guinea Pigs Photosensitized to TCSA
3,3',4',5-Tetrachlorosalicylanilide (TCSA)	Negative	Strong positive	. . .
3,4',5-Tribromosalicylanilide (TBS)	Negative	Negative	Negative
Bithionol	Negative	Positive	Positive
Trichlorocarbanilide (TCC)	Negative	Negative	Negative
Hexachlorophene (G-11)	Negative	Negative*	Weak positive

* Erythema develops in both stages, indicating phototoxic effect, not photosensitization.

The effect of hexachlorophene as a cross photosensitizer to TCSA-sensitized animals is observed only when it is applied in olive oil. No cross photosensitization was noted for hexachlorophene when applied in alcohol or in soap solution. Thus, the importance of the vehicle in the evaluation of the safety of a topical agent should not be neglected.

In the standard Landsteiner-Jacobs Test (8), wherein a series of intradermal injections of the test agent is given, the results indicated that none of the germicides tested were sensitizers in the classic sense.

Discussion and Conclusions

1. A guinea pig test for assessing photosensitizing and cross photosensitizing potential of topical germicides is described. Results confirm, in guinea pigs, reports on the photosensitizing action of TCSA and bithionol in humans. The test procedure employs guinea pigs that are subjected to repeat insult with the test material in two solvents—absolute alcohol and olive oil—both having the effect of reducing the skin resistance to toxicants and increasing the reactivity of the skin to such agents.

2. TBS despite its structural relationship to TCSA is neither a photosensitizer nor a cross photosensitizer. TCC also is free of such action. Reports by Wilkinson that TBS was found to be a cross photosensitizer when tested on TCSA-sensitized human subjects (4) may be explained by the likelihood that the TBS sample employed by Wilkinson contained such isomers as tetrabromosalicylanilide, which has been found to be a photosensitizer. The need for TBS free of the tetrabrom contaminant is quite apparent.

3. Hexachlorophene is not a photosensitizer but has been shown to be a mild cross photosensitizer when tested on TCSA-photosensitized guinea pigs. The practical significance of this finding can be questioned in view of the severity of the testing conditions. However, this observation is of interest in the light of findings reported by Baughman (10), in this country, and the English workers that TCSA-sensitized subjects may, on occasion, react to hexachlorophene.

4. The described guinea pig photosensitization test should prove valuable in the primary screening of topical agents for photosensitizing potential. It is important to point out that, before deciding on the practical significance of marginal photosensitizers, tests should be extended to the study of the action of the test material in the vehicle for which it is intended (Stage 3 of the test procedure described).

5. If the results of the guinea pig photosensitization test and the Landsteiner-Jacobs test are both negative, the test material probably can be tested on humans with good assurance that no photosensitization problem will develop. If an agent passes both tests but shows cross photosensitizing activity, additional tests on the preparation in the intended vehicle should be conducted.

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ACKNOWLEDGMENT

The authors are indebted to Dr. Henry Lemaire of the Lever Organic Section who prepared samples of halogenated salicylanilides reported here.

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Book Reviews

THE CHEMICAL FORMULARY, VOLUME XII, edited by H. Bennett, Chemical Publishing Co., Inc., New York. 1965. 502 pages, indexed. Price $8.00.

This volume is the twelfth of a series representing a compilation of formulas for chemical compounding and treatment. With the exception of the introduction, all formulas are new and not repetitious of previous volumes, and for this the author is to be commended.

The series was designed to aid the inexperienced in getting started in new fields, and for this reason the introduction, which is a chapter on procedure, has been repeated in each volume. It appears to this writer that a modernization of the introduction is in order. Since formulas for aerosols are given, a discussion of their compounding would be desirable. Also, the author allotted considerable space to the units used in formulas but neglected to point out that formulas are often written with some ingredients stated by weight and others stated by volume.

The formulas, in general, are good, although sometimes superfluous. There are a few errors. For example, Aerosol Shave Cream No. 1 specifies use of trichloromonofluoromethane, a propellent which cannot be used in the presence of water.

The book is recommended for the beginner, but not for the experienced formulator.—W. R. NETZBANDT, Lever Bros. Co.

COMPREHENSIVE BIOCHEMISTRY, VOLUME 6, LIPIDS AND AMINO ACIDS AND RELATED COMPOUNDS, edited by Marcel Florkin and Elmer H. Stotz, Elsevier Publishing Co., Amsterdam, London, New York. 1965. 323 pages, indexed. Price $17.

This rather nonhomogeneous volume contains nine chapters prepared by different authors. As a result of its diversity, this book is of considerable interest and holds the reader's attention.

The three chapters on lipids cover the subjects of fatty acids, alcohols, waxes, neutral fats and oils, and phospho- and glycolipids. Most of this material is concerned with the chemistry and the physicochemical description of a broad variety of lipids. Almost no attempt is made to discuss the important physiological functions which these lipids perform in biological systems. The second half of this volume is concerned with nitrogen-containing compounds of biochemical interest. The two major chapters in this portion are devoted to the chemistry and description of amino acids and nitrogenous bases. Four accessory chapters discuss the chemistry of melanins, the synthesis of peptides, capsular polypeptides, and the synthesis of bacterial polypeptides. The emphasis, again, is strictly on the chemistry of these materials and not on their physiological properties.

There can be little doubt about the fact that this volume is an excellent introduction and description of the innumerable chemical entities which can be found in biological systems. Despite omissions (e.g., the chemistry of the disulfide bond in cystine is not discussed; the prostaglandins are not mentioned; and lipofuscin is ignored), this volume still deserves study. It should prove to be a valuable desk reference or dictionary to hundreds of diverse chemicals which are of biological interest.—M. M. RIEGER, Warner-Lambert Research Institute.