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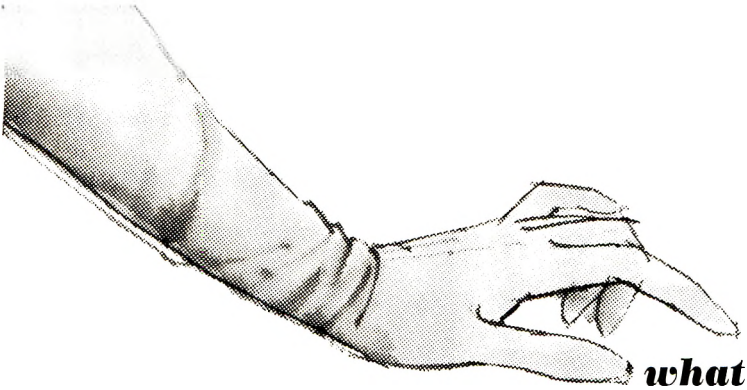

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Journal of the Society of Cosmetic Chemists

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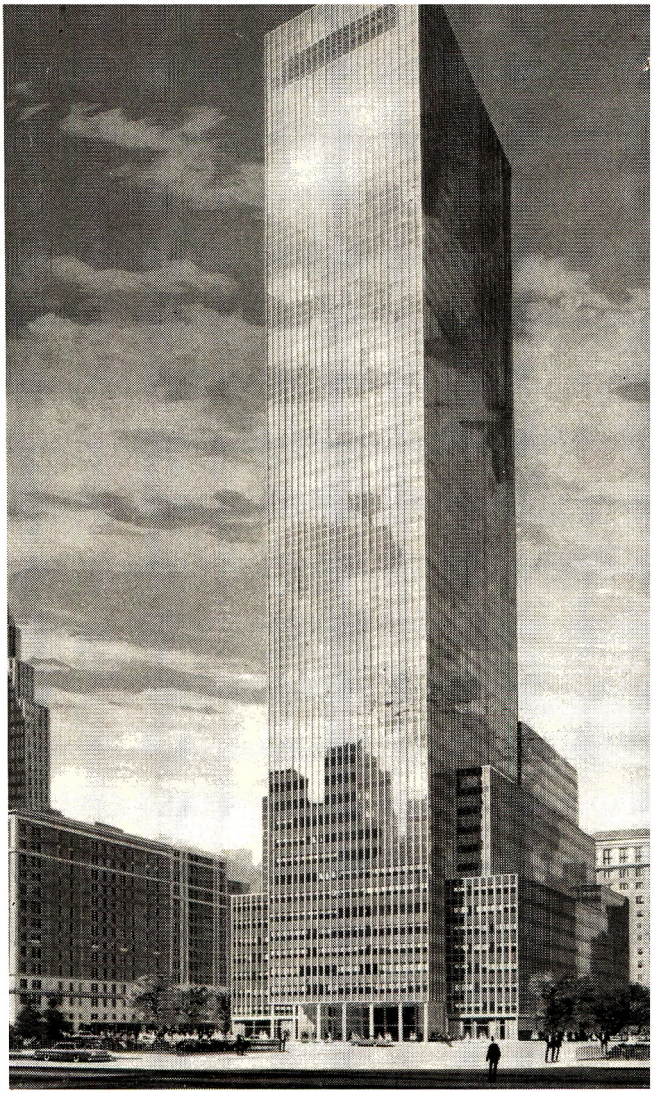

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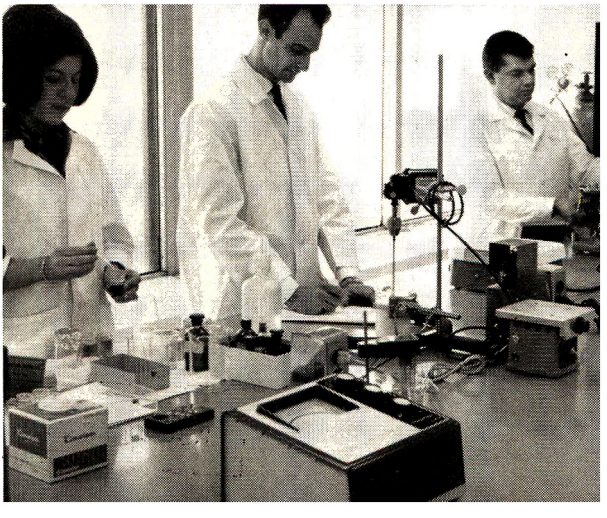

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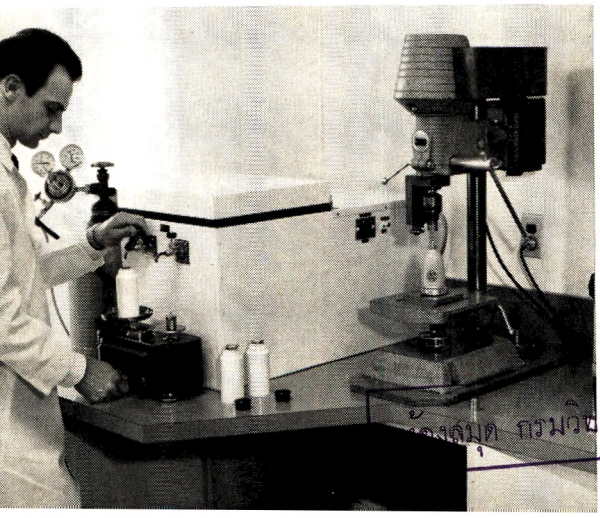

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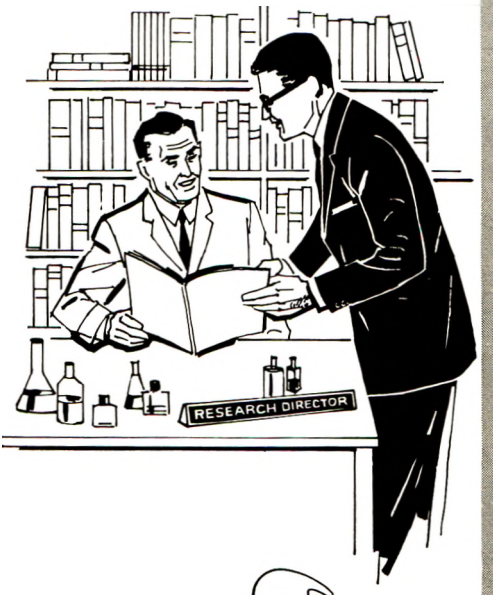

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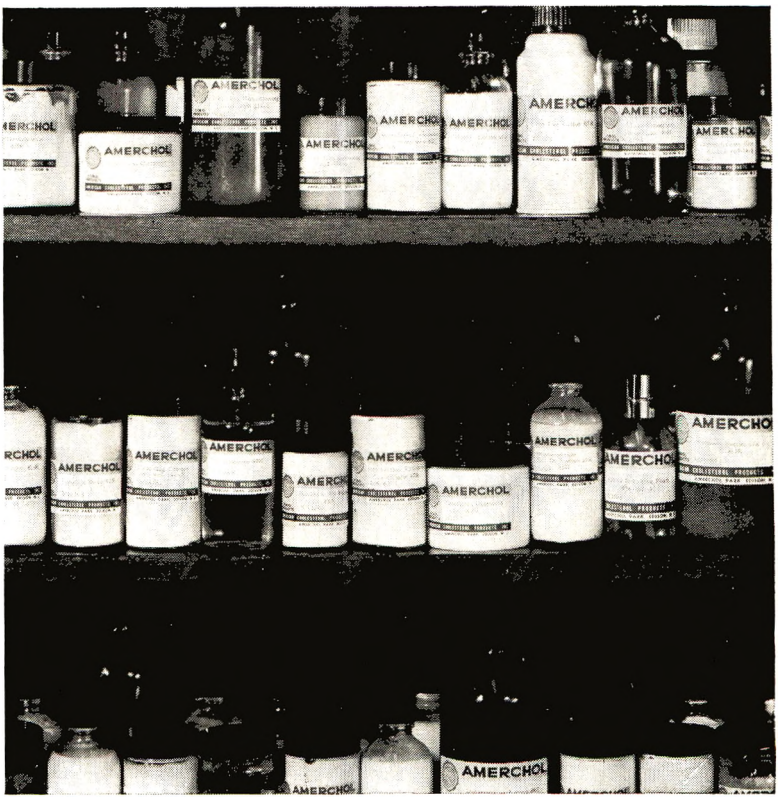

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SYNOPSES FOR CARD INDEXES

The following synopses can be cut out and mounted on 3 × 5 in. index cards for reference, without mutilating the pages of the Journal.

Approaches to a prophylaxis of skin aging: Margot Ippen and Hellmut Ippen. *Journal of the Society of Cosmetic Chemists* **16,** 305 (1965).

Synopsis—It is shown that smoking has a deleterious effect on skin condition and that this effect can be differentiated from that of damage by sunlight. Smoker's skin is identified as skin which suffers from loss of "turgor" and shows signs of flabbiness; in addition, the color of the smoker's skin is pale, with a grayish hue. Dermatological examination of 224 women up to now showed no strong correlation between their smoking habits and the appearance of their skin, as defined above. By contrast, smoking seems to have only a very minor effect on the skin of male smokers.

The action of hair sprays on hair: Martin G. Brookins. *Journal of the Society of Cosmetic Chemists* **16,** 309 (1965).

Synopsis—Observations are made concerning the mechanism of hair spray application and holding. Indirect evidence leads to the author's hypothesis that wetting by alcohol *per se* is not responsible for curl relaxation.

Use of anti-irritants in cosmetic formulating: Robert L. Goldemberg. *Journal of the Society of Cosmetic Chemists* **16,** 315 (1965).

Synopsis—An anti-irritant is defined as an agent which, when used in conjunction with skin or eye irritants, reduces their irritation potential sufficiently to be tolerated when applied to the body.

Three different mechanisms are postulated for the activity shown by various anti-irritants: Some operate by "complexing" the irritant itself. Others react with the skin, blocking reactive sites so that the irritant cannot react with it. A final group seems nonreactive and apparently protects by merely preventing complete physical contact between irritant and skin. Examples of each mode of action are given.

The major portion of the report presents irritation test data showing specific anti-irritant activity, or lack thereof, for a number of agents which were added to various types of cosmetic formulas. In particular, an antiperspirant formula is developed step by step, with the irritant effect of each component determined.

An appendix lists several dozen agents for which anti-irritant properties have been claimed, together with a summary of the evidence backing such claims.

Soluble brominated salicylanilides: W. E. Lange and M. R. Mezikofsky. *Journal of the Society of Cosmetic Chemists* **16**, 339 (1965).

Synopsis—The low aqueous solubility of the brominated salicylanilides (I) limits their usefulness in cosmetic or pharmaceutical preparations. Nonionic surface active agents and compounds chemically related to I did not increase solubility. Preparation of the salts of I gave compounds with good microbiological activity and aqueous solubility but with limited light stability. Aqueous solutions of formulations utilizing the salts of I showed good stability when they were protected from U.V. light.

Pyridoxine-3,4-diacylates and their use in cosmetics: Haruyasu Ohta. *Journal of the Society of Cosmetic Chemists* **16**, 347 (1965).

Synopsis—Pyridoxine-3,4-diacylates can be prepared by a new process in good yield and high purity. Data are presented to demonstrate the oil solubility and the heat and light stability of these esters. Acute and chronic toxicities of these indicate that they are suitable for inclusion in cosmetics. It is further shown that the esters are hydrolyzed by tissue homogenates at rates which are influenced by the acid moiety used for esterification. Finally, clinical data are presented to demonstrate the utility of pyridoxine-3,4-dipalmitate in dermal therapy.

A new procedure for the preparation of polyethylene-mineral oil gels: Paul Thau and Charles Fox. *Journal of the Society of Cosmetic Chemists* **16**, 357 (1965).

Synopsis—A new procedure is described for the preparation of polyethylene-mineral oil gels. This procedure utilizes high shear mixing equipment to maintain a fine dispersion of the polyethylene wax during a critical phase of the cooling process. The consistencies of gels produced by this procedure are independent of cooling rates. In contrast to existing methods of preparation, this innovation offers advantages in terms of simplified processing and greater formulation flexibility.

The Eleventh Literature Award

Dr. Paul W. Jewel, President of the Society of Cosmetic Chemists, presented the Eleventh Literature Award of the Society to Drs. William C. Griffin and Paul Becher during the scientific meeting of the Society at the Hotel Biltmore on May 4, 1965.

The Literature Award is given each year for the publication during the preceding two years of scientific research judged to be of value to cosmetic science and technology.

The Award was made in recognition of Drs. Griffin's and Becher's many years' study of emulsions and their development of a practical procedure for the determination of the type of emulsifiers needed. These authors have been instrumental in the development of the HLB system, which is widely employed in the cosmetic and related industries.

I. F. F. Award 1964

The I. F. F. Award for the best paper published in an American issue of the JOURNAL OF THE SOCIETY OF COSMETIC CHEMISTS during the calendar year of 1964 was awarded to Messrs. John Facq, David L. Kirk and G. Rebell during the May meeting of the Society of Cosmetic Chemists. The selected paper, "A Simple Replica Technique for the Observation of Human Skin," describes a process and the equipment required for the preparation of dimensionally accurate plastic replicas of surfaces. The paper appeared in the February, 1964, issue of the JOURNAL, pages 87–98.

The I. F. F. Award is made possible through the generosity of International Flavors and Fragrances, Inc., and is administered by the Editorial Committee of the JOURNAL OF THE SOCIETY OF COSMETIC CHEMISTS.

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Obituary

Dr. Ralph Liggett Evans, President and a Director of Evans Chemetics, Inc., and of Evans Research and Development Corp., died on March 21 after a brief illness.

Dr. Evans' research activities covered many fields, especially cosmetics. It is said that Evans was the first formally trained chemist who organized a research staff to investigate the problems of the cosmetics industry. His research on substituted mercaptans, for example, led to the marketing of depilatory products having lower odor than those previously available. During the 1920's, his studies on the composition of hair dyes helped reduce the incidence of allergic reactions to these materials. During World War II he developed a gas protective ointment and operated four plants employing 1200 people to produce it and gas detector kits. He was also instrumental in the development of a process for the production of stabilized hydrogen peroxide. During the war years, his research and development organization also carried on investigations ranging from work on new high explosives to certain phases of chemical warfare.

Dr. Evans was born in Texarkana, Ark. He received a B.S. degree at the University of Chicago in 1919 after his studies were interrupted by a tour of service in the Army during World War I. He received his Ph.D. degree in chemistry from Columbia University in 1925 where he studied under Prof. Bogert. Dr. Evans lectured at Columbia from 1920 to 1924 and then became associated with Inecto, Inc., as part owner and technical director.

Dr. Evans was a member of the Society of Cosmetic Chemists and received the Society's second Medal Award in 1949. Evans was also a member of numerous honorary societies, scientific associations and governmental agencies.

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J. Soc. Cosmetic Chemists, 16, 305–308 (1965)

Approaches to a Prophylaxis of Skin Aging*

MARGOT IPPEN, M.D., and HELLMUT IPPEN, M.D.†

Synopsis—It is shown that smoking has a deleterious effect on skin condition and that this effect can be differentiated from that of damage by sunlight. Smoker's skin is identified as skin which suffers from loss of "turgor" and shows signs of flabbiness; in addition, the color of the smoker's skin is pale, with a grayish hue. Dermatological examination of 224 women up to now showed no strong correlation between their smoking habits and the appearance of their skin, as defined above. By contrast, smoking seems to have only a very minor effect on the skin of male smokers.

The problem of aging of the skin is an especially important area in the field of cosmetics. Numerous methods for combating and covering up the aged skin are known. On the other hand, little attention has been directed until now toward investigation of the causal factors and the basic origin of skin aging—especially with reference to aging of the face.

When the skin becomes slack and loose, "crow's feet" and other small wrinkles appear, and the skin becomes thinner. These developments are generally regarded as a physiological process which often can be retarded but never decisively stopped by the use of appropriate cosmetics. Examination of the skin qualities of women of equal age demonstrates that the differences between the skin qualities increase with the age of the women. Such differences cannot fully account for individual or constitutional variations. Furthermore, if one examines

* This communication is a condensation of a paper presented before the Third Congress of the International Federation of Societies of Cosmetic Chemists on June 25, 1964, New York City.

† Am Massenberger Kamp 23, 4000 Düsseldorf-Holthausen, Germany.

and compares the skin of different parts of the body of the same person, one finds in many cases great differences between the degree of aging from area to area, e.g., between the skin of the face and that of the back.

Such observations stimulated the authors to examine the state of the facial skin of women systematically and to determine possible causes which may have accelerated aging of the skin.

From these investigations a remarkable parallelism between the following two factors was found:

1. Exposure to sunlight
2. Cigarette consumption

There is a considerable amount of data concerning the damaging effects of long exposure to sunlight on the skin. In contrast, the authors have found no reference on the role of tobacco smoking on aging of the skin. In order to establish the relationship between smoking and skin aging more conclusively, these examinations were extended, and the following facts were determined.

1. The longer and the more a woman has smoked, the more frequently poorer skin conditions are observed. Certain features of this damage could be differentiated from the sunlight-damaged skin.

2. More specifically, the skin changes resulting from long years of smoking manifest themselves mainly through a loss of "turgor" and reduced circulation in the deeper layers of the skin. On the other hand, the light-induced skin changes are characterized by a degeneration of the superficial connective tissue and an atrophy of the epidermis.

3. Correspondingly, the skin of the smokers is pale, with a grayish hue, and without local variations of the pigmentation. Also prevalent are wrinkles and folds, which sometimes cover the whole face but are especially noticeable on the cheeks. Between these folds and wrinkles the skin is abnormally thick. It is probable that the reduction of turgor plays an important role in this development.

4. In extreme cases this loss of turgor results in a slackness and flabbiness of the skin of the cheeks with women who had not yet reached the age of forty.

The authors have examined 224 women, aged 35 to 84 years. At first the skin of the face and neck was examined. From these dermatological studies conclusions were drawn concerning the patients' smoking habits. Subsequently, the women were asked about their cigarette smoking, and the following relations were found: In 93 (41.5%) the characteristics of "cigarette skin" were described; in 131 (58.5%)

the skin was not characterized as such. Of the 131 women without "cigarette skin," 113 (86%) have never smoked whereas only 18 (14%) of them have smoked. The group of 93 women with cigarette skin included 66 (71%) smokers and 27 (29%) non-smokers. In other words, 66 (79%) of the 84 smokers were recognized from their skin appearance, and 113 (80%) out of the 140 non-smokers had no signs of cigarette skin. In the case of the 27 non-smokers with "smoker's skin" one must consider constitutional factors separating this group of mostly elderly ladies from the real smokers. In contrast, most of the 18 smokers without smoker's skin had not yet reached the age of fifty. Therefore, their skin changes seem to have not progressed far enough to be noticed.

The main differences between cigarette skin and light-damaged skin, which can be seen occasionally on the face after long and intensive application of sunlight, are in color and firmness. This follows from the different pathogenesis of these two types of skin damage. The primary reaction following chronic sunlight damage takes place in the blood-vessels adjacent to the epidermis. As a result, the parts of the connective tissue lying just under the epidermis degenerate, and finally the epidermis itself degenerates. What follows is a certain rigidity, sometimes intensified by a superficial elastoidosis. Deeper wrinkles are seldom found. Especially noticeable, however, is the color, which is irregularily brownish due to hyperpigmentation, but also has a reddish hue, due to the intact circulation in the deeper layers of the skin.

In contrast to this, nicotine seems to have a much stronger effect upon the deeper blood vessels of the cutis. The constriction of vessels by nicotine is evident in the pale gray color of the face, caused by reduced circulation and followed by a degeneration of the connective tissue in the deeper layers of the cutis. This degeneration results in deep wrinkles and loss of turgor. Since the relatively unaffected epidermis does not atrophy, it is easier to discern the changes in skin relief caused by the damage in the deeper layers of the cutis.

These investigations have been limited thus far to women. It would appear that smoking has less or hardly any effect on the skin of men. With women the investigations should be limited to those between the ages of 35 and 70. Women over 70, who have never smoked, are affected by other processes of degeneration, which result in a very similar morphological picture. These observations show that consumption of tobacco by younger women can produce the appearance of "senile" skin. Hardly any difference can be seen between the skin of a

forty year old smoker and a seventy year old non-smoker. This is even more apparent when neither subject has been extensively exposed to sunlight.

The premature aging of women's facial skin is mainly the consequence of three basic factors:

1. The physiological process of aging of the entire integument, characterized by the folds resulting from habitual facial movements such as smiling and frowning.

2. Those chronic changes on the outermost skin layers which are caused by long exposure to sunlight. Such changes, as a rule, are not found on the skin of the rest of the body except on the neck, forearms, and hands.

3. Combined with the first two factors are those changes in the circulation and the quality of the deeper connective tissue which follow long years of smoking and which are mainly noticeable on the face and on the neck.

J. Soc. Cosmetic Chemists, 16, 309–315 (1965)

The Action of Hair Sprays on Hair

MARTIN G. BROOKINS, M.S.*

Presented before the New England Chapter, April 23, 1964, Framingham, Mass.

Synopsis—Observations are made concerning the mechanism of hair spray application and holding. Indirect evidence leads to the author's hypothesis that wetting by alcohol *per se* is not responsible for curl relaxation.

Introduction

Since holding in a hair spray is due mainly to the mechanical rigidity of the resin deposit formed on hair fibers, its application becomes important. By studying how the resin deposit is formed on hair fibers, the degree of holding of different types of film formers and the effect of resin distribution throughout the entire mass of hairs can be assessed. The application also depends upon the wetting properties of the solvent vehicle on hair. In most commercial aerosol hair sprays today, the main solvent is alcohol, with halogenated hydrocarbons used as solvents and propellants. By the time the liquid hair spray droplet strikes the hair, most of the propellant has evaporated, leaving only a residual amount present in the droplet. The amount of "flow-out" of the droplet on the hair fiber depends upon the degree to which the droplet wets the hair fiber and also depends upon the mobility of the droplet after it strikes the hair fiber. It is known, for instance, that a hair spray container packed with 50% alcoholic concentrate and 50% propellant provides a much wetter spray than one packed with 70% propellant and 30% alcoholic concentrate. A wet spray, 50/50 type (assuming that the

* John H. Breck, Inc., Springfield, Mass.

same valve, pressure, and button system is used on both types of spray), will wet the hair much faster and more thoroughly than a 70/30 pack.

Results and Discussion

The Holding Effect

An attempt will be made to assay the dynamics of distribution, impingement, and holding by citing experimental results derived from the examination of a typical dry spray (i.e., 70/30 pack) *versus* a typical wet spray (50/50 pack). It may be stated at this point that there are other factors which influence the wetness of a hair spray. Valve orifices and internal container pressures are also important, but the

TABLE I

Experimental Design—Wet *Versus* Dry Spray Droplet Volume

I. Variables	
A. Product	
1. A_1 = Product *A* (dry spray)	
(a) Alcoholic concentrate	30%
(b) Freon 11/12	70%
2. A_2 = Product *B* (wet spray)	
(a) Alcoholic concentrate	50%
(b) Freon 11/12	50%
B. Spraying time	
1. B_1 = One-second burst	
2. B_2 = Two-second burst	
C. Drying time	
1 C_1 = No drying time	
2. C_2 = One minute after spraying	
3. C_3 = Three minutes after spraying	
II. Parameter	
Observed droplet volume as a function of all variables	

most important factor will be the amount of dilution of the concentrate with propellant. A series of experiments were conducted in accordance with the design outlined in Table I. In this experiment, cans representing variable *A* were held in a fixed position and sprayed on hair shanks at a distance of 12 in. Time sequence photographs were taken so that measurements of approximate droplet diameters could be made with an optical comparator. Examples of time sequence photographs appear in Figs. 1 and 2. Droplet volume was calculated and recorded in cubic inches. Results were reported as mean droplet volume where N (number of droplets) varied from five to ten (Table II). Figures 3

and 4 represent graphs in which drying time was plotted against Log$_e$ mean droplet size in cubic inches.

As can be seen in Fig. 3, the two-second spray yields larger droplets than the one-second spray. The droplets are fairly evenly spaced along the hair fiber, and a regularly diminishing droplet size is observed during drying. In Figure 4, it may be seen that, after a one-second

Figure 1. Photograph of hair sprayed with dry hair spray

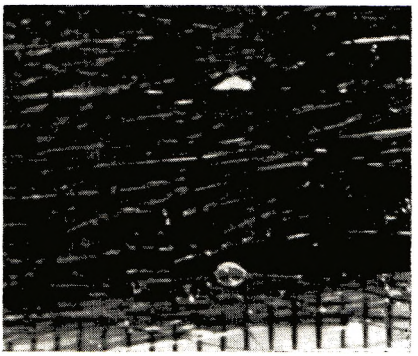

Figure 2. Photograph of hair sprayed with wet hair spray

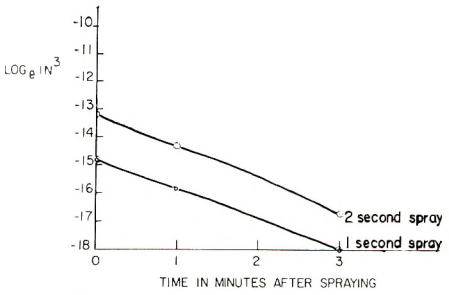

Figure 3. Mean droplet volume in cubic inches: product "A"

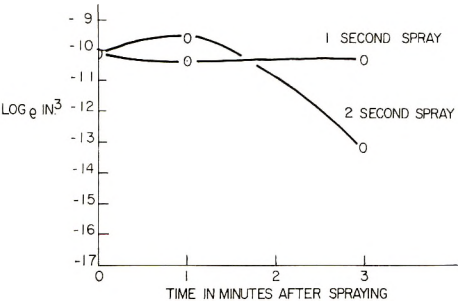

Figure 4. Mean droplet volume in cubic inches drying time as a change in volume: product "B"

spray, giant droplets are formed, which then dry. However, after a two-second spray, droplets tend to disappear, probably because the alcohol thoroughly wets the hair fiber and forms a layer about the fiber and between the fibers.

Microscopic examination of hair fibers sprayed with dry sprays *versus* wet sprays reveals the following: Figure 5 illustrates the case where hair is sprayed with a dry spray for two to three seconds, which appears to be normal usage since the average volume of a coiffure is 1000–3000 cc. The droplets, which dry considerably before striking

TABLE II

Drying Rates of Hair Sprays on Hair from the Aspect of Droplet Size and Distribution

Experimental Treatment			Cubic Inches	Log_{e} cu in
A_1	B_1	C_1	3.44×10^{-7}	−14.88
A_1	B_1	C_2	0.46×10^{-7}	−16.89
A_1	B_1	C_3	0.15×10^{-7}	−18.01
A_1	B_2	C_1	18.30×10^{-7}	−13.22
A_1	B_2	C_2	6.81×10^{-7}	−14.20
A_1	B_2	C_3	0.56×10^{-7}	−16.70
A_2	B_1	C_1	385.00×10^{-7}	−10.17
A_2	B_1	C_2	333.00×10^{-7}	−10.32
A_2	B_1	C_3	337.00×10^{-7}	−10.30
A_2	B_2	C_1	394.00×10^{-7}	−10.15
A_2	B_2	C_2	670.00×10^{-7}	−9.61
A_2	B_2	C_3	19.00×10^{-7}	−13.13

TABLE III

Experimental Layout and Analysis of Variance

Curl Length Before and After Spraying					
A_1[a]	B_1[c]	3.25	A_2[b]	B_1	2.75
A_1	B_1	2.75	A_2	B_1	3.25
A_1	B_1	2.75	A_2	B_1	2.75
A_1	B_1	2.75	A_2	B_1	3.25
A_1	B_2[d]	3.75	A_2	B_2	4.50
A_1	B_2	3.25	A_2	B_2	4.75
A_1	B_2	3.50	A_2	B_2	4.50
A_1	B_2	3.25	A_2	B_2	4.75

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square
Between A's	1	1.72	1.72
Between B's	1	4.78	4.78
Interaction	1	1.14	1.14
Error	12	0.68	0.06
Total	15	8.32	

$$F_A = \frac{MSA}{MSE} = \frac{1.72}{0.06} = 28.67 \qquad F_I = \frac{MSI}{MSE} = \frac{1.14}{0.06} = 19.00$$

$$F_B = \frac{MSB}{MSE} = \frac{4.78}{0.06} = 79.67 \qquad F_{0.05} = 4.75$$

$$F_{0.01} = 9.33$$

[a] A_1 = Dry spray with small droplets.
[b] A_2 = wet spray.
[c] B_1 = Length of tress before spraying.
[d] B_2 = Length of tress after spraying.

the hair, are small, even though there is some coalescence. Thus, a larger amount of surface area is exposed to the atmosphere, and drying takes place rapidly. Small droplets impinge upon hair fibers, and the effect on holding is statistical, i.e., droplets that do not land on fiber junctions are ineffective in holding except that they act as a reservoir for setting with a wet comb. With a spray of this type, soft holding and a fairly soft feel on hair can be expected.

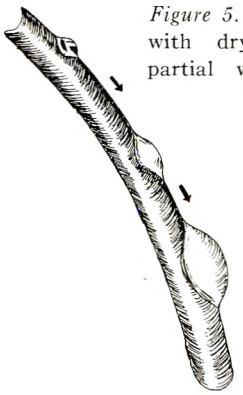

Figure 5. Brief spraying with dry spray (note partial wetting of hair shaft)

Figure 6. Long spraying with dry spray (note agglomeration to form large droplets)

Figure 6 represents a case in which hair is sprayed for a long period of time with a dry spray. The same results occur when a wet spray is used for a short period of time. In this instance, the bombardment of hair with liquid droplets is so heavy that the droplets coalesce at a greater rate and run along the fiber until they reach hair junctions and, at this point, stop and dry. Heavy coalescence may take place when a dry spray is concentrated on one area for a relatively long time. Because of cooling, droplet evaporation is decreased. Droplets are cool when they strike the hair fiber because, during their flight from the can, the propellant is evaporating at a high rate, and the temperature of the droplets is decreasing proportionately.

Figure 7 represents heavy spraying with a wet spray. Large droplets form, coalesce, and, because of their heavy concentration at the impact site, flow along the fiber and wet it. Droplets are so large that flow-out between adjacent or intersecting hair fibers will occur quite easily.

Figure 8 represents typical junctions that are observed on hair sprayed with dry hair sprays. It can be seen that, with a dry spray or a light application of a wet spray, definite bonding or bridging between adjacent or intersecting hair fibers occurs. There are many

points of intersection on the outer layer of the mass of hair fibers where bridges may be formed, and definite holding may be expected. With a heavy wet spray, similar to the case in which the hair fiber is saturated with alcoholic concentrate, much broader connecting links and, therefore, greater holding may be expected; but the connecting links are

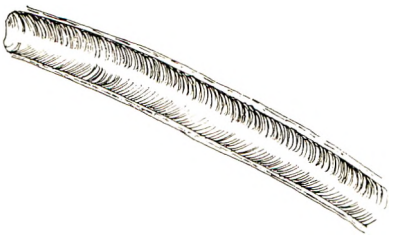

Figure 7. Long spraying with wet spray (note complete wetting of hair shaft by hair spray)

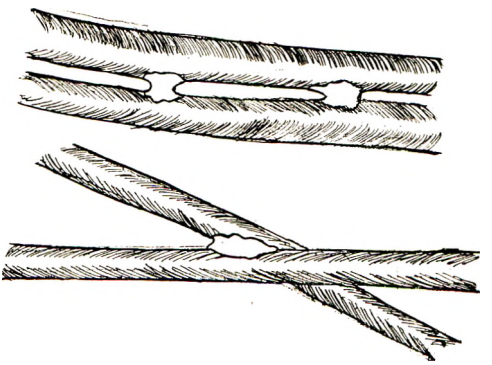

Figure 8. Formation of bonds or bridges between adjacent or intersecting hair fiber

only effective where hair fibers cross or are adjacent. However, the strength of the holding is dependent upon the much higher area of contact between the resin and the hair junctions.

Application Effect

Since alcohol wets hair very easily, it seems reasonable that a water-set tress might easily relax if saturated with hair spray. In order to confirm this, two groups of hair tresses were set in water pin curls, allowed to dry, unpinned, and their length measured in inches. The tresses were then sprayed with the respective sprays for a three-second period at a distance of 10 in. Tresses were again measured after drying. The results of this experiment are tabulated in Table III. It may be

seen that the A variable, the B variable, and the interactions of AB are significantly different. Although no rankings were determined, the data permit the conclusion that a wet spray tends to change or relax the initial water wave.

Another experiment was performed in order to determine the relative relaxation of water-set tresses after immersion in water, in 75% ethanol, in 95% ethanol, and in anhydrous ethanol. Tresses of hair were set with water, wound on peg boards and dried. After unwinding, groups of six dried tresses were immersed in water and in each of the ethanol/water solutions. Length measurements were made after distinct periods

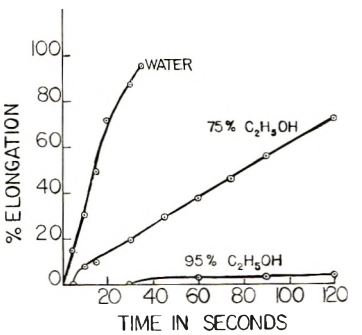

Figure 9. The effect of ethanol/water mixtures on curl retention of wound tresses

of immersion. Figure 9 summarizes the results of the experiment. It may be observed that tresses wet with water relax very rapidly, whereas the other groups of tresses relax according to the amount of water present in solution.

Summary

The mechanism of hair holding by hair spray differs depending upon the size and distribution of liquid droplets impinging upon hair fibers and is a function of the wetting of the fiber by the liquid vehicle. The application of a hair spray and its effect depends upon the wetness of the hair spray and the degree at which curls relax.

The hypothesis is made that the relaxation of a hair tress after being sprayed with a hair spray depends upon the amount of moisture in the form of water vapor from air absorbed during the application of the hair spray.

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Use of Anti-Irritants in Cosmetic Formulating

ROBERT L. GOLDEMBERG, B.S.*

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Synopsis—An anti-irritant is defined as an agent which, when used in conjunction with skin or eye irritants, reduces their irritation potential sufficiently to be tolerated when applied to the body.

Three different mechanisms are postulated for the activity shown by various anti-irritants: Some operate by "complexing" the irritant itself. Others react with the skin, blocking reactive sites so that the irritant cannot react with it. A final group seems nonreactive and apparently protects by merely preventing complete physical contact between irritant and skin. Examples of each mode of action are given.

The major portion of the report presents irritation test data showing specific anti-irritant activity, or lack thereof, for a number of agents which were added to various types of cosmetic formulas. In particular, an antiperspirant formula is developed step-by-step, with the irritant effect of each component determined.

An appendix lists several dozen agents for which anti-irritant properties have been claimed, together with a summary of the evidence backing such claims.

Introduction

It has been known since pre-history that certain natural materials have a soothing effect when applied to irritated skin. Primitive witch doctors often included such ingredients in magic potions which thereby developed mysterious curative powers, especially when applied to the accompaniment of suitable incantations and dances.

Many of these same ingredients, plus a number of newer synthetic agents, are used today in cosmetic and dermatologic preparations for their actual or supposed curative powers. It is assumed that they promote the healing of various types of skin irritation. Many formu-

* Charles of the Ritz, South Norwalk, Conn. 06854.

lators feel it "self-evident" that such soothing ingredients must also act as *anti-irritants* if applied to the skin in conjunction with known irritants.

Unfortunately, this self-evident assumption is not always justified. In recent years it has been learned that safety is a relative matter. No material is *absolutely* safe to use on the skin unrestrictedly, nor does anything exist which is always unsafe. Materials which are known to be soothing to irritated skin will not always act as anti-irritants when mixed with inflammatory or otherwise irritating agents.

The purpose of this paper therefore is not to establish absolutes nor to provide lists of ingredients guaranteed to make products safe. Instead, the purpose is to show that *the skin and eye irritation potential of various cosmetic ingredients can vary greatly, depending on their "environment"* (i.e., other components of the formulation), *and on the method of use and bodily area to which the finished formulation is applied.*

A corollary of this argument is the inescapable conclusion that "positive" (safe) and "negative" (unsafe) lists of cosmetic ingredients, such as have been suggested in several European countries as "guides" or as devices for regulating the activities of cosmetic manufacturers, have no sound scientific basis. There is no question that the irritative properties of many ingredients can be altered drastically by suitable compounding techniques. Therefore, it must also be evident that the irritation potential of a cosmetic cannot be determined solely on the basis of the known irritative properties of each of its individual components. The irritation characteristics of components are *not* additive. They often exhibit a synergism, either positive or negative, which appears at random and is unpredictable. These synergistic effects are the basis of several recent patents (1–3) concerned with anti-irritant combinations.

It would not be wise, therefore, to draw generalizations from the anti-irritant effects noted in this paper. Some agents may be useful only in the specific formulations which were tested. It will also be shown later that some materials can act as *anti*-irritants in one type of formula and then reverse their roles and *increase* the irritation potential of a different type of product.

General Background

Cosmetic chemists must beware the temptations of two sirens, medicine and cosmetology, who stand on opposite shores of the narrows through which they sail, waiting to seduce and destroy those who

draw too near. Formulators must not be tempted to practice healing, and (except for testing purposes) their business is not primarily the art of applying cosmetics to the human integument. Their proper concern is the preparation of products which are both efficacious and safe to use.

Unfortunately it is sometimes difficult to prepare products which have both of these properties. By definition, topical preparations which produce more than mere cosmetic effects are said to "have activity." This activity often results from their ability to react with that portion of the body to which they are applied. Both in theory and in fact, therefore, the more "active" a product the greater is the likelihood that it may be either a primary irritant or a skin sensitizer. Although long experience may eventually prove an ingredient perfectly safe, the cosmetic chemist may be somewhat concerned the first time he tries it. Many formulators therefore routinely include "soothing" ingredients in vehicles intended as carriers for such active agents, in order to forestall possible primary skin or eye irritation.

Their premise is reasonable. They assume that a material which is itself soothing to irritated skin will also act as an anti-irritant when combined with such active ingredients.

Often, however, inexperienced workers use such anti-irritants without checking two factors:

(a) Does it actually reduce irritation, measurably and substantially?
(b) Does it function without unduly reducing the efficacy of the active ingredient?

Unless a proposed anti-irritant fulfills both of these conditions, there is no point to using it. It would be more logical simply to reduce the total quantity of active ingredient in the formula.

Many workers are convinced that inclusion of protective colloids is helpful in reducing the irritation potential of certain types of cosmetic formulas. Others feel that aqueous solutions of irritants are rendered less irritating by emulsifying them with oils. Finally, some believe that it is possible to "complex" certain irritants in such a way that they still retain their useful properties, yet are no longer irritating.

Each of these beliefs can be dramatically justified in certain special cases. No one questions the fact that certain bases are "safer" than others when used as vehicles for applying irritants to the skin. Unfortunately, however, although extravagant claims are made for many ingredients, rigorous proof of anti-irritant activity is almost nonexistent today in the literature.

A major purpose of this paper, therefore, is to present irritation test data showing specific anti-irritant activity, or lack thereof, for a number of agents which have been claimed to possess this property.

The use of such adjuncts is becoming ever more important in formulating cosmetics and toiletries. Many countries are now adopting laws which will circumscribe the ability to formulate freely. Since these laws result primarily from increased governmental concern over the safety of cosmetic products, it is evident that we need to *know* whether certain agents can serve as anti-irritants, so that they can be used with assurance when the need arises.

Definitions and Mechanism of Action

For purposes of this discussion, an anti-irritant is not merely a material which is soothing to the skin or which helps heal already existing skin irritation. Neither is it simply a lubricant film or coating of powder or cream which reduces frictional (chafing) skin irritations.

Broadly defined, *an anti-irritant is an agent which, when used in conjunction with skin or eye irritants, reduces their irritation potential sufficiently so that they can be tolerated when applied to the body.*

Does this include all anti-inflammatory agents? No. Even though such activity is evidently beneficial and often may be desirable, anti-inflammatory activity *per se* cannot reduce opacification of the cornea nor prevent degradation of other tissue by corrosive agents.

The fact that certain agents act as topical anesthetics is sometimes a "fringe benefit" if they are also anti-irritants. This quality alone however, does not make them anti-irritants. In one classic case (4), the inadvertent use of a mildly anesthetic wetting agent (in a permanent wave neutralizer) resulted in *increased* eye irritation for the simple reason that, feeling no pain, users who accidentally introduced the product into their eyes made no effort to rinse it out.

Occlusion of the skin by lipophilic materials can prevent irritation caused by aqueous irritants if they are thereby prevented from contacting it. Combining the two is not always beneficial, however. A lipophilic film-former can increase irritation if it forms an occlusive layer over the irritant and holds it in better contact with the skin.

These exceptions merely point up the fact that anti-irritant activity is usually quite specific. The agent which works well in conjunction with one irritant may work poorly or not at all with another. Formation of physical or chemical barriers to prevent the irritant from contacting the skin is only one way by which anti-irritants can confer protection.

The specific protective mechanism depends on the nature of both the irritant and the anti-irritant used.

Since very little reliable data on the subject are currently available, the following is necessarily speculative. At this writing, there seem to be three routes of action by which anti-irritants can confer protection. None of these three routes fits the "intuitive" picture of an anti-irritant as "a soothing ingredient which heals the skin and thus repairs or reduces the damage concurrently being caused by the irritant."

The three mechanisms postulated are:

(i) By "Complexing" the Irritant

This is the never-never land of chemistry. Molecular adducts (complexes) are known to form between many materials. The bonding is often quite loose; complexes sometimes seem to exist and then not. Their properties are equally bewildering. The PVP (polyvinyl pyrrolidone) iodine complex is a classic case: Adding PVP to elemental iodine results in a product which does not produce normal iodine stains, has no detectable vapor pressure, is completely nonirritating to mucous membrane and skin, and whose acute toxicity is only one-tenth that of elemental iodine; yet its germicidal activity is higher than that of iodine alone. For all practical purposes, therefore, it is *detoxified* iodine (1). Similar complexes of iodine can be formed with nonionic (5) and cationic (6) surfactants. It has also been shown that urushiol, the irritant material in the poison ivy leaf, can be detoxified by complexing with zirconia (7), silver salts and certain ion exchange resins (8).

(ii) By Preventing Complete Contact with the Skin

Many thickening agents seem to reduce irritation, especially eye irritation caused by products such as shampoos. It has even been reported (9) that methyl cellulose allows the eye to tolerate dilute solutions of sodium hydroxide The reason postulated was that the thickening agent did not allow the irritant to spread easily; thus the solution was not in actual contact with all of the cornea.

There is perhaps a more subtle reason why gums and thickeners sometimes act as anti-irritants: If a *rigid* chunk of irritant is put on the skin, only that portion in direct contact can cause irritation; and the concentration of irritant at that point soon drops, due to reaction with the skin. The softer the irritant mass, however, the better is the initial contact with the skin and the greater is the likelihood that the

irritant can diffuse throughout the mass. As the local concentration is depleted by reaction with the skin, more irritant continually diffuses to the point of skin contact. Any material which retards diffusion thus reduces skin irritation simply by reducing the total amount of irritant making contact with the skin. Irritant motility can be reduced by thickening or even by complexing in such a way as to reduce solubility in the vehicle.

Another way of reducing contact between the skin and irritants is the use of emulsions with the irritant present only in the discontinuous phase. For example, use of W/O emulsions as vehicles for water-soluble irritants generally results in the skin being "wet out" first by the oil phase. This oily layer on the skin can then act as a physical barrier against contact with the hydrophilic irritant.

(*iii*) *By Blocking the Reaction Sites on the Skin*

There are various ways of doing this. One is the use of a phenomenon which is primarily physical, i.e., adsorption of oils onto keratin (see ii). Many highly nonpolar fatty materials (such as mineral oil) adsorb very strongly onto keratin (10, 11). Small amounts of these oils in shampoos adsorb on the hair and leave a sheen, even though the active ingredients of the shampoo are excellent emulsifiers for just such oils. In antiperspirant emulsions, inclusion of mineral oils and waxes may reduce irritation by oil-insoluble astringent aluminum salts *via* this type of selective adsorption.

Keratin is also highly reactive chemically. It is amphoteric, reacting with both acids and bases. The cysteine portion of the softer keratins reacts readily with heavy metals, forming mercaptides. Keratin is also fairly susceptible to oxidation and reduction, and to materials such as phenols or urea which affect its hydrogen bonding. All of these are routes by which irritants may attack the skin chemically, and by which anti-irritants may also react with it in such a way as to block further reaction with irritants. When anti-irritants exhibit very specific protective activity, it is probably due to chemical reaction with the irritant. When the protection is of a broader nature, the probable mechanism is *via* some sort of reaction with the body keratin.

Practical Application

The foregoing theoretical discussion will now be illustrated with the aid of some practical examples.

Aerosol Colognes

After the customary fragrance evaluations, a certain perfume compound was chosen and combined in the following "concentrate" for filling in aerosol bottles:

2.5% Perfume Compound
1.5% Propylene Glycol
96.0% Alcohol SD 39C
100.0%

It should be recognized that this formula includes about 1% diethyl phthalate, the U. S. government-specified denaturant for the SDA #39C ethanol which was used.

Rabbit eye tests (see Control, Code "A" in Table I) showed that this particular cologne formula was a rather strong eye irritant (scores reported in this and following tables are according to the method of Draize (12), averaged over 4–12 rabbits, with product *not* washed out after eye instillation). The product evidently had to be modified before marketing: Either the perfume had to be changed or an anti-irritant found to make this cologne safer if it should accidentally be discharged into a consumer's eye.

TABLE I
Draize Eye Test Scores—Cologne Series
(No wash after instillation into eye)

Code	Anti-Irritant Used	72 Hour Scores		7-Day Total Points (Cumulative)	
		Cornea Only	Total Score	Cornea Only	Total Score
A	Control	8	17	34	80
B	2.0% polyprop. glycol P2000	0	4	0	28
C	0.1% azulene	0	5	0	28
D	0.14% Miranol C2M	0	6	0	29
E	0.5% polyprop. glycol P2000	0	8	0	39
F	0.3% PVP-K30	0	9	0	56
G	0.3% thiodiglycolic acid	5	11	13	44
H	0.3% Miranol 2MCA	7	17	27	92

As can be seen in Table I, a number of agents were found to act as anti-irritants for this particular cologne. Not all were commercially

usable due to their adverse effect on the fragrance. However, the reasons for testing these particular agents for anti-irritant activity may be of interest.

The polypropylene glycol (P2000, Dow Chemical Co.) was tested because of previous successes with "block polymer" surfactant polyols. Glycol P2000 reduced irritation scores by approximately one-half when added to the formula at 0.5% and by three-quarters when used at 2.0% in this cologne. It also eliminated all traces of corneal opacity.

The Azulene (guaia-azulene, Dragoco, Inc.) was tried because of claims for effectiveness against various types of primary skin irritations, such as those caused by razor burn during shaving and underarm chafing connected with antiperspirants. Azulene is a component of camphor. It was distinctly useful as an anti-irritant in this particular cologne

TABLE II

Draize Eye Scores—Mentholated Alcoholic Product

(No wash after instillation into eye)

Code	Product Description	Corneal Scores, hours			Total Scores, hours		
		24	48	72	24	48	72
A	Control—no menthol	0	0	0	10.0	6.2	5.0
B	Control + 0.7% menthol	5.4	5.0	2.5	14.7	12.4	6.5
C	Control + 0.7% menthol + 0.3% PVP	0	1.7	1.7	16.0	16.0	12.7
D	Control + 0.7% menthol + 0.14% Miranol C2M	0	0	0	0	0	0

formula, reducing total "Draize" eye scores to one-quarter and eliminating all corneal opacity when used at 0.1% concentration in the cologne.

The use of small amounts of PVP (polyvinyl pyrollidone, General Aniline Film Corp.) is now fairly common in shampoo formulations, for two reasons; it leaves the hair more manageable and reduces eye irritation. Table I shows that 0.3% PVP-K30 eliminated all corneal opacity produced by this cologne and reduced total irritation scores considerably.

The Miranol C2M Concentrated (Miranol Chemical Co., Inc.) was tried because it had previously been found to eliminate completely eye irritation caused by menthol in an alcoholic medium (cf. Table II). The current principal commercial use for this amphoteric surfactant is in shampoos which do not sting the eyes. As can be seen (Table I),

it was an effective anti-irritant for this cologne formula, eliminating all corneal opacity and reducing total irritation scores to about one-third. An interesting insight into the mechanism by which this anti-irritant operates is provided by Formula "H" which contains Miranol 2MCA modified, the equi-molar reaction product of Miranol C2M with sulfated lauryl alcohol, which quite obviously is not an anti-irritant. One is led to believe that the anti-irritant activity of Miranol C2M derives from its ability to combine chemically with an irritant and that combination with one irritant leaves no activity against others.

Finally, thiodiglycolic acid was tried because of claims in a British patent (3) indicating that this material was valuable as an anti-irritant for certain scalp preparations. It was only partially successful against eye irritation in this aerosol cologne formula. In other tests it actually increased the eye irritation caused by an antiperspirant formula, but lowered the primary skin irritation produced by a topical proteolytic enzyme preparation (Table III). This pattern, of a material acting sometimes as an irritant and sometimes as an anti-irritant, will be observed again in the case of other additives.

As a matter of interest, four of the above anti-irritants were also tested in a "Cologne Ice" type of preparation containing 2.5% perfume in a hydroalcoholic system gelled with an amine-neutralized "Carbopol" polymer (B. F. Goodrich Chemical Co.). This preparation was judged "mildly irritating" after producing primary skin irritation

TABLE III

Patch Test of Proteolytic Enzyme Preparations

	Reactions to 24-Hr. Nonocclusive Patch		
	0	1+	2+
Controls			
Oil gel placebo	10	0	0
Oil gel + 2% protease	10	0	0
O/W emulsion placebo	0	9	1
O/W emulsion + 2% protease	0	9	1
Anti-irritant study—			
O/W Emulsion + 2% protease			
(a) Plus 6% Na lactate	1	3	6
(b) Plus 1% glycogen	2	3	5
(c) Plus 0.5% dithioglycolic acid	3	7	0

Note: Severity of reactions: Scoring was performed immediately after removal of patch, 24 hr after application of 0.05 g. of test material, as follows: 0—no visible reaction; 1+—mild erythema, no edema; and 2+—moderate erythema, moderate edema and induration.

indexes (12) varying from 0.5 to 2.0 when applied to rabbit skins. Each of the following agents, when added separately to the base formula in the quantities shown, reduced primary skin irritation to zero:

0.15% Miranol C2M (Miranol Chemical Co.)
2.00% Pluronic F68 (Wyandotte Chemical Corp.)
0.30% PVP-K30 (General Aniline Film Corp.)
0.50% Polypropylene Glycol P-2000 (Dow Chemical Co.)

Mentholated Alcoholic Product

An alcoholic facial preparation had been marketed for a number of years without causing skin or eye irritation complaints. Although its alcohol content was very high, the product did not sting, apparently because it contained over 10% of a bland, liquid fatty acid ester.

When an effort was made to formulate a "mentholated" version of the same product, it was found necessary to add an unexpectedly large percentage of menthol (0.7%) to achieve noticeable skin cooling in the presence of this fatty ester.

As can be seen in Table II, the resulting product (Code B) was fairly irritating to the rabbit eye. Addition of PVP (K30) (Code C) reduced corneal opacity, but on the other hand its presence resulted in slightly increased conjunctival scores. In contrast, addition of Miranol C2M was dramatically successful, reducing the eye irritation to zero at all stages for all the rabbits tested.

Topical Proteolytic Enzyme Preparation

As part of a study to determine the irritation potential of topical preparations containing proteolytic enzymes, several vehicles were evaluated, and the effect of various additives to these vehicles was then determined. After preliminary screening by repeated insult techniques on rabbits, nonocclusive "Band-Aid" patches were applied to ten human volunteers for twenty-four hours. The results are shown in Table III.

The proteolytic enzyme was included at 2% concentration in two different bases, one a W/O gel, the other a typical nonionic O/W emulsion. Quite clearly, the oily gel proved to be the vehicle of choice from a safety standpoint.

It produced no irritation at all, either as a placebo or when carrying the protease. In fact, its very inertness raised doubts regarding the potential efficacy of the product.

For this reason, the O/W emulsion was chosen, even though it appeared more irritating. It was hoped that an anti-irritant could be found which would not affect the enzyme stability, yet prove helpful in reducing primary skin irritation. Three additives were investigated: sodium lactate, a combination buffer-humectant normally produced by the body and present on the skin; glycogen, demonstrated by Opdyke (13) to be present in "accommodated skin" which no longer reacts to irritants; and the previously discussed thiodiglycolic acid.

The results of this rather limited test are shown in Table III. Quite clearly, addition of the protease did not increase the irritation potential of either vehicle. Addition of glycogen or sodium lactate to the O/W proteolytic emulsion made it considerably more irritating. Addition of 0.5% thiodiglycolic acid reduced its irritation by what may be a significant amount. This small test should be confirmed by using higher levels of thiodiglycolic acid and on a larger group of subjects.

A Shampoo Problem

The creation of a safe high-foaming concentrated gel shampoo is a typical example of a formulator's nightmare and will illustrate the difficulties encountered during the development of cosmetic products.

The basic formulating problem is quite "simple," and acceptable laboratory batches of gel shampoos can be formulated readily. However, it soon becomes apparent that formulations containing 25–40% detergent might be irritating to the eye. The formulator then starts irritation testing of his product, using leading gel shampoos as controls. He quickly learns that his "simple" product is a severe eye irritant and cannot be marketed safely.

The "active" ingredients of his formula are 20% triethanolamine lauryl sulfate (TLS) and 5% monoethanolamine "super amide" of coconut fatty acids (MEAC) (Fig. 1). Unfortunately, these ingredients are far "too active" when the gel is instilled pure into rabbit eyes, with the seventy-two-hour readings showing considerable corneal opacity and some iritis.

At this point, the formulator recognizes that solid gel shampoos are quite unlikely ever to enter the eye undiluted. The eye irritation test is, therefore, repeated on a 50% dilution. This reduces corneal and iris damage by one-half (Fig. 1), but the product is still considered to be too irritating.

Addition of 1% PVP-K30 to the gel shampoo also reduces irritation by one-half, but the best results are obtained by adding 1% PVP-

K30 and also diluting the shampoo by 50% (Fig. 1). This reduces eye irritation almost to zero and yields a salable liquid product; and plans are promptly made to go into full scale production.

Unfortunately, just before full scale production is scheduled to begin, somebody in the laboratory gets nervous and decides to repeat the eye irritation test. The final pilot batch, containing raw materials about to be used in the first full-scale production batch, provides the

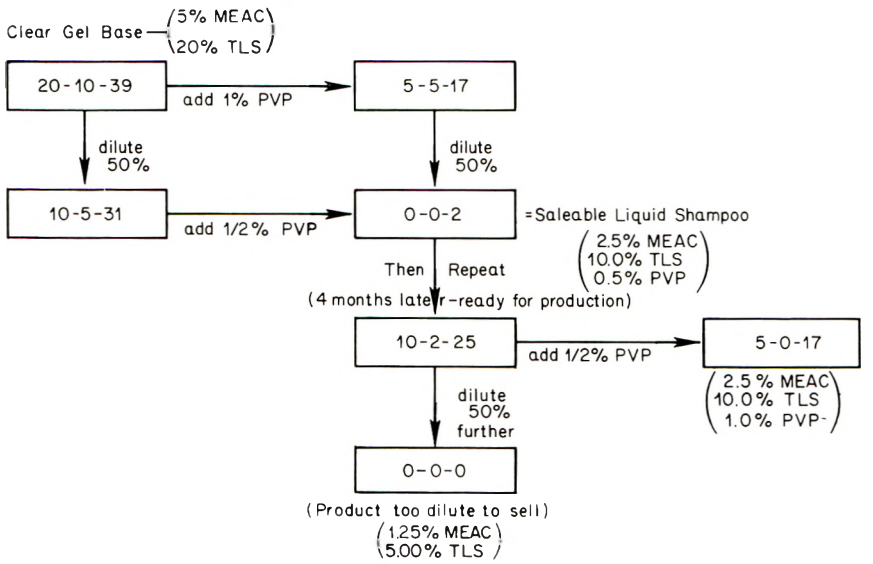

Figure 1. Illustration of the development of a gel shampoo. Numbers in boxes are 72-hour Draize test scores of rabbit eyes (unrinsed) in the order, cornea-iris-total points

sample for this retest. As can be seen in Fig. 1, retesting for eye irritation produces entirely different results. The shampoo considered salable four months ago now requires reformulation through addition of more PVP or by dilution with water. The latter modification yields an unsatisfactory product. Thus the shampoo with 1% PVP—with some rabbit eye irritation—is the one selected for sale on the assumption that it will be diluted at least 50% before accidentally entering the eye.

Developing an Antiperspirant Formula

Antiperspirants present many special problems in terms of skin and eye irritation. They are routinely applied to portions of the body which are usually moist, warm, and subject to constant chafing. They must be quite "active" in order to satisfy the consumer; and this same ac-

tivity has caused F.D.A. to classify *all* antiperspirants as drugs. Finally, "spray" antiperspirant containers are likely to discharge accidentally into the consumer's eyes, due to the normal juxtaposition of armpit and face as the user looks down in order to aim correctly.

Tables IV and V summarize the results of an extensive series of eye irritation tests performed during the development of an antiperspirant. Each step in the development of a finished antiperspirant formulation was checked on six rabbits, with eye irritation and primary skin irritation being determined *simultaneously on the same rabbit.* This was done in order to reduce the number of test animals required. Even so, 84 rabbits were used in this particular study, which was carried out in cooperation with John D. Paul, Jr., of Bio-Toxicology Laboratories.*

The formulations of the products used in this test series are detailed in Table IV. Table V summarizes the rabbit's eye irritation reading seventy-two hours after instillation of 0.1 ml. of product with no rinsing. (The lids were held together gently for one second after instillation to prevent loss of material.) Table V illustrates the major defect of the standard eye irritation test, i.e., the gross variations which sometimes occur from one animal to the next within a particular test series. These variations force the investigator to use large groups of test animals in order to "smooth out the curve," yet the very fact that the variations are so gross makes such averages somewhat suspect. Nevertheless, such averages do show trends which are quite real. Through their use, the investigator can rank a series of products in order of decreasing irritation potential. This is often quite sufficient if proper controls are available.

The development of a "spray" antiperspirant started (see A, Table IV) with a simple mixture of aluminum chlorhydroxide, alcohol and water. This combination produces moderate eye irritation. As expected, addition of a cationic antiseptic (Hyamine 1622, Formula B) for long-lasting deodorant qualities made the formula much more irritating. Many formulators prefer to use phenolic antiseptics in deodorant-antiperspirants rather than risk this increase in irritation. The decision to use the quaternary salt was made, nevertheless, to avoid any staining problems which may develop due to use of phenolics.

Next the effect of adding the nonionic surfactant, Tween 20 (Formula C), was studied. It was required in order to solubilize Myvacet 940, an acetylated monoglyceride whose oily feel nicely counteracted the

* Merchantville, N. J.

TABLE IV

Composition of Antiperspirant Formulations

	A	B	C	D	E	F	G	H	I	J	K
Water	22.25	22.00	17.00	17.00	21.70	20.00	21.75	12.00	11.70	10.00	11.75
95% ethanol (note 1)	65.75	65.75	65.75	65.75	65.75	65.75	65.75	65.75	65.75	65.75	65.75
Aluminum Chlorhydroxide (note 2)	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00
Quaternary ammonium cpd (note 3)	...	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Polysorbate 20 (note 4)	...	...	5.00	...	...	...	...	5.00	5.00	5.00	5.00
Acetylated monoglyceride (note 5)	...	...	...	5.00	...	...	...	5.00	5.00	5.00	5.00
Amphoteric surfactant (note 6)	...	...	...	...	0.30	...	...	...	0.30	...	...
Surfactant polyol (note 7)	...	...	...	...	...	2.00	...	...	...	2.00	...
Aluminum chlorhydroxy allantoinate (note 8)	...	...	...	...	...	...	0.25	...	...	...	0.25

Notes:

1. S.D.A. #40.
2. Aluminum Chlorhydrol, Reheis, Inc.
3. Hyamine 1622, Rohm and Haas Corp.
4. Tween 20, Atlas Chemical Industries, Inc.
5. Myvacet 940, Distilled Products Industries
6. Miranol C2M, Miranol Chemical Co., Inc.
7. Pluronic F68, Wyandotte Chemicals Corp.
8. Schuylkill Chemical Co.

harshness of the aluminum salt. Each of these additives (at 5%) was a very effective anti-irritant, reducing scores in half (see Formulas C and D).

On the other hand, addition of the amphoteric surfactant Miranol C2M (at 0.3%, Formula E), or of the surfactant polyol, Pluronic F68 (at 2%, Formula F), to the control base formula had little or no effect.

The most surprising result of this whole test series was the increase in eye irritation apparently caused by the addition of 0.25% aluminum chlorhydroxy allantoinate (Formula G). This material has been mentioned several times by dermatologists (14) for its ability to reduce skin irritation caused by astringent aluminum salts. Allantoin itself

TABLE V

Draize Eye Test Scores—Antiperspirants

(No wash after instillation into eye)

Code	Individual 72 Hr. Scores for Rabbit						Average, @ 72 Hr.	Cumulative 7 Days (Average)
	1	2	3	4	5	6		
A	6	6	2	4	6	4	4.6	27.0
B	8	12	4	8	6	4	7.0	36.6
C	8	2	0	2	4	0	2.7	20.3
D	4	4	6	2	2	2	3.3	21.6
E	10	6	6	2	10	8	7.0	36.7
F	0	12	12	4	2	4	5.7	36.2
G	13	41	18	6	10	32	20.0	108.2
H	2	2	4	0	0	0	1.3	21.3
I	2	0	0	6	2	6	2.7	16.6
J	2	4	4	10	8	8	6.0	32.3
K	6	4	2	2	4	12	5.0	32.0

is noted for its ability to disperse keratin scales, being recommended for various pathological skin conditions and dandruff. It is possible that this property made the eye more susceptible to attack by the quaternary in this formula, or that the allantoinate in some way "activated" the Hyamine 1622 through direct reaction with it. It has been repeatedly demonstrated that neither allantoin itself nor the aluminum allantoinates are skin or eye irritants. As a matter of fact, they are often added to topical preparations because of the healing and soothing effects which they provide (15, 16, 22). The author has long been convinced that addition of allantoin to lipsticks containing "bromo acid" dyes can make them tolerable to women who cannot otherwise use the "high stain" type of product for fear of cheilitis type reactions.

The most significant anti-irritant effect was noted when both Tween 20 and Myvacet 940 were present in the antiperspirant spray (Formula H). The seventy-two-hour eye irritation scores for this formula averaged only one-fifth those of the control, Formula B. Additions of Pluronic F68 (Formula J) or aluminum chlorhydroxy allantoinate (Formula K), seemed to nullify some of the anti-irritant effects produced by the Tween-Myvacet combination.

The *primary skin irritation* test results for this series were not interesting at all. Draize (12) defines topical preparations as "mildly irritating" if they show a primary irritation (PI) index no higher than 2.0. The control product for primary skin irritation Formula A, was applied to each rabbit simultaneously with the various test products. It gave PI indices which varied from 0 to 0.25; the test formulation PI indices varied from 0 to 0.44. In order to try to visualize primary irritations more clearly, Trypan Blue injections were attempted. Since none of the formulations was a primary irritant (when applied according to the techniques of Draize), all of these attempts to determine possible *topical* anti-irritant effects were useless.

Conclusions

Some will question the validity of the test results reported in this paper, saying that the irritation tests themselves are not valid because of inability to reproduce them exactly. The eye is too sensitive and too variable an organ to react consistently when subjected to the type of insult called "the eye irritation test" (see Table V). In contrast, the skin's role of acting as a protective layer for the body means that it is inherently resistant to insults by various foreign materials. As a result, irritation test results sometimes vary wildly and at other times show almost nothing at all.

This is unfortunate, but nevertheless the fact remains that some products are irritating to the body, and some are not. Crude as they are, no one should doubt that animal irritation tests of this sort are worth carrying out. Even "average" results are better than no indication at all, and such averages in fact are sufficiently reliable to *rank* a series of products to determine their order of irritation potential to humans.

We will not know the exact extent of the irritancy or anti-irritant usefulness of various materials until we have developed more refined irritation testing procedures. In the meantime, we must work with what is available to us. *The available evidence points very strongly to*

the conclusion that certain materials can act as potent anti-irritants for others. Furthermore, ingredients may change roles, varying from irritant to "safe" to anti-irritant, depending on what other materials are used in conjunction with them in a formulation. No material should ever be considered absolutely safe or absolutely unsafe for application to the human body. Safety data on individual ingredients are very useful (giving an indication of problems which may arise), but no formulator should depend solely on so-called positive and negative lists of permitted or forbidden ingredients.

Someone once said, "Wisdom would be easy if we only had to choose between the black and the white." Unfortunately, the cosmetic formulator is rarely offered a clear-cut choice in trying to decide whether a particular product will be "safe" when used by the general public. The cosmetic formulator must do the best he can with test data of the sort *currently* available to him, resulting from applying the *finished product* in the manner intended for use by the ultimate consumer. This gives him the greatest possible flexibility and allows the use of any ingredients he chooses, so long as he can show that the final product is not injurious.

Appendix

Following is a list of two dozen cosmetic ingredients for which reasonably credible anti-irritant claims have been made. Reference to the original published data is strongly recommended to those interested in using these products as anti-irritants. Not all of the claims have been rigorously substantiated. Regardless, confirmatory irritation testing should always be carried out on finished formulations even though they contain materials previously shown to possess anti-irritant properties.

Inclusion in this list does not constitute general endorsement. Instead, it is hoped to bring these materials, and the claims made for them, to the attention of cosmetic chemists for further investigation of possible anti-irritant activity.

Aloe Vera

Several references (17, 18) claim remarkable curative and detoxifying powers (topical and internal) for the hexosan gel and other polyuronide extracts of this cactus. They also claim topical anesthetic effects and (17, 19) promotion of healing (granulation) of damaged tissue. No published data are available proving anti-irritant activity in controlled tests.

Allantoin

Several dermatologists have been reported by Mecca (14) to have shown that aluminum allantoinates enhance antiperspirant action of other aluminum salts while reducing their irritation potential considerably. Kahan and others (15, 16) have reported that 0.2% allantoin in creams or talcums help prevent diaper dermatitis (generally considered to be caused by ammonia liberated from the urine).

The author observed (cf. preceding pages) that addition of allantoin to lipsticks containing bromo acids made them tolerable to women who could not otherwise use them. In contrast, it was shown in the preceding pages that addition of 0.25% aluminum chlorhydroxy allantoinate to an antiperspirant containing both aluminum chlorhydroxide and a quaternary antiseptic increased eye irritation, perhaps due to activation of the cationic agent.

Anion-Cation Complexes

Use of equimolar mixtures of anionic and cationic surfactants in certain shampoo compositions (which contain substantial amounts of amphoteric surfactant) is claimed by Goff (20) to result in preparations which foam well and leave the hair in good condition. The amounts of cationic recommended (up to 4.9%) would normally be extremely irritating to the eye. Eye irritation is not discussed in the patent, but it must be presumed that the anti-irritant activity of the amphoteric is greatly helped by neutralizing the cationic via "complexation" with the anionic surfactant.

Aryloxypropionates

A rather well documented paper by Northover and Subramanian (21) shows that formaldehyde-induced inflammation can be inhibited by a number of these substances, some of which will also inhibit reaction to intradermal injection of histamine. Cortisone acetate was inactive. This study did not involve cosmetic ingredients and was performed via intradermal techniques rather than topical application. Nevertheless, it may have considerable application to cosmetics.

Azulene

Ruemele (22) used a large quantity (0.25%) of 1,4 dimethyl-7 isopropyl azulene in an unspecified alkaline depilatory formula which was routinely applied to the face as well as arms and legs. He claims distinct anti-irritant action but offers no data to prove it. It was shown

above (cf. preceding pages) that inclusion of 0.1% of the same ("guaia") azulene in an aerosol cologne greatly reduced eye irritation. Hertz (23) showed the value of 0.02–0.50% azulene in reducing eye irritation caused by deliberate instillation of mustard oil. Hertz also points out that its activity is lost if the azulene is solubilized with Tween 60.

Carboxymethyl Cellulose

Kuchinka (24) discusses the skin protective effect of CMC when used in combination with various surfactants.

Cetyl Alcohol

A number of cosmetic chemists feel that cetyl alcohol reduces eye irritation of shampoos, and eye and primary skin irritation of anti-perspirant emulsions. The cetyl alcohol urea complex was claimed (25) to have mild anti-irritant activity *vs.* certain dishwashing detergent components.

Diethyl Phthalate

The author has found that mixing perfume oil with equal parts of diethyl phthalate (before extending with alcohol) yields colognes exhibiting lower eye irritation scores than those resulting from simple dilution with alcohol alone.

Emcol E607

This cationic surfactant (N-caproyl colaminoformyl methyl pyridinium chloride produced by Witco Chemical Co.) is the preferred example of a patent (6) covering germicidal iodine compositions which do not exhibit the characteristic skin irritation, sensitizing or toxic qualities of iodine. The E607 seems to act in a manner similar to PVP in this case. Data substantiating these claims are not presented in the patent.

Ethanolamine

This compound was found to be active (26) in inhibiting the inflammatory response normally produced in rats by implanting cultures of *micrococcus pyogenes* var. *aureus*.

Glycogen

Opdyke (13), in a paper on the "accommodation phenomenon," discussed the appearance of glycogen-bearing cells in skin which has

become immune to irritants. This suggested its possible use as an anti-irritant. However, it was shown above that addition of 1% glycogen to a cream containing proteolytic enzymes increased primary irritation in one very small scale test.

Lanolin

Masters (27) quotes a 1935 paper that addition of lanolin to diphtheria antitoxin helped guinea pigs survive 40X normally lethal doses. Hatschek and Rogicky (28) reported that benzpyrene-induced cancer growth is retarded by subsequent application of lanolin.

Russell and Hoch (29) published detailed documentation of eye irritation tests on a shampoo containing 3% ethoxylated lanolin alcohols plus 1% liquid lanolin ("Nimcolan S" and "Lantrol" of the Malmstrom Chemical Co.). Significant reduction in Draize test scores were reported by three out of five testing laboratories. Similarly, the addition of 2% acetylated ethoxylated lanolin alcohols and esters (Solulan 98 of American Cholesterol Products, Inc.) to a commercial shampoo reduced total eye irritation to about one-third in one test (30).

N(2-Hydroxyethyl) Palmitamide

This substance was found to be the active factor common to egg yolk, peanut oil and soybean lecithin which provides anti-inflammatory activity *vs.* cultures of *micrococcus pyogenes* var. *aureus* (26).

N-Lauroyl Sarcosinates

A well-documented patent by Dvorkovitz (25) shows the benefit of adding "Sarkosyl NL-100" (sodium N-lauroyl sarcosinate, Geigy Chemical Co.) to various dishwashing detergent formulations. Skin irritations (after intradermal injection of rabbits) were reduced to as low as one-eighth "normal" by addition of up to 9% of this substance.

Maypon 4C

Nassau (31) claimed that a mixture of 25% of this protein-coconut fatty acid condensate (available from Stepan Chemical Co.) with 75% sodium lauryl sulfate gives much less eye irritation than the lauryl sulfate alone. Steiger (32) claimed it will protect the eye from harmful effects of other surfactants as well. No proof has been offered by the manufacturer, but this author and others agree that Maypon 4C probably shows anti-irritant activity in certain cases.

Mineral Oils

An exceptionally well controlled study by Hoekstra and Phillips (33) showed that certain mineral oil fractions are highly irritating when applied topically to guinea pigs. All aromatic fractions caused problems; mid-range paraffinic material (b.p. 322–333°C) was the worst of the nonaromatic fractions. Mixing these with high boiling (over 402°C) fractions reduced irritation to zero, showing the dramatic anti-irritant activity of these high boiling point fractions.

Rieger and Battista (34) reported that skin irritation from products containing combinations of light mineral oil with sodium lauryl sulfate, amine soaps or nonionic wetting agents can be alleviated by switching to a heavier grade mineral oil.

Miranols

Miranol C2M Concentration is a patented (35) lauroylcycloimidinium amphoteric surfactant (Miranol Chemical Co. Inc.) which apparently reduces eye irritation by directly complexing certain irritants. For example, Miranol 2MCA Modified (36), an equimolar complex of Miranol C2M with sulfated lauryl alcohol, is completely nonirritating to the eyes, according to data published by the manufacturer. It was shown earlier in this paper that 0.14% C2M reduced eye irritation of an aerosol cologne to one-third and that of a highly mentholated (0.7% menthol) alcoholic product to zero. Miranol C2M was not particularly effective as the sole anti-irritant in an antiperspirant but did further reduce total eye irritation somewhat when used as an "auxiliary" anti-irritant.

Myristyl Lactate

This ester reportedly is useful at a level of 0.25% in alcoholic body rubs to reduce stinging. Similarly, it can be used in alcoholic aftershaves. However, when added at a level of 5% to an alcoholic antiperspirant, it significantly raised eye irritation.

Polypropylene Glycol

The P 2000 grade (Dow Chemical Co.) of polypropylene glycol reduced eye irritation and completely eliminated skin irritation in colognes, as described in the preceding pages.

Polyvinyl Pyrrolidone (PVP)

The basic patent showing this material's detoxifying and anti-irritant properties (when complexing iodine and other halogens) was granted to Shelanski (1) in 1956. This patent states that the PVP-iodine complex has only 10% of the toxicity of free iodine and none of its skin irritation or sensitization properties. The complex is odorless and nonstaining, yet has more antiseptic activity than iodine itself.

Guttman and Higuchi (37) pointed out that phenols are also strongly complexed by PVP, retaining their activity while showing reduced irritation potential. Wilkinson *et al.* (38) gave details of repeated insult testing, showing reduction in reactions to both hexachlorophene and bithionol in the presence of PVP. Burnette (39) described work of Chambron wherein induction of cancer by 3,4-benzopyrene injections was reduced from 100% when the vehicle was vegetable oil to 10.7% when 40% aqueous PVP was used as the vehicle.

Prescott *et al.* (40) make many unsupported claims that PVP can reduce allergic response and the "irritating effects of skin fatiguing agents" in cosmetics. On the other hand, PVP has been shown previously (41) to reduce eye irritation in shampoos. It was not found too useful (cf. preceding pages) at 0.3% in reducing eye irritation caused by menthol but did reduce the skin and eye irritation of several cologne formulations. Orentreich (42) tested 2% paraphenylene diamine (PPD), with and without 1% PVP-K30, on 14 subjects, six of whom were known sensitives to PPD. Reactions to both preparations were almost identical, and it appears that PVP does not "desensitize" PPD.

Tertiary Amine Oxides

Drew and Voss (2) disclosed interesting irritation data in a Canadian patent covering combinations of tertiary amine oxides and alkyl benzene sulfonates in detergent formulations. Ratios of lauryldimethylamine oxide to sodium dodecylbenzene sulfonate varying from 1:4 to 2:1 gave the least irritation. The cetyl and myristyl analogues of this amine also increased the mildness of the sulfonate detergent.

Thiodioglycolic Acid

A British patent (3) claims that this acid and its amide or esters (at 0.2–10%) reduce irritation of aqueous or alcoholic hair preparations, including those containing cationic surfactants. The only substantiated data concerning the efficacy of this compound are those described in the

preceding pages. The acid was added at 0.5% to an alcoholic antiperspirant containing a cationic surfactant; its presence increased eye irritation; at 0.3%, however, it decreased eye irritation of a cologne by one-third and at 0.5% it reduced primary skin irritation of an O/W protease-containing emulsion.

Zirconia

Blumenthal (7) states that hydrous and carbonated hydrous zirconia form nonirritating complexes with urushiol, the diphenolic irritating factor of poison ivy. This diphenol may also be detoxified by binding with anion exchange resins of the polystyrene quaternary amine type (8).

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Soluble Brominated Salicylanilides

W. E. LANGE, Ph.D.,* and M. R. MEZIKOFSKY, M.S.†

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Synopsis—The low aqueous solubility of the brominated salicylanilides (1) limits their usefulness in cosmetic or pharmaceutical preparations. Nonionic surface active agents and compounds chemically related to 1 did not increase solubility. Preparation of the salts of 1 gave compounds with good microbiological activity and aqueous solubility but with limited light stability. Aqueous solutions of formulations utilizing the salts of 1 showed good stability when they were protected from U.V. light.

Introduction

Antimicrobial agents are used in many cosmetic and pharmaceutical products to protect and preserve them from deterioration due to growth of bacteria, fungi, or yeasts. Many of the higher molecular weight agents such as hexachlorophene, dichlorophene, bithionol, the parabens and substituted salicylanilides have extremely low water solubilities. Because of their low water solubility their use is somewhat limited. Thus, with the great interest today in the salicylanilides it was thought that the preparation of a water soluble compound or mixture would be of value in product formulations.

Recently, considerable interest has centered about the halonitrosalicylanilides (1) and halogenated salicylanilides, especially various chlorinated and brominated derivatives (2, 3). The halogenation of the salicylanilide molecule enhances the activity of the parent compound (4).

* Massachusetts College of Pharmacy, Boston, Mass.
† Gillette Safety Razor Co., Boston, Mass.

In 1959 Stecker (5) reported that a synergistic mixture existed between 5,4′-dibromosalicylanilide and 3,5,4′-tribromosalicylanilide (Diaphene® *) when combined in the proper proportions. By a modified fresh calfskin technique he demonstrated the substantivity and antibacterial properties of the mixture (6).

At about the same time Mattson (7) reported another similar synergistic mixture consisting of 3,5-dibromosalicylanilide (approximately 15%), 3,5,4′-tribromosalicylanilide (approximately 85%), and traces of a monobromosalicylanilide derivative. This mixture is referred to as ET-394 †.

The fact that Stecker (6) noted that the brominated salicylanilides were not inactivated by the presence of various emulsifiers and surface active agents suggested the possibility of physical solubilization of ET-394. All attempts to prepare a 0.1% aqueous solution of ET-394 by the addition of various nonionic or anionic surface active agents were unsuccessful. Even the addition of 50% ethanol failed to dissolve ET-394. Attempts to add ET-394 as a solution in polyethylene glycol 600 monolaurate to various combinations of ethanol, surface active agents and water were also unsuccessful.

Occasionally a chemical similar in structure to the material under investigation is capable of increasing the compound's solubility. Thus, the use of salicylanilide as a solubilizing agent was attempted, but without success.

Recently Russell (8) reported the solubilization of Diaphene to the extent of 0.8% in a mixture of 4% nonionic surface active agent and either 40% detergent or potassium coconut oil soap. Bacteriological testing of these solutions showed activity equal to that of a similar solution containing hexachlorophene.

Thus it appeared that the use of complexation or simple physical means would not work to enhance the solubility of ET-394 in water or in 50% ethanol at low surfactant level. On the other hand, it seemed likely that the brominated salicylanilides as their sodium, potassium or ammonium salts might exhibit improved water solubility.

Experimental

Preparation of Salts

Sodium ET-394 was the first salt to be prepared, and its preparation was accomplished in the following manner: Fifteen milliliters of a 10%

* Diaphene is a registered trademark of the Stecker Chemicals, Inc., Ho-Ho-Kus, N. J.

† Manufactured by The Dow Chemical Company, Midland, Mich.

solution of sodium hydroxide in absolute ethanol was triturated for 30 minutes with 10 g. of ET-394 in a mortar at room temperature. The insoluble product produced was collected on a filter, dried, and recrystallized from hot 25% ethanol. The melting point was >300°C, and the salt (sodium ET-394) did not fluoresce under U.V. light. In a similar manner the sodium and potassium salt of the two major components of ET-394 were prepared. These are listed in Table I.

The ammonium salts could not be prepared by the above method. Thus, ammonium ET-394 was prepared by shaking for one hour at room temperature a mixture of 2 g. of ET-394, 50 ml. of 50% ethanol and 50

TABLE I
Salts of Brominated Salicylanilides

		Yield		Calcd., %		Found, %	
Salicylanilide	Salt	%	M.p. °C	C	H	C	H
ET-394	Na	73	>300	...	..	...	..
ET-394	K	90	>300	...	..	...	..
ET-394	NH_4	55	227–9	...	..	...	..
3,5,4′-tribromo	Na	65	>300	33.08	1.49	32.46	1.80
3,5,4′-tribromo	K	63	>300	31.99	1.45	31.63	2.02
3,5,4′-tribromo	NH_4	71	232–4	33.43	2.37	34.10	2.39
3,5-dibromo	Na	74	>300	39.95	2.04	39.55	2.20
3,5-dibromo	K	65	>300	38.05	1.95	37.78	2.15
3,5-dibromo	NH_4	74	140–2	40.21	3.09	39.66	3.01

ml. of 28% ammonium hydroxide in a pressure bottle containing glass beads. After cooling of the mixture, the pressure bottle was opened. The mixture was warmed to remove the excess ammonia, filtered and cooled to precipitate the product. After collection on a filter and recrystallization from 25% ethanol, a 55% yield of ammonium ET-394 was obtained which fluoresced under U.V. light and melted at 227–9°C. The ammonium salts of the components of ET-394 were similarly prepared.

Infrared Absorption Data

As proof of salt formation, the infrared spectra of the various new compounds were compared with those of the parent molecules.

3,5,4′-Tribromosalicylanilide gave bands at 3525 for stretching OH, 1645, 1590, and 1540 for the amide group and 1175 $cm.^{-1}$ for the deformation of the OH group. The higher amide bands and the presence of the stretching OH bands indicated that the parent molecule exists in the β form (9) [H-bonding between (NH) and (OH) with the carbonyl group

free]. Sodium, potassium and ammonium 3,5,4′-tribromosalicylanilide showed no phenolic stretching band but a sharp band at 1225 (Na), 1210 (K), and 1220 cm.$^{-1}$ (NH_4) which correlated with the (OH) deformation vibration. Ammonium 3,5,4′-tribromosalicylanilide showed a (NH) stretching vibration at 3410 cm.$^{-1}$. In all cases shifts of the amide I bands of the salts were slight, but the amide II band shifted to a slightly higher frequency due to the absence of H-bonding with (NH).

In the case of the salts of 3,5-dibromosalicylanilide and the parent molecule, the infrared spectra indicated that the absence of the 4′-bromo

TABLE II

Solubility of Salts of Salicylanilides in Various Solvents[a]

	Compounds	Gm./100 ml. at 25°	
		Water	50% Ethanol
	ET-394	0.00086	0.050
Na	ET-394	0.270	3.055
K	ET-394	0.645	10.737
NH_4	ET-394	0.106	3.866
	3,5,4′-Tribromosalicylanilide	0.0042	.....[b]
Na	3,5,4′-Tribromosalicylanilide	0.347	.....
K	3,5,4′-Tribromosalicylanilide	0.972	.....
NH_4	3,5,4′-Tribromosalicylanilide	0.145	3.448
	3,5-Dibromosalicylanilide	0.036	.....[b]
Na	3,5-Dibromosalicylanilide	1.298	.....
K	3,5-Dibromosalicylanilide	3.645	.....
NH_4	3,5-Dibromosalicylanilide	0.555	4.731

[a] The solubilities were determined gravimetrically.

[b] Solubilities of the various salicylanilides could not be determined at this time because of lack of material for study.

group had very little effect on the (OH) or amide bands. Thus, spectral changes due to salt formation closely approximated those described for the tribromo compound.

Solubility Determinations

Distilled water and 50% ethanol were chosen as solvents for the determination of the solubility of the various salts as well as of the base compounds.

In all cases accurately weighed samples of the compounds were shaken for at least 24 hours in the given solvent at room temperature. The insoluble material from each sample was collected on a filter, the filter dried and weighed, and the solubilities calculated. Table II gives the solubilities of the brominated salicylanilides and their salts.

Antibacterial Studies

Antibacterial studies of the ET-394 salts (0.5% in 50% ethanol in amber bottles) were conducted over a period of six months to determine whether or not a loss of activity occurred. As shown in Table III, the salts retained their potency during this time.

The tests were conducted with six different organisms. Nutrient agar plates were smeared with the organisms, and discs were placed on the smears. The plates were incubated for 72 hours at 37°C. Ethanol (50%) was used as a standard.

Stability Studies

Aqueous solutions of the salts of the brominated salicylanilides turned brown within two weeks after exposure to room light. Solutions of the salts in 50% ethanol decomposed much more slowly and to a lesser extent. Solutions in amber bottles did not show a color change after one year. It appeared that light was necessary for the degradation. Salt solutions containing a trace of iron as an oxidizing catalyst did not change color in amber bottles.

Several antioxidants were used in an attempt to prevent the degradation. To 0.1% solutions of sodium and potassium ET-394 were added 0.1% of sodium bisulfite, sodium nitrite, sodium sulfite, ascorbic acid, and sodium metabisulfite, respectively. In every solution an immediate precipitate appeared. Similarly glycerin and 2-methyl-2,4-pentanediol in concentrations of from 0.05–5.0% yielded yellow solutions with heavy precipitation.

Sodium formaldehyde sulfoxylate and tetrasodium ethylenediaminetetraäcetic acid (38%) in concentrations of 0.001–0.1% in combinations with the sodium or potassium salts of ET-394 (0.1%) dissolved in water or 50% ethanol produced varying shades of brown with sedimentation. Chemical degradation also occurred even when various ultraviolet light absorbers were added to the solutions.

At this point it was realized that the mechanism and kinetics of the degradation of the salts in solution was beyond the scope of this project. Thus, this information will be presented in a separate publication.

Practical Use

Because of its unusually high solubility, potassium ET-394 was selected for incorporation into an aftershave lotion, a preshave lotion and a shampoo.

TABLE III

Antibacterial Activity of Salts of ET-394[a]

	ET-394[b]	G-11[b]	Na ET-394			K ET-394			NH_4 ET-394		
			Time, mo.								
Organism	0	0	0	3	6	0	3	6	0	3	6
E. coli	0	0	0	0	0	0	0	0	0	0	0
A. faecalis	6[c]	11	3	2	3	3	6	3	2	2	3
Ps. aeruginosa	0	0	0	0	0	0	0	0	0	0	0
S. lutea	21	18	11	14	12	15	20	13	13	14	11
Staph. aureus	8	12	15	16	11	12	17	15	11	12	13
Staph. albus	17	13	8	11	14	11	19	16	8	13	13

[a] A 0.5% solution in 50% ethanol, using agar plates incubated 72 hr. at 37°C.

[b] ET-394 (mixture of tri- and di-brominated salicylanilides) (0.025%) in 0.5% cetyl alcohol and a sufficient quantity of 70% isopropanol to make 100 ml. Same solvent for 0.1% G-11 (hexachlorophene).

[c] Numbers are millimeters of inhibition.

A typical aftershave formulation containing sorbitol, menthol, boric acid, perfume oil, dye, and 50% denatured alcohol was prepared. A sample of the product was kept as a control. To the remaining solution was added 0.2% potassium ET-394 The solution immediately changed to a lighter color which could not be rematched exactly to the intensity of the control by the addition of more dye. The solution was divided in half; one sample was stored in a clear glass bottle, and the other sample was stored in an amber bottle. These two solutions and the control were subjected to periodic antibacterial testing.

The second formulation, a preshave lotion, contained sorbitol, a nonionic surface active agent, perfume, color, and 50% ethanol. Again three samples were prepared, one as a control and two containing the antibacterial agent.

The third preparation, a triethanolamine lauryl sulfate liquid shampoo, was prepared and divided into three samples, two of which contained potassium ET-394.

After two months of storage the preparations were subjected to antibacterial testing. The same organisms and methods were used as described under "Antibacterial Studies." The products containing potassium ET-394 were extremely effective against gram-positive organisms and displayed little, if any, inhibitory effect on gram-negative organisms. The zones of inhibition closely approximated those given in Table III for potassium ET-394.

The aftershave lotion decomposed after standing in direct sunlight

for several days in a clear bottle. The preshave lotion and the shampoo retained their original appearances even after remaining in direct sunlight for a month. All of the preparations retained their original color when stored in amber bottles.

Conclusions and Discussion

Unsuccessful attempts were made to increase the solubility of ET-394 by various physical methods. It was found possible, however, to increase its solubility in aqueous media by formation of its alkali metal salts without any hydrolysis of the amide linkage.

When the potassium, sodium, and ammonium salts are dissolved in distilled water or ethanol (50%) and exposed to sunlight, they developed a brown color with precipitation after short periods of time. Amber bottles, which have been used in the past to prevent light degradation, proved useful in preventing chemical decomposition of the salt solutions. Solutions of potassium, sodium, and ammonium ET-394 (0.5%) in ethanol (50%) were tested for antibacterial activity when fresh and after six months' storage in amber bottles. At the end of the six month period the solutions retained their original antibacterial activities, clearness and colorless appearance. Thus, it seems that solubility is not a primary factor in the mechanism of action of the brominated salicylanilides. I.R. studies of the various salts indicated further that only slight changes in the internal bonding of the compounds took place during salt formation.

Because of its high solubility, good antibacterial action and ease of manufacture, potassium ET-394 (0.2%) was eventually tested in each of three formulations, an aftershave lotion, a preshave lotion, and a shampoo. After a few days a brown color was detectable only in the aftershave lotion in the clear glass bottle, while the remaining preparations appeared unchanged. Antibacterial testing, however, produced no evidence to support loss of activity by degradation since the activity of the brown solution was equal to that of the clear ones.

It is concluded that the salts of brominated salicylanilides have solubility properties which can be utilized in preparations in which other antibacterial agents would be insoluble or possibly inactivated by components of the system.

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Pyridoxine-3, 4-Diacylates and Their Use in Cosmetics

HARUYASU OHTA, M.Sc.*

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Synopsis—Pyridoxine-3,4-diacylates can be prepared by a new process in good yield and high purity. Data are presented to demonstrate the oil solubility and the heat and light stability of these esters. Acute and chronic toxicities of these esters indicate that they are suitable for inclusion in cosmetics. It is further shown that the esters are hydrolyzed by tissue homogenates at rates which are influenced by the acid moiety used for esterification. Finally, clinical data are presented to demonstrate the utility of pyridoxine-3,4-dipalmitate in dermal therapy.

Introduction

Vitamin B_6 is one of the most important factors for nutrition and for health and beauty of the human skin. Hence, many attempts have been made to use vitamin B_6 as a cosmetic additive. Pyridoxine hydrochloride, which is a commercially available form of vitamin B_6, is not suitable for topically applied cosmetics because of its insolubility in oils and fats and its instability to heat and light. It is therefore desirable to prepare a heat- and light-stable, fat-soluble and percutaneously absorbable pyridoxine derivative for cosmetic use.

In 1956, Sakuragi and Kummerow (1–4) first synthesized long chain fatty acid triesters of pyridoxine and confirmed that they are sources of fat-soluble, heat- and light-stable and biologically active vitamin B_6 when applied to the rat.

In 1961, Rocheggiani (5) reported on the cutaneous actions of

* Nihon Surfactants Industries Co. Ltd., 29, 3-chome, Hasune-cho, Itabashi-ku, Tokyo, Japan.

TABLE I

Physical Properties of Pyridoxine-3,4-Diacylates

Pyridoxine Diacylate	M.P., °C	Formula	M.W.
Dibutyrate	57–58	$C_{16}H_{23}O_5N$	309.37
Dioctanoate	69–71	$C_{24}H_{39}O_5N$	421.58
Di-*iso*-octanoate	Liquid	$C_{24}H_{39}O_5N$	421.58
Dilaurate	79–80	$C_{32}H_{55}O_5N$	533.80
Dipalmitate	88–89	$C_{40}H_{71}O_5N$	646.01

TABLE II

Solubilities of Pyridoxine-3,4-dioctanoate

Solvent	g./100 g. at 25°C
Isopropyl myristate	2
Olive oil	1
Oleyl alcohol	3.5
Oleic acid	5
Liquid paraffin	0.07
70% ethanol	0.3 at $-5 \sim -10$°C
60% ethanol	0.1 at $-5 \sim -10$°C

TABLE III

Solubilities of Pyridoxine-3,4-dipalmitate

Solvent	g./100 g. at 25°C	g./100 g. at 75°C
Ethanol	0.5	
Isopropyl myristate	0.1	3
Olive oil	0.1	5
Oleyl alcohol	0.2	5.5
Oleic acid	0.1	5.5
Liquid paraffin	0.01	0.5

TABLE IV

Sunlight Stability of Pyridoxine Derivatives

Derivatives	Irradiation Time, hr.	Transmittance, %
Pyridoxine hydrochloride	0	99
	15	92
	30	87
Pyridoxine-3,4-dibutyrate	0	100
	15	99
	30	98
Pyridoxine-3,4-dioctanoate	0	100
	15	99.5
	30	98

pyridoxine tripalmitate. He concluded from a series of experiments that pyridoxine tripalmitate is very effective in keeping the human skin healthy and beautiful. The large-scale preparation of pyridoxine tripalmitate is not easy, nor is this compound satisfactory for cosmetic use because of its insufficient fat-solubility.

A new commercial method for the synthesis of heat- and light-stable and fat-soluble derivatives of pyridoxine, pyridoxine-3,4-diacylates, has been developed in this laboratory. Patents for this method of preparation are now pending in the United States of America, Great Britain, France, Switzerland, West Germany, and Japan.

The chemical and physical properties, biological activity, toxicity and effects on the skin of these diacylates have been examined. It appears that the higher fatty acid diesters are heat- and light-stable, fat-soluble and hydrolyzed into free pyridoxine *in vivo* and show the biological activity of vitamin B_6.

The present report deals mainly with the dibutyrate, dioctanoate, dilaurate, and dipalmitate of pyridoxine.

Experimental and Discussion

Materials

All the diesters used were white crystalline powders, except the di-*iso*-octanoate. Some of the properties of these diesters are tabulated in Tables I, II, and III.

Heat Stability

Two grams of pyridoxine-3,4-dipalmitate was dissolved in 10 g. of olive oil and heated for six hours at 150–160°C. At the end of this heating period, the oil was brown. The oil was then diluted with 100 ml. of petroleum ether and cooled in the refrigerator for two days. The precipitate was removed by filtration and washed with petroleum ether. The crystalline precipitate was pure white and weighed 1.6 g. The crystals showed no depression in melting point when mixed with authentic pyridoxine-3,4-dipalmitate. The dilaurate and dioctanoate were tested in a similar manner, and the recovered unchanged esters weighed 1.4 and 1.1 g. respectively. The dibutyrate, however, could not be recovered from the heated brown oil, presumably because most of the diester was destroyed by heat.

Light Stability

One gram of each of the pyridoxine derivatives was dissolved in 100 g. of 50% aqueous ethyl alcohol. Samples of these solutions were

TABLE V

LD_{50} of Pyridoxine-3,4-dipalmitate and Related Compounds (Mice)

Compound	Administration	LD_{50}, g./kg.	
		24 Hr.	7 Days
Pyridoxine-3,4-dipalmitate	Oral	7.1	5.1
	Subcutaneous	4.4	1.6
Pyridoxine hydrochloride	Oral	3.8	3.8
	Subcutaneous	1.7	1.4
Palmitic acid	Oral	5.0	4.2
	Subcutaneous	...	4.2

sealed into test tubes and placed into sunlight. The transmittance of the irradiated solutions was read at 435 mμ with a spectrophotometer. The data shown in Table IV indicate that the esters are not severely discolored during long exposure to sunlight and are more stable than pyridoxine hydrochloride.

*Toxicity**

Acute Toxicity

The acute toxicity of pyridoxine-3,4-dipalmitate was studied in mice and is recorded as LD_{50} in Table V. Pyridoxine hydrochloride and palmitic acid were also tested as control materials. The ester and palmitic acid were dissolved in ethanol and then mixed with propylene glycol. Pyridoxine hydrochloride was studied in an aqueous solution. The mixture and the solution of samples were administered orally and subcutaneously to mice.

From the results shown in Table V, it can be concluded that pyridoxine-3,4-dipalmitate is less toxic than pyridoxine hydrochloride.

Chronic Toxicity

Six groups each of five male and five female rats weighing from 85 to 135 g. were used in this test and fed for six months as follows:

Group A: Standard Diet
Group B: Standard Diet + 40 mg./kg./day of pyridoxine-HCl
Group C: Standard Diet + 50 mg./kg./day of palmitic acid

* This work was conducted at the Osaka City Institute of Hygiene (6).

Group D: Standard Diet + 7 mg./kg./day of pyridoxine-dipalmitate

Group E: Standard Diet + 70 mg./kg./day of pyridoxine-dipalmitate

Group F: Standard Diet + 700 mg./kg./day of pyridoxine-dipalmitate

Groups A, B, and C were control groups. The weights of the rats were recorded daily for six months, and the growth rate is shown in Fig. 1. When pyridoxine-3,4-dipalmitate was orally administered daily to rats (in an amount of $\frac{1}{1000}$ the oral LD_{50} for mice) for six

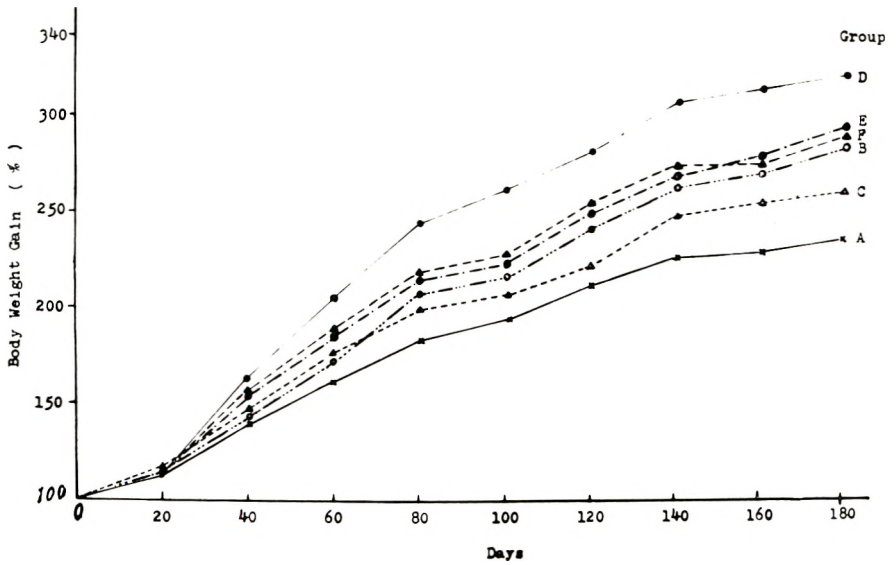

Figure 1.—Change in body weight of rats fed with various amount of pyridoxine-3,4-dipalmitate

months, the increase of the animal's weight was greater than when the equivalent amount of pyridoxine hydrochloride was administered. All rats used in this test survived during the test and were killed at the end of the test for observation of organs. No harmful effect of pyridoxine-3,4-dipalmitate was observed in organs at autopsy.

Percutaneous Absorption (8)

Rabbits weighing from 2 to 3 kg. were used for this test. An area of 5×15 cm.^{2} on the abdomens of the rabbits was clipped, and the hair was completely removed with a depilatory. After 24 hours, 6 g. of hydrophilic ointment containing one of the pyridoxine derivatives was

applied after ascertaining that there was no inflammation on the part to be tested. Blood samples were collected from the ear lobe by intravenous puncture and assayed for vitamin B_6 content.

The composition of the hydrophilic ointment is as follows:

Isopropyl myristate	1 g.
Cetanol	0.25 g.
Stearic acid	0.4 g.
Paraffin wax	1 g.
NIKKOL BL-9*	0.2 g.
NIKKOL BC-5†	0.15 g.
Mineral oil	1.35 g.
10% Triethanolamine solution	1ml.
Pyridoxine derivative	1%
Water to make	10 g.

In the preparation of the ointment containing pyridoxine hydrochloride, the triethanolamine solution was omitted from the above formulation.

The vitamin B_6 content in blood was determined as follows:

Standard curve: In the case of pyridoxine hydrochloride and of pyridoxine-3,4-dibutyrate, 1 ml. of an aqueous sample solution of known concentration (about 0.5 γ/ml.) was acidified with 6 ml. of 15% H_2SO_4, and the solution was heated at 100°C for one hour. After cooling, the pH of the solution was adjusted to 5.4, and the volume made up to 50 ml. with water. Samples of this solution (0.25, 0.5, 1 and 2 ml.) were pipetted into test tubes and diluted with water to 2.5 ml. After adding 2.5 ml. of culture medium and sterilizing at 100°C for 15 minutes, 1 drop of preincubated suspension of *Saccaromyces Carlsbergensis* culture was added, and the solution was incubated at 30°C for 20 hours. Absorbancy was then measured at 610 mμ, and a standard curve was constructed.

For the construction of the standard curve for pyridoxine-3,4-dioctanoate, 1 ml. samples of ethanolic solutions were hydrolyzed as mentioned above.

Pyridoxine assay in blood: A mixture of 1 g. of blood and 6 ml. of 15% H_2SO_4 was heated at 100°C for one hour. After cooling, the pH of the solution was adjusted to 5.4, and the liquid was centrifuged to remove blood pigments. The supernatant solution was separated, and its volume was adjusted to 50 ml. with water. The microbio-

* Polyoxyethylene lauryl alcohol ether. Nikko Chemicals Co., 1, 1 chome, Nihonbashi Bakurocho, Chiyoda-ku, Tokyo.

† Polyoxyethylene cetyl alcohol ether. Nikko Chemicals Co.

logical assay was carried out similarly as mentioned above, and the amount of pyridoxine was determined by reference to the standard curves.

The results are shown in Fig. 2. Pyridoxine and pyridoxine-hydrochloride were absorbed immediately, but their content in blood decreased rapidly. In contrast, the dibutyrate was also absorbed immediately, but the blood concentration remained at a constant level. The absorption of the dioctanoate and di-*iso*-octanoate was delayed, but the blood concentration increased gradually. The absorption of dilaurate and dipalmitate was not studied in this experiment. These

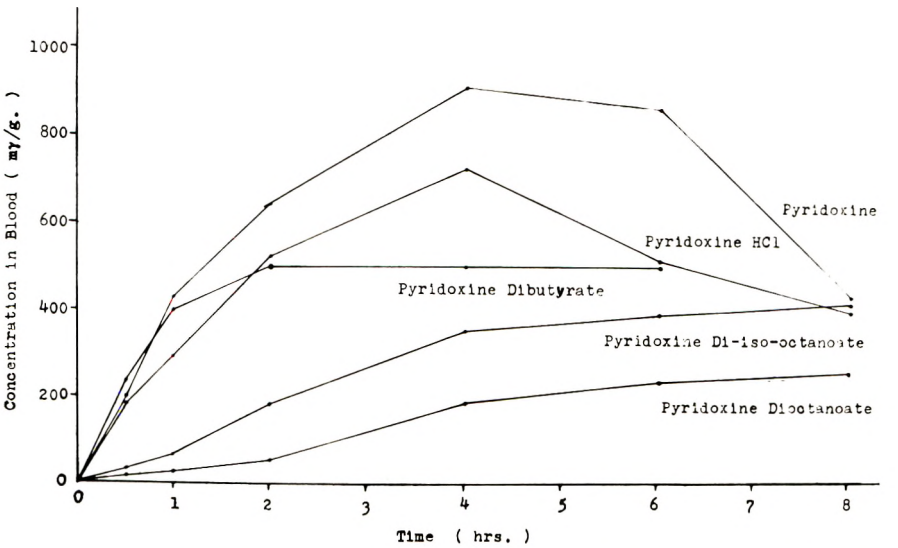

Figure 2.—Percutaneous absorption of pyridoxine and its derivative (1% in O/W cream base)

facts might suggest that cosmetics or ointments containing intermediate chain fatty acid diester of pyridoxine maintain higher levels of vitamin B_6 in the living body for a longer period of time than products containing pyridoxine.

Hydrolysis of Diacylates in Organs (9)

Liver, kidney, intestine, and blood of the mouse were used in this experiment. Liver, kidney, and intestine, from which as much blood as possible was removed, were washed with water. One gram of liver, 0.4 g. of kidney, 0.7 g. of intestine and 0.4 ml. of blood were homogenized with Tyrode's solution. These homogenates were poured into 50 ml. Erlenmeyer flasks, and the contents were adjusted to 7 g. with Tyrode's

TABLE VI

Hydrolysis of Pyridoxine-3,4-dibutyrate

Sample No.	Time for Hydrolysis	Amount Hydrolyzed, wt. %			
		Liver	Kidney	Intestine	Blood
1		105.8	98.9	98.9	80.1
2	2 hrs.	94.6	90.9	...	74.2
3		95.4	106.8	104.5	81.8
Average		98.6	98.8	101.7	78.7
1		106.6	108.0	92.8	70.4
2	1 hr.	...	97.5	107.6	69.6
3		98.4	98.9	104.4	66.2
Average		102.5	101.4	101.6	68.7
1		105.6	106.2	99.2	64.6
2	0.5 hr.	89.2	104.8	106.8	71.1
3		107.9	108.0	88.4	56.7
Average		100.9	106.3	98.1	64.1

TABLE VII

Hydrolysis of Pyridoxine-3,4-dioctanoate

Sample No.	Time for Hydrolysis	Amount Hydrolyzed, wt. %			
		Liver	Kidney	Intestine	Blood
1		91.5	82.3	82.2	0
2	2 hr.	87.6	69.2	82.3	0
3		101.7	79.0	87.2	0
Average		93.6	76.8	83.6	0
1		74.5	66.8	84.2	0
2	1 hr.	85.2	85.8	84.2	0
3		84.7	75.6	82.7	0
Average		83.9	76.1	80.2	0
1		63.1	72.4	64.1	0
2	0.5 hr.	62.9	61.6	59.8	0
3		84.0	76.4	79.9	0
Average		70.0	70.1	67.9	0

TABLE VIII

Hydrolysis of Pyridoxine-3,4-dilaurate

Sample No.	Time for Hydrolysis	Amount Hydrolyzed, wt. %		
		Liver	Kidney	Intestine
1		11.1	0	0.9
2	2 hr.	7.6	0	1.0
3		10.1	0	0.8
Average		9.6	0	0.9

solution. One ml. of one of the pyridoxine-3,4-diacylates solutions was added, and the flasks were shaken for 0.5, 1 or 2 hours at 37°C to hydrolyze the ester. After shaking, 3 ml. of 10% aqueous trichloroacetic acid solution was added, and the mixture was centrifuged. Five ml. of the supernatant was neutralized with 1.5% NaOH solution. For 1 ml. of the solution thus obtained, concentration of pyridoxine was determined by using 2,6-dibromoquinone chloroimide at 650 mμ.

The results are shown in Tables VI, VII, VIII, and IX. It can be seen that the dibutyrate was rapidly hydrolyzed in the blood and

TABLE IX

Hydrolysis of Pyridoxine-3,4-dipalmitate

Sample No.	Time for Hydrolysis	Amount Hydrolyzed, wt. %		
		Liver	Kidney	Intestine
1		0	0	0
2		2.3	0	0
3	2 hr.	1.3	0	0
4		0.4	0	0
Average		1.0	0	0

organ homogenates. The dioctanoate was not hydrolyzed in the blood but slightly in the organ homogenates. On the other hand, dilaurate and dipalmitate were not hydrolyzed even in the liver homogenate.

Dermal Therapy

During the clinical test, which was designed to demonstrate efficacy against several kinds of dermatitis, such as eczema and seborrhoea, hydrophilic ointments and lotions containing 0.2% and 0.02% pyridoxine-3,4-dipalmitate respectively were applied topically. The results showed that pyridoxine-3,4-dipalmitate was an effective treatment for skin diseases without any harmful side effects.

It is also noted that this substance showed marked antidandruff and anti-itching properties, as judged from the following studies. Fourteen dermal outpatients (7) suffering from eczemas and seborrhoea were treated with a hydrophilic ointment containing 0.2% pyridoxine-3,4-dipalmitate for seven to twenty days. This treatment was very effective in six cases, satisfactory in six cases and ineffective in two cases.

In three cases of seborrhoea and especially dermatitis of the face, patients felt a cooling sensation immediately after application; sebum vanished day by day. In one case of rosacea (of the first degree), reddening was reduced, oily luster vanished after ten days, and the disease was cured completely on the fourteenth day. In two cases of seborrhoea

capitis neonatorum, the sebum leaking scab was no longer observed after four days, and it was nearly cured in eight to ten days.

In two cases of facial pimples, no new ones developed after ointment application had begun, and the number of existing pimples decreased until none were observed at all. In two cases of desquamating eczema, scale decreased remarkably after four days, and the scale on the head and face almost vanished. Further, in two cases of eczema erythematosum and contact dermatitis, reddening decreased after three days.

In the two ineffective cases, the symptoms were those of serious cases of dermatitis; even oral or topical steroid hormone therapy (even in massive doses) was not fully effective, especially if the side effect induced by this hormone is considered.

Further, 162 cases of pityriasis simplex capitis and seborrhoea capitis were treated with a lotion containing ethyl alcohol, Tween 80* and 0.02% pyridoxine-3,4-dipalmitate. This lotion was effective in 75% of cases of scaling, in 77% of cases of itching and in 85% of cases of dry dandruff (10).

Summary

Pyridoxine-3,4-diacylates have been shown to be useful cosmetic ingredients.

The diesters of pyridoxine are considered to be more effective than the corresponding triesters since the former's content of the pyridoxine moiety is considerably larger.

When heat- and light-stability, fat-solubility, percutaneous absorbability and the effective content of pyridoxine are taken into account, pyridoxine-3,4-dioctanoate emerges as the most suitable derivative for cosmetic purpose.

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A New Procedure for the Preparation of Polyethylene-Mineral Oil Gels

PAUL THAU, B.S., and CHARLES FOX, B.A.*

Synopsis—A new procedure is described for the preparation of polyethylene-mineral oil gels. This procedure utilizes high shear mixing equipment to maintain a fine dispersion of the polyethylene wax during a critical phase of the cooling process. The consistencies of gels produced by this procedure are independent of cooling rates. In contrast to existing methods of preparation, this innovation offers advantages in terms of simplified processing and greater formulation flexibility.

Introduction

In recent years, polyethylene-mineral oil gels have been employed as vehicles in various dermatologicals (1). The advantages of this type of base over the conventional oleaginous bases are: (a) very little change in consistency over a wide range in temperature, (b) excellent stability at elevated temperatures, (c) improved spreadability (2, 3, 4), (d) release rates of various medicaments which exceeds that from other oleaginous bases (5), and (e) bland and inert characteristics.

This type of vehicle is, of course, also useful for the preparation of various cosmetic formulations. However, the previously published procedure (6) for preparing these polyethylene-mineral oil gels has limitations which severely reduce its application to the manufacture of cosmetic preparations. For example, a temperature of 130°C is required to dissolve the high molecular weight (approximately 20,000) polyethylene in mineral oil, and a three hour holding period is said to be required to effect solution. The solution which is then allowed to cool to a temperature just above its cloud point (95°C–100°C) must then

* Warner-Lambert Research Institute, Morris Plains, N. J. 07950.

be "shock cooled" to a temperature just above its gel point. This rapid cooling is accomplished by spreading a thin film of the hot solution on a constant temperature, water cooled, metal surface and removing the film from the surface when it reaches 50°C. This type of processing requires highly specialized equipment, and the high processing temperature precludes the addition of volatile and heat sensitive materials.

The new simplified process for preparing polyethylene-mineral oil gels, which utilizes commonly available high shear mixing equipment in conjunction with lower molecular weight polyethylene waxes, is readily adaptable to the preparation of cosmetic and pharmaceutical formulations. The use of lower molecular weight (1500–2000) polyethylene waxes makes it possible to reduce the dissolution temperature from 130°C to 90°C–95°C and the holding time from three hours to one hour. However, a higher concentration of wax is required to obtain desirable consistencies. The Eppenbach Homo-Mixer®*, utilizing a high speed turbine-stator mechanism with a fixed clearance, has been found to give satisfactory high-shear mixing.

Results

To prepare a basic gel using this procedure, 8–15% of polyethylene wax (M.W. 1500–2000) is dissolved in mineral oil at 90°C–95°C, using a propeller type mixer with moderate agitation. After complete solution is achieved, the propeller stirrer is replaced with an Eppenbach Homo-Mixer. The speed of the Homo-Mixer is adjusted to produce moderate turbulence in the solution. This mixing operation is continued until the mixture has air-cooled to 65°C (approximately 10°C below the cloud point). The Homo-Mixer is then replaced by a conventional loop or paddle mixer to minimize air entrapment in the formulation. Cooling with moderate agitation is continued until the temperature drops to about 45°C, and the preparation is then poured into tubes or jars. The mixture forms a gel after packaging as further cooling occurs, and it reaches maximum consistency within 24 hours. When perfumed formulations are prepared, the fragrance is conveniently incorporated after the mixture has cooled to 50°C.

Polyethylene-mineral oil gels prepared by this high shear process have distinct advantages over identical compositions prepared completely with conventional loop, paddle, or propeller mixers. Processing with the Homo-Mixer within the described temperature range enhances

* Gifford-Wood Co., 420 Lexington Ave., New York, N. Y. 10017.

the gelling action of the polyethylene, as the data in Table I clearly show. This, in turn, results in a more elegant product with more desirable spreading characteristics. The consistency of gels prepared by conventional mixing procedures varies as a function of cooling rates. Softer gels result as the cooling rate decreases. This variable is substantially eliminated when the high shear mixing process is employed, as shown in Table I.

The gels prepared by the high shear process are much more stable at all storage temperatures than those prepared by conventional mixing and have a low temperature viscosity index. They do not liquefy at high summer temperatures nor harden excessively at low winter temperatures. The effect of temperature on cone penetration of a polyethylene-mineral oil gel and of Petrolatum U.S.P. is shown in Fig. 1. In addition, the polyethylene-mineral oil base can tolerate the addition of a high concentration of solids without making it unduly pasty. For

TABLE I

Consistency of Polyethylene Wax-Mineral Oil Gels as a Function of Processing Procedure

	Composition				Cooling Rate,[g] °C/min.
	A	B	C	D	
Polyethylene wax—M.W. 1500[a]	120 g.	120 g.	...	...	...
Polyethylene wax—M.W. 2000[a]	...	...	120 g.	...	...
Polyethylene wax—M.W. 7000[b]	...	...	...	120 g.	...
Light white mineral oil[c]	880 g.	...	880 g.	880 g.	...
Heavy mineral oil[d]	...	880 g.	...	...	...
Penetration readings[f] (0.1 mm. div., "Precision" penetrometer with brass cone)	...	...	...	...	...
High shear mixing process	215	195	191	300[e]	0.35
	212	...	...	...	0.50
	210	...	...	...	3.00
Conventional mixing process	370	370	620	340[e]	0.35
	270	...	...	...	0.50
	190	...	...	...	3.00

[a] Allied Chemical Corporation, Solvay Process Div., 40 Rector St., New York, N. Y. 10006.

[b] Eastman Chemical Products, Inc., Kingsport, Tenn.

[c] 65/75 Saybolt Universal seconds at 100°F.

[d] 300/360 Saybolt Universal seconds at 100°F.

[e] Gel displays slight oil separation at time of measurement.

[f] ASTM Designation: D217-60T.

[g] Cooling rate controlled from 90° to 45°C. Preparation was then poured into jars and tubes.

example, a polyethylene-mineral oil gel containing 30% of zinc oxide possesses superior consistency and spreadability characteristics than an identical preparation made with petrolatum.

Mutimer *et al.* (6) point out that in the formulation of a hydrocarbon gel a crystalline fraction is required to confer rigidity and an amorphous fraction is necessary to confer thickening. They further conclude that polyethylene is a good gelling agent because it contains crystalline and

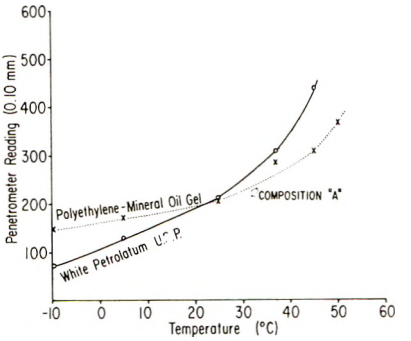

Figure 1.—Consistency of white petrolatum USP and polyethylene-mineral oil gel as a function of temperature

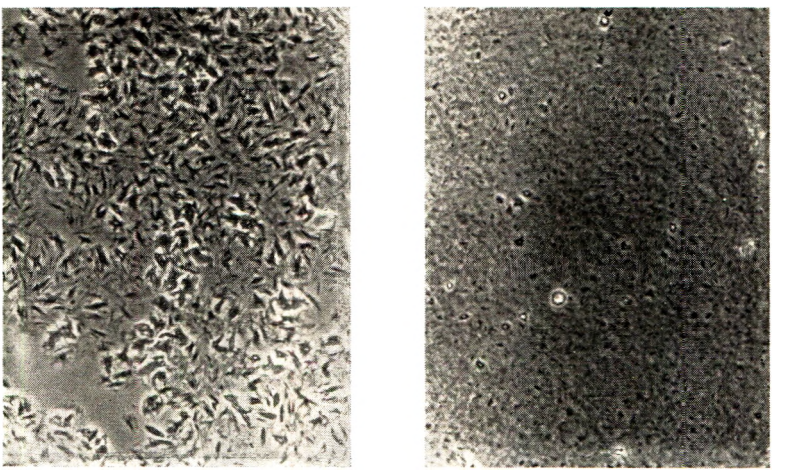

Figure 2.—Photomicrographs (360 X) of polyethylene-mineral oil gels prepared by conventional mixing process (left) and a high-shear mixing process (right)

amorphous fractions. Polyethylene precipitates in mineral oil as small crystallites surrounded by long fibrous amorphous filaments, which intermesh and produce a sponge-like structure (6). The resultant three-dimensional lattice is responsible for the gel structure.

Photomicrographs of composition A (Table I) prepared by the conventional and by the high-shear processes are shown in Fig. 2. It is evident that the high shear process yields a finer dispersion of the wax than the conventional process. This results in a sponge-like structure with smaller pore size which probably is responsible for the greater rigidity of the gel prepared by the high shear process.

Summary

A process for the preparation of polyethylene wax-mineral oil gels using commercially available high shear equipment has been described. The properties of several gels prepared by the high shear method have been compared to gels prepared by the use of conventional mixing equipment. This procedure is more adaptable for the preparation of cosmetic and dermatological formulations than previously described methods.

Acknowledgment

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Book Reviews

THE EPIDERMIS, edited by William Montagna and Walter C. Lobitz, Jr., Academic Press, New York. 1964. 649 pages, illustrated and indexed. Price $15.

This volume, the proceedings of a symposium held at Lake Arrowhead, Calif., is dedicated to Stephen Rothman. Dr. Rothman has left an indelible mark on the history of dermatology, and this volume is a fitting memorial to him.

This reviewer has always had serious reservations about the publication of monographs of this type, i.e., books which consist of contributions by many experts with various specialties. However, this volume contains so much of interest that it deserves careful attention by all who study or treat skin. Each of the 32 chapters in "The Epidermis" has been contributed by outstanding experts in their respective fields, and it is difficult (if not impossible) to review every chapter in detail. Briefly, this volume is intended to serve as an introduction and background to present knowledge of epidermal keratinization and of the structure of the elaborated tissue and its composition and functioning. Some of the chapters are strictly of a review nature; others present provocative new ideas; and still others are research papers with novel experimental documentation.

In the opinion of this reviewer, the outstanding chapters include those by Rothman, Mercer, Rogers, and Kligman. Rothman's historical notes should serve as a lesson to us all that good scientific work is not exclusively recent scientific work. Mercer's chapter is noteworthy because, for the first time, an attempt is made to introduce the operon to the science of cell differentiation in the epidermis. Rogers' chapter on the structure and biochemistry of the hair follicle deserves special mention because of the magnificent photomicrographs and the presentation of new results of amino acid analyses. Finally, Kligman's discussion of the stratum corneum as a continuous sheet is very readable and thought-provoking and should be of interest to all cosmetic chemists.

The enumeration of these four chapters in no way detracts from the value of the remaining chapters,

most of which are of a review nature. Nobody interested in skin can even remotely hope to read all the pertinent material which appears in the technical literature; perforce we must depend on high-caliber predigested versions in the form of reviews which may cover either broad or very narrow areas. As is customary with reviews, some are more worthy of mention than others. This reader considers Nicolaides' review of lipids in the epidermis and Weber's of carbohydrate metabolism the most outstanding. The latter should be of particular interest to cosmetic chemists and dermatologists alike in view of the recent postulates that uridyl diphosphate sugars are the precursors of hyaluronic acid and that enzymes may affect the synthesis of chondroitin sulfate. Few today question that faulty carbohydrate metabolism (i.e., the formation of ground substance) is somehow related to hyperkeratoses due to increased mitotic activity (psoriasis) and hyperkeratoses due to retention.

With a few exceptions, the proofreading of this volume is excellent. Each chapter is thoroughly documented by extensive up-to-date bibliographies.—M. M. RIEGER—Warner-Lambert Research Institute.

MUCOPOLYSACCHARIDES by J. S. Brimacombe and J. M. Webber, Elsevier Publishing Co., Amsterdam. 1964. 181 pages, indexed. Price $10.

This small book represents Volume VI in the *Biochimica et Biophysica Acta* Library and is a comprehensive account of the chemistry of mucopolysaccharides. Although the volume is concerned primarily with the organic chemistry and the elucidation of structures of the various acid mucopolysaccharides, the reader will find, in addition, much information on on the occurrence, properties and function of hyaluronic acid, chondroitin sulfates, heparin, and keratosulfates. In addition, the related subjects of chitin and of blood group substances are adequately covered.

Mucopolysaccharides are major constituents of the ground substance of animals and men. They have been widely studied, and it is no surprise that their nomenclature has been in a state of confusion since the term "mucopolysaccharides" was first coined by Meyer in 1938. Until recently, the study of these compounds has been the domain of the physiologist and of the biochemist. However, today clinicians, cosmetic chemists, and pharmacologists have become concerned with the influence that the mucopolysaccharides may have on disease and health of the cutaneous tissues. Thus, mucopolysaccharides are believed to be involved in both hair growth and the etiology of psoriasis. There has even been a suggestion that mucopolysaccharides may influence nutrition of cutaneous and subcutaneous tissues, a subject of vital interest to the cosmetic chemist. With this in mind, this reviewer agrees with Stacey's statement in the Foreword, "The book will be of value to all those who are interested in the rapidly expanding field of nitrogen-contain-

ing carbohydrate substances and I am pleased to commend it."—M. M. RIEGER—Warner-Lambert Research Institute.

CONTACT ANGLE, WETTABILITY, AND ADHESION, Vol. 43 in Advances in Chemistry Series, American Chemical Society, Washington, D. C., 1964. ix + 389 pages with index. Price $8.

This book represents the series of papers presented by a group of distinguished surface chemists at the Symposium in 1963 of the Division of Colloid and Surface Chemistry; the symposium was held in honor of William A. Zisman upon receipt of the Kendall Award.

The first chapter by Zisman, entitled "Relation of the Equilibrium Contact Angle to Liquid and Solid Constitution," is an excellent review of all the requirements involved in the studies of wetting and adhesion.

The other twenty-seven represent original contributions by various authors, both academic and industrial. These cover the whole gambit of studies on wetting, spreading, and adhesion as applied in many facets of modern technology.

At first glance, few, if any, of the systems used by these investigators would appear to be of direct interest to the cosmetic chemist. However, no one can read Zisman's initial chapter without gaining a greater insight into, and comprehension of, cosmetic problems of spreadability and of formulating difficulties in wetting of powders. From there on, many of the other chapters will give insight into other specialized problems. Thus the various chapters on adhesion might well stimulate ideas for improved chip resistant nail polishes.

Although probably only a few cosmetic chemists may care to own their own copy, a careful perusal of this book might well stimulate useful avenues for formulation study. In this regard, the index is excellent, providing an access not usually found in books of this type.—JOHN H. WOOD—Bristol-Myers Products Div.

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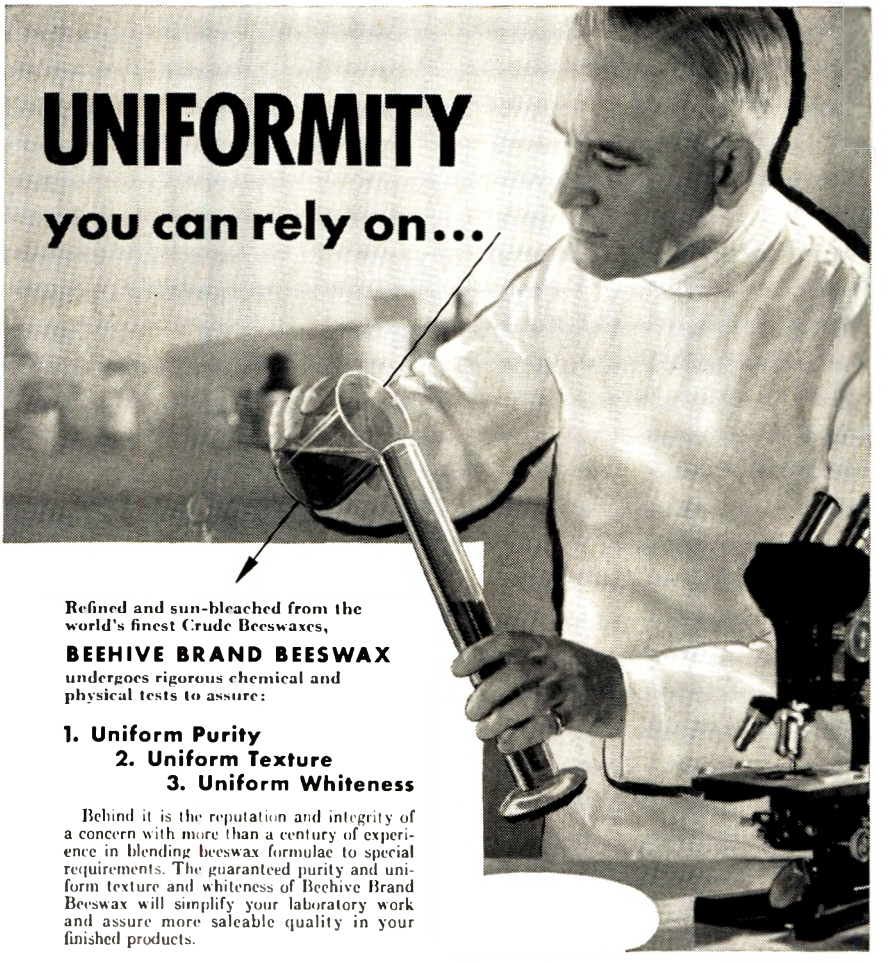

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