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Journal of the Society of Cosmetic Chemists

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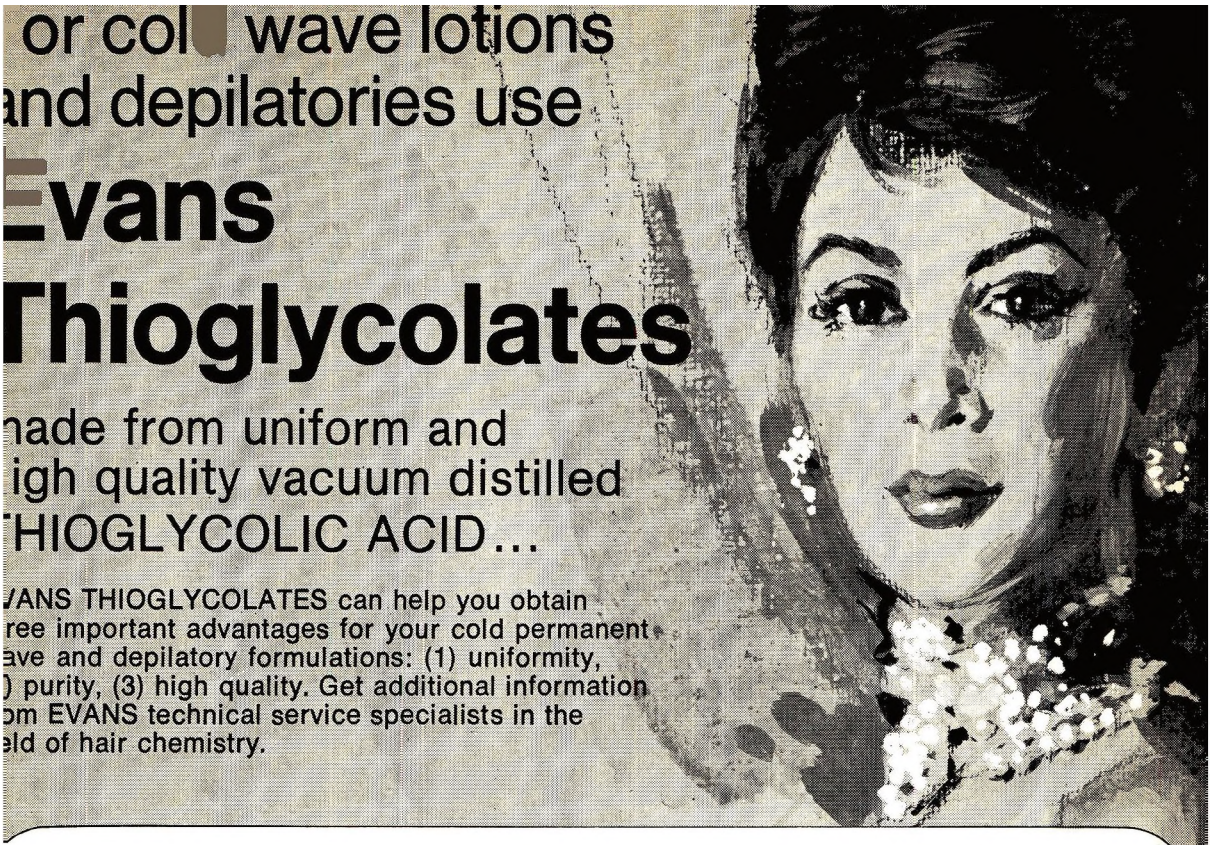

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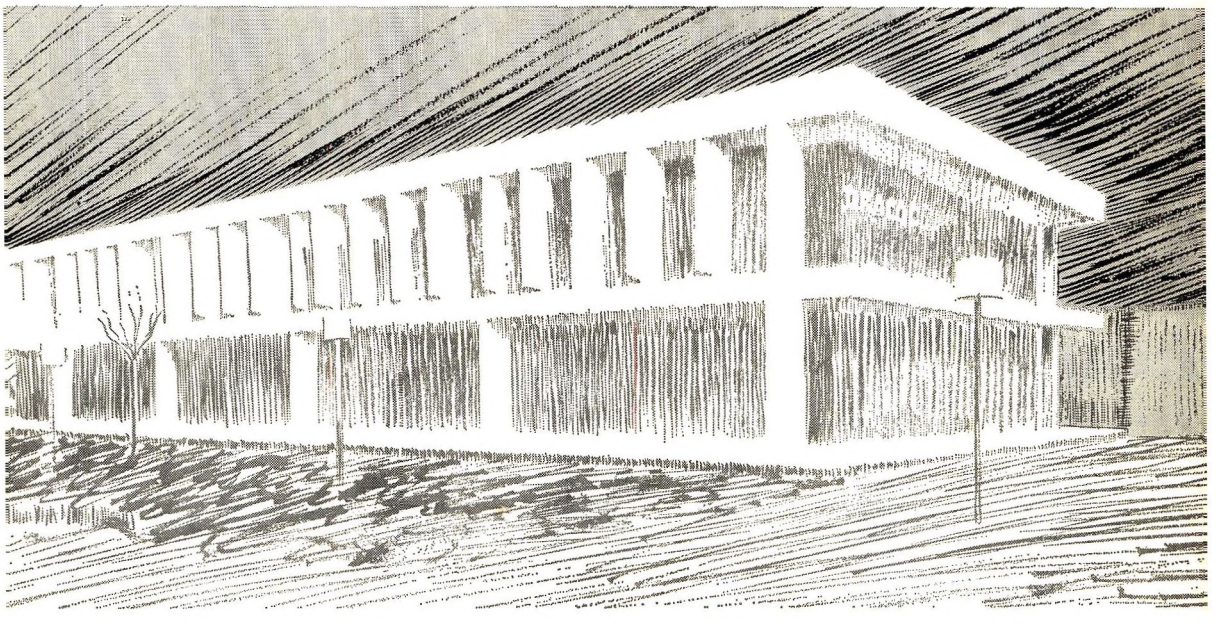

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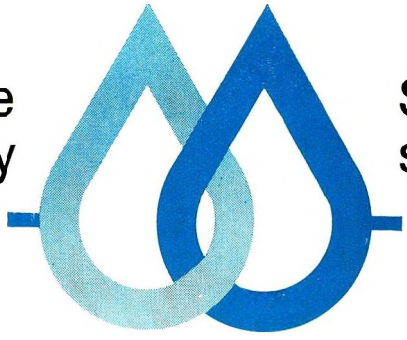

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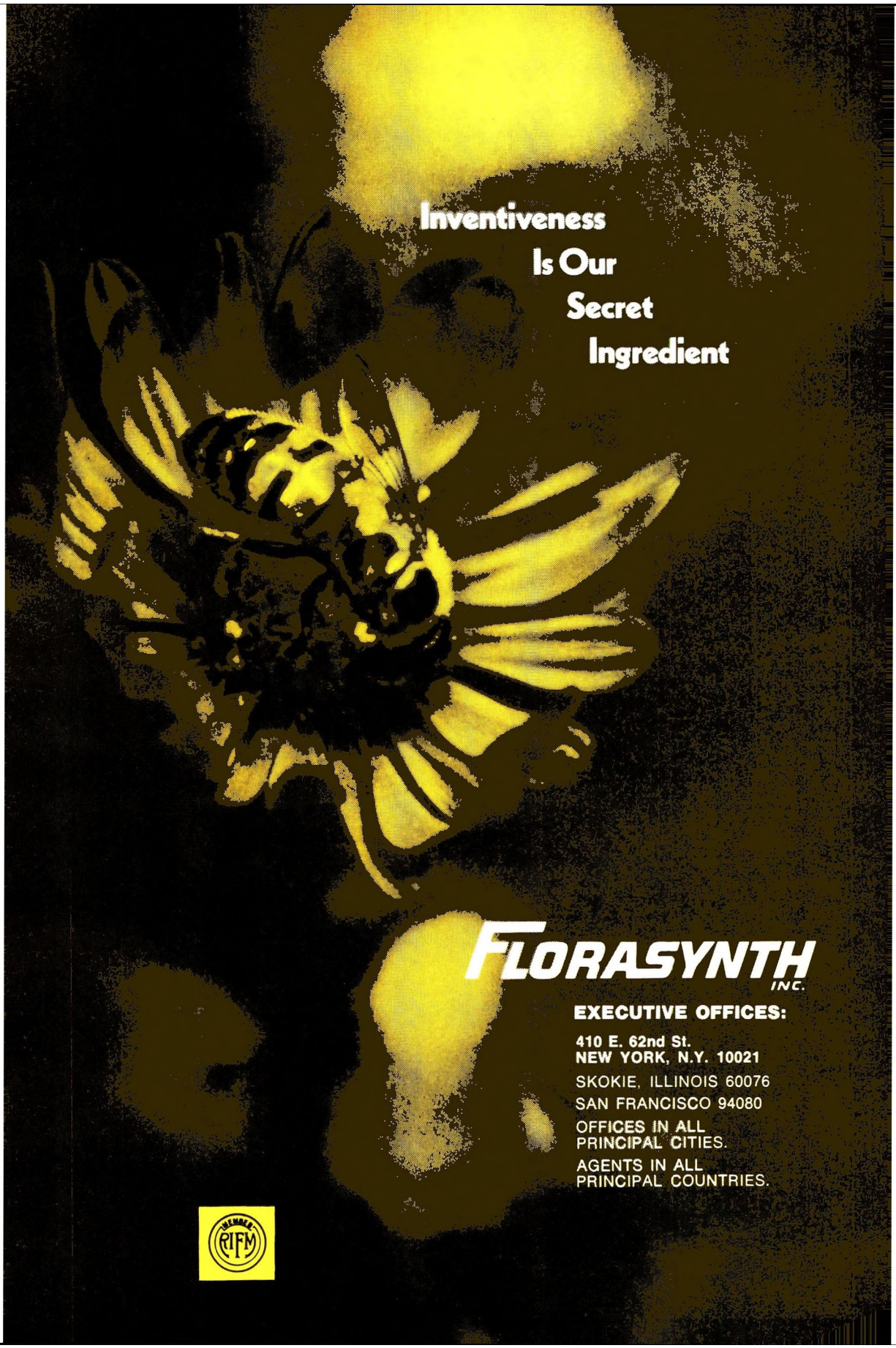
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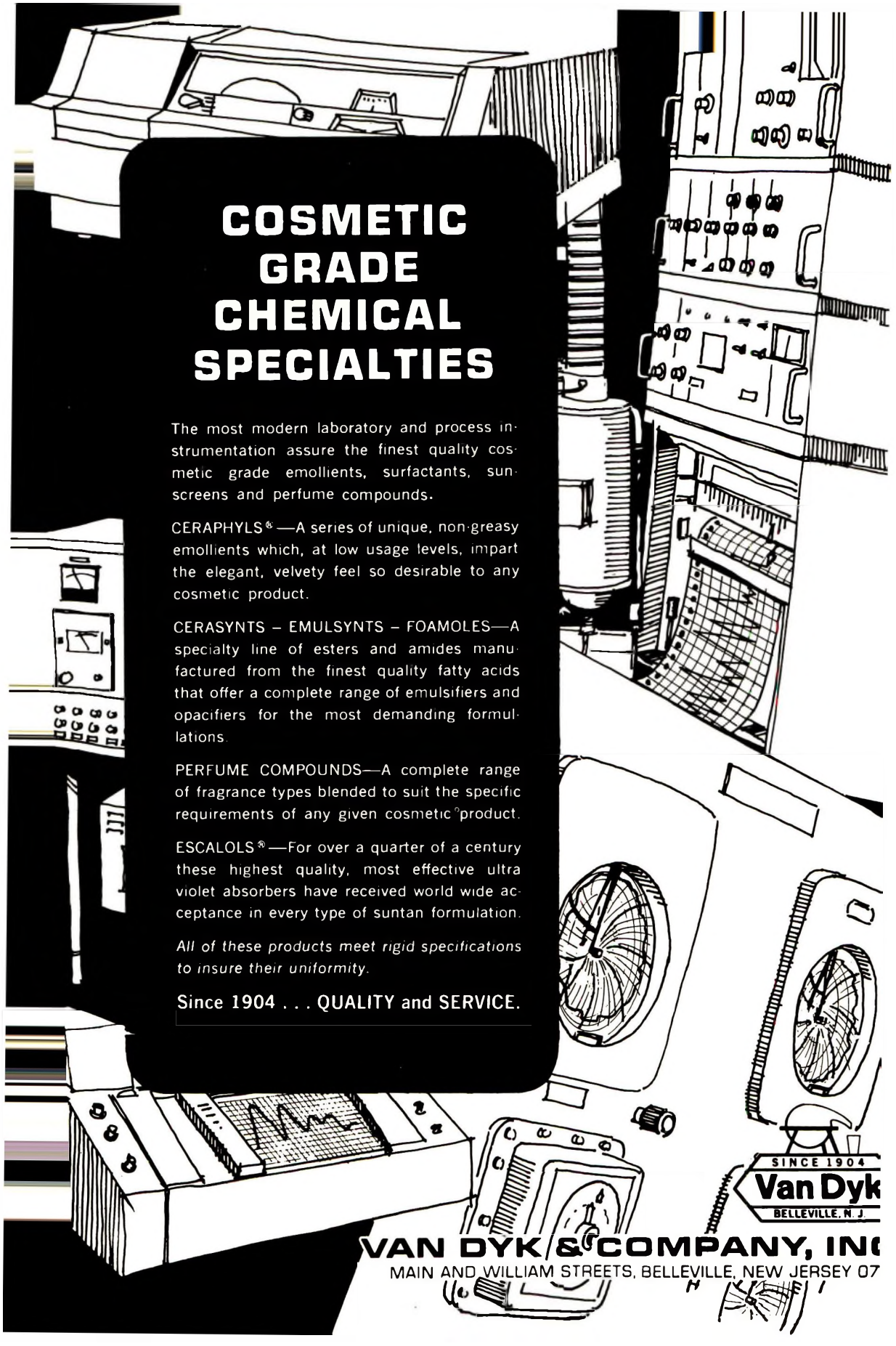

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SYNOPSES FOR CARD INDEXES

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

The presumptive role of amino acid derivatives and catecholamines in the etiology of vitiligo: Robert Brun. *Journal of the Society of Cosmetic Chemists* **25**, 61 (February 1974)

Synopsis—Based on the hypothesis that vitiligo could be a phenomenon of the same type as chemically-induced leukoderma, an attempt was made to find some physiological or physiopathological *p*-hydroxyphenyl derivatives which could be responsible for melanogenesis inhibition. Thus, the inhibitory effect of many derivatives of tyrosine and also sympathomimetic substances on a Dopa-melanocyte system was tested. The main result was that adrenaline (epinephrine) was found to be a strong inhibitor of the Dopa reaction whereas noradrenaline (norepinephrine) was found to have no such effect. Other strong inhibitors were *p*-hydroxyphenylpyruvic acid and *p*-hydroxyphenylcinnamic acid, which could be metabolites of aromatic amino acids.

Fluorometric determination of formaldehyde in cosmetic products: Clifton H. Wilson. *Journal of the Society of Cosmetic Chemists* **25**, 67 (February 1974)

Synopsis—To overcome interference by perfume ingredients, a method has been developed for determining formaldehyde in cosmetics by forming a fluorescent lutidine derivative and measuring the fluorescence on a spectrophotofluorometer, Satisfactory recoveries were obtained from samples of shampoos, bath oils, hair cosmetics, lotions, and creams to which formaldehyde had been added. Formaldehyde was also determined in commercial samples of nail hardener, bubble bath, hair rinse, and shampoos. Of seven other aldehydes examined, only an aryl sulfonamide-formaldehyde resin gave a false positive test.

Appraisal of efficacy of antidandruff formulations: Albert M. Kligman, Richard R. Marples, Larry R. Lantis, and Kenneth J. McGinley. *Journal of the Society of Cosmetic Chemists* **25,** 73 (February 1974)

Synopsis—The effectiveness of antidandruff shampoos and grooming agents can be reliably assessed in a month's time on groups as small as 10 persons. The important prerequisites are that the subjects have at least moderately severe dandruff and that estimations be made at a fixed interval after washing the scalp.

Two modes of evaluation are utilized: (a) a subjective one in which the amount of scaling is scored on a 0 to 10 scale, and (b) an objective one in which the quantity of horny cells produced is measured in a hemocytometer. Data are given for two widely used efficacious shampoos and for a nonmedicated control. These are valuable benchmarks which enable products to be compared on a scale of comparative merit.

Quantitative aspects of absorption of cosmetics by skin: Hans Schaefer. *Journal of the Society of Cosmetic Chemists* **25,** 93 (February 1974)

Synopsis—The physico-chemical processes after application of cosmetics to the skin are related quantitatively to the skin's physiological structure and function. The optimum quantity of a cosmetic cream which can be applied to the skin is limited, and only part of it is absorbed by the horny layer. Beyond a certain depth of the horny layer, the individual components—including the incroporated active constitutents—obey their own penetration kinetics. At the same time, the lipid-like materials applied to the skin are continuously diluted by skin lipids and transported to the surface. Incorporated solids can also penetrate and remain in deeper layers of the horny layer. The magnitude of this process depends on the particle size. After a discussions of methods suitable for quantitation of these processes, several points are noted: 1. The penetration of particles can be eliminated by selection of their particle size. 2. The duration of action of a cosmetic preparation on the skin normally lasts about five hours. 3. So-called "nutrients" penetrate into living cell layers in such small amounts that any influence on cell nutrition is excluded. 4. It is, nevertheless, possible to influence cells cosmetically by studying the physiological regulation of cell nutrition.

The scientific basis for FDA regulatory activities in cosmetics: Alfred Weissler. *Journal of the Society of Cosmetic Chemists* **25,** 99 (February 1974)

Synopsis—Increased safety for users of cosmetics is the goal of Food and Drug Administration activities in cosmetics. In order for these activities to be effective, they must have a sound scientific basis. This paper surveys the scientific projects and capabilities at FDA in the field of cosmetics, in terms of their impingement on regulatory matters.

It deserves note that the scientific basis for regulatory actions may involve not only facts, but also judgments as well; the reason is that in some cases the available factual information is not complete or definitive. A brief discussion is given of recent examples, such as bubble baths, asbestos in talcum powders, and mercury preservatives in cosmetics.

J. Soc. Cosmet. Chem., 25, 61–66 (February 1974)

The Presumptive Role of Amino Acid Derivatives and Catecholamines in the Etiology of Vitiligo*

ROBERT BRUN, M.D.†

Presented May 25, 1972, 14th International Congress of Dermatology, Venice

Synopsis—Based on the hypothesis that vitiligo could be a phenomenon of the same type as chemically-induced leukoderma, an attempt was made to find some physiological or physiopathological *p*-hydroxyphenyl derivatives which could be responsible for MELANOGENESIS INHIBITION. Thus, the inhibitory effect of many derivatives of TYROSINE and also sympathomimetic substances on a DOPA-meloanocyte system was tested. The main result was that ADRENALINE (epinephrine) was found to be a strong inhibitor of the Dopa reaction whereas noradrenaline (norepinephrine) was found to have no such effect. Other strong inhibitors were *p*-hydroxyphenylpyruvic acid and *p*-hydroxyphenylcinnamic acid, which could be metabolites of aromatic amino acids.

Introduction

In previous research on the mode of action of the hydroquinone derivatives in the phenomenon of depigmentation, it was concluded that these substances were active as competitive inhibitors of tyrosinase (1). In effect, after four applications of *p*-ethoxyphenol (or monoethylether of hydroquinone or MEH) the melanocytes of the basal layer of guinea pig skin had already exhausted their reserves of melanin granules, but at this stage the Dopa-reaction was still positive. This clearly demonstrates that in this first step the melanocytes do not produce any more melanin unless the inhibitory action is arrested.

When the treatment is prolonged (10–20 days), melanocytes are no longer found, that is, the Dopa reaction is negative and the repigmentation *in vivo*

*Work supported by Grant 3.606.71, Swiss National Fund for Scientific Researches.
†Department of Dermatology, Hospital Cantonal, CH-1211 Geneva 4, Switzerland.

can no longer produce itself. Therefore, a vitiligo-like lesion is artifically produced. The examination of guinea pig skin treated with MEH under electron microscopy confirmed the death of the melanocytes. In effect, Frenk (2) has demonstrated that in the first stage the melanocytes show important changes and then rapidly die. Furthermore, this author confirmed that this toxic effect is specifically directed against the melanocytes and that neither the keratinocytes nor the cells of Langerhans are influenced by this treatment; these facts were previously established by our experiences *in vivo* and through examination under light microscope (3). With our present knowledge of vitiligo, it can be verified that, apart from small changes probably due to the absence of protection against ultraviolet light, vitiligo and areas of leukoderma produced artificially by phenol derivatives are similar, if not identical, lesions.

Consequently, it seems logical to examine the following hypothesis: "Vitiligo could be due to the inhibitory action on the tyrosine-tyrosinase system by a phenol derivative; for example, a substance produced in the body (physiological or pathological) or a metabolite of such a substance. This product could then provoke the blockage of the melanogenesis (by competition), and after some days of inhibitory action, the death of the melanocytes. The presence of the inhibitory substance at the level of the melanocytes could be a consequence of a pathological phenomenon, likewise localized and confined in time."

In effect, only several days of inhibition of the melanogenesis can provoke the disappearance of the melanocytes. Therefore, a transitory pathological phenomenon could be the source of a vitiligo lesion. At the nonprogressive stage, vitiligo could be no more than a sequela of such a pathological phenomenon. This hypothesis could equally explain the relatively limited results that have been obtained in the study of vitiligo.

The artificial inhibitors previously studied were derivatives of phenol with "para" substituents. It is normal, therefore, to try to discover in which group of substances in the organism an inhibitor of this type could be produced pathologically. Thus, we have considered two families of compounds which could play an important role in this field; tyrosine derivatives on one hand and adrenaline derivatives on the other. It is clear that other related chemical families should also be studied.

Experimental

A modification of the method of Ijima and Watanabe (4), namely, the inhibition of the Dopa recation, was used. The modification consisted of the use of unfixed fresh tissue, frozen to −80°C quickly after the biopsy and cut by the cryostat to 8–10 μm. The competitive inhibitors are mixed with the Dopa solution according to a molar ratio "substrat (Dopa)/inhibitor" from 1/1 to 1/1/32 by successive dilution of the inhibitor.

$$1/1 \text{ corresponding to } \frac{5.10^{-6} \text{ mole/ml Dopa}}{5.10^{-6} \text{ mole/ml inhibitor}}$$

$$1/\tfrac{1}{32} \text{ corresponding to } \frac{5.10^{-6} \text{ mole/ml Dopa}}{0.156\ 10^{-6} \text{ mole/ml inhibitor}}$$

The dilutions were made in a buffered phosphate solution (Soerensen) of pH 7.35 with traces of copper sulphate. The pH is adjusted, if necessary, after the addition of the inhibitor.

For testing, the standardized tissue used was the nipple of the male colored guinea pig. Verification was also made with normal human skin. The reaction is performed on slides in damp boxes; incubation time is 2½ hours at 37°C.

It is important to test pure chemical substances and not the pharmaceutical forms of these products because of the common presence in the latter of preservative agents which can interfere with the Dopa-reaction.

Results and Discussion

It must be emphasized that the method of Ijima and Watanabe (4) is not recommended in the study of all inhibitors of melanogenesis but, after our experiences, we have found it to be adequate and to give accurate results with competitive inhibitors. The results are shown in Table I.

Derivatives of Tyrosine and L-Dopa

It was found that MEH, which is very active *in vivo*, is already an inhibitor at a molecular concentration 1/16 of that of Dopa. Moreover, we have been able to show that two substances which are derivatives of tyrosine present an inhibitory activity of the same order (1/16 and 1/8). These substances are *p*-hydroxycinnamic acid and *p*-hydroxyphenylpyruvic acid. It is conceivable that under the influence of a pathological phenomenon (to be determined) these degradation products of tyrosine could be liberated at the level of the melanocytes.

In this aromatic amino acid family, the presence of one or two hydroxyphenolic groups does not seem to play an important role in inhibitory activity. On the other hand, as long as the molecule possesses a free amino function no inhibitory effect could be found.

Epinephrine and Derivatives

The substances of this family are also either physiological or chemical derivatives of tyrosine and Dopa. The results found in this group are very surprising in view of the strong inhibitory action of adrenaline (epinephrine) in comparison with the complete inactivity of noradrenaline (norepine-

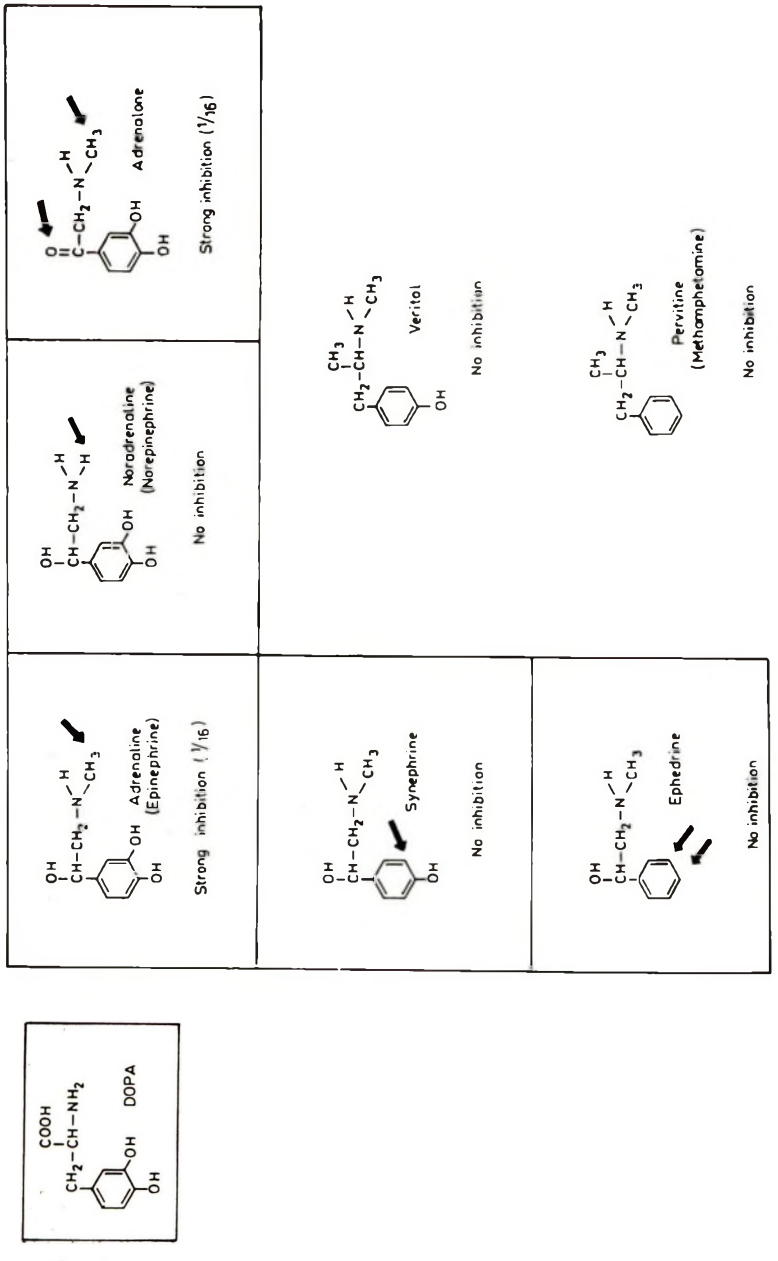

Figure 1. Dopa-oxidase inhibitory activity of epinephrine and related products

Table I
Inhibitory Effect on a Dopa-Melanocyte System

Inhibitors	Diln. Limit[a]	Inhib. Effect[b]
Tyrosine and Related Products		
Tyrosine	>1	0
Tyramine	>1	0
p-Hydroxyphenylpropionic acid	½	+
p-Hydroxyphenylpyruvic acid	⅛	++
p-Hydroxycinnamic acid	1/16	+++
p-Hydroxyphenylacetic acid	>1	0
p-Hydroxymandelic acid	>1	0
p-Ethylphenol	⅛	++
p-Ethoxyphenol (MEH)	1/16	+++
p-Hydroxybenzoic acid	½	+
Methyl-*p*-hydroxybenzoate	>1	0
p-Hydroxybenzaldehyde	>1	0
p-Hydroxybenzyl alcohol	>1	0
Dopamine	>1	0
3,4-Dihydroxyphenylpropionic acid	½	+
3,4-Dihydroxyphenylacetic acid	½	+
Phenylpyruvic acid	>1	0
Adrenaline and Related Products		
Adrenaline	1/16	+++
Noradrenaline	>1	0
Adrenalone	1/16	+++
Synephrin®[c]	>1	0
Veritol	>1	0
Ephedrine	>1	0
Pervitine®[d]	>1	0

[a]Ratio at which the activity of the inhibitor is still detectable, e.g., ⅛ = molar concentration of inhibitor 8 times inferior to that of Dopa.
[b]0 = nil, + = weak, ++ = fair, +++ = strong.
[c]Winthrop Laboratories, New York, N.Y.
[d]Temmler, Germany.

phrine). In this category of substances, the inhibitory effect seems bound with the presence of two hydroxyphenolic groups and the substitution of the amino group (i.e., the effects of adrenaline, noradrenaline, adrenalone, synephrine). This can be seen in Fig. 1.

If we take into account only the strongest inhibitors of the Dopa reaction found in this work, we can see that three of them correlate and strengthen the starting hypothesis. Indeed, *p*-hydroxyphenylpyruvic acid as well as *p*-hydroxycinnamic acid may be the result of a defect of the metabolism of tyrosine. However, the inhibitory effect of adrenaline in relation to the lack of the inhibitory power of noradrenaline may be of greatest significance.

A few years ago, Shelley and Öhman (5) found that a simple injection of epinephrine in rats produced a spot of white hair at the site of injection. They concluded that intense vasoconstriction was the reason for this selective damage of the melanocytes. But at the same time, the injection of nor-

epinephrine did not produce the whitening of the rat hair. These results are too similar to ours not to make a correlation between them.

(Received February 14, 1973)

References

(1) Brun, R., Contribution à l'étude de la dépigmentation expérimentale, *Bull. Inst. Nat. Genevois*, **61**, 1–71 (1961).
(2) Frenk, E., Experimentelle Depigmentierung der Meerschweinchenhaut, *Arch. Klin. Exp. Dermatol.*, **235**, 16–24 (1969).
(3) Brun, R., Effect of the ethyl ether of hydroquinone on pigmentation and on the cells of Langerhans, *Dermatologica*, **134**, 125–8 (1967).
(4) Ijima, S., and Watanabe, K., Studies on Dopa-reaction, *J. Invest. Dermatol.*, **26**, 235–7 (1956), and **28**, 1–4 (1957).
(5) Shelley, W.-B., and Öhman, S., Epinephrine induction of white hair in ACI rats, *Ibid.*, **53**, 155–8 (1969).

J. Soc. Cosmet. Chem., 25, 67-71 (February 1974)

Fluorometric Determination of Formaldehyde in Cosmetic Products

CLIFTON H. WILSON, Ph.D.*

Presented October 11—14, 1971, Joint Symposium of the Society of Cosmetic Chemists and the Association of Official Analytical Chemists, Washington, D.C.

Synopsis—To overcome interference by perfume ingredients, a method has been developed for determining FORMALDEHYDE in COSMETICS by forming a FLUORESCENT LUTIDINE DERIVATIVE and measuring the fluorescence on a SPECTROPHOTOFLUOROMETER. Satisfactory recoveries were obtained from samples of shampoos, bath oils, hair cosmetics, lotions, and creams to which formaldehyde had been added. Formaldehyde was also determined in commercial samples of nail hardener, bubble bath, hair rinse, and shampoos. Of seven other aldehydes examined, only an aryl sulfonamide-formaldehyde resin gave a false positive test.

Introduction

Formaldehyde is used in a variety of cosmetics, particularly shampoos, as an antibacterial agent and preservative. It is usually determined colorimetrically with chromotropic acid (1). One difficulty with this technique is that some perfume ingredients used in shampoos liberate formaldehyde in an acid medium and give a false positive test.

A method using fluorometry (2) has been developed for determining formaldehyde. In this method, formaldehyde is condensed with acetylacetone and ammonia to give a colored, highly fluorescent lutidine derivative. This reaction is shown in Fig. 1.

*Division of Cosmetics Technology, Food and Drug Administration, U.S. Department of Health, Education, and Welfare, Washington, D.C. 20204.

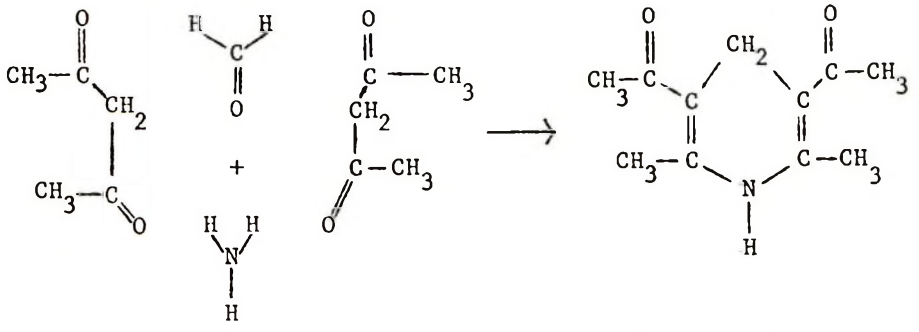

Figure 1. Condensation reaction of acetylacetone and formaldehyde

Experimental Materials and Methods

The acetylacetone* should be freshly distilled and free of color or fluorescence. An aqueous solution containing 0.2 ml of acetylacetone, 0.3 ml of glacial acetic acid, and 15.4 g of ammonium acetate in 100 ml of distilled water is prepared fresh each week.

Standard solutions of formaldehyde are prepared fresh each day. From a Mohr pipet, 0.27 ml of 36.8% commercial formaldehyde solution† is added to a **100-ml** volumetric flask and made to volume with 10–12% methanol (0.1%, 1 mg/ml formaldehyde); a 1-ml aliquot of this solution is diluted to 100 ml with 10–12% methanol (0.001%, 0.01 mg/ml formaldehyde). Four standards are prepared by placing 8-, 6-, 4-, and 2-ml aliquots of the 0.001% formaldehyde solution in separate 100-ml volumetric flasks and diluting to volume with 10–12% methanol (0.8, 0.6, 0.4, and 0.2 μl/ml formaldehyde, respectively).

To prepare the sample, about 100 mg of cosmetic is weighed into a 10-ml graduated cylinder and diluted to volume with 10–12% methanol.

Preparation of 3,5-Diacetyl-1,4-dihydrolutidine

A convenient volume (e.g., 2 ml) of the sample solution is pipetted into a small stoppered graduated cylinder or Erlenmeyer flask and an equal volume of acetylacetone reagent is added. The sample and standard solution are incubated at 37°C for 1 hour in an oven (2) or water bath and then cooled to room temperature.

Fluorescence Determination

The Aminco-Bowman spectrophotofluorometer‡ was used for these determinations, usually with the multiplier setting at 0.03. We used 411 nm for

*Analabs, Inc., 80 Republic Dr., North Haven, Conn. 06473.
†Certified ACS, Fisher Scientific Co., 711 Forbes Ave., Pittsburgh, Pa., or equivalent.
‡American Instrument Co., Inc., Silver Spring, Md.

the exciting wavelength and 510 nm for the emitting wavelength (these wavelengths may vary with other instruments) with the following slit arrangement: 4-mm slits in the path of the fluorescent light; 1-mm slits in the positions on the opposite side of the cuvette from the light path.

The dilution of the reacted sample solution necessary to obtain fluorescence intensity readings within those of the standards is determined. Another sample solution of the proper dilution is prepared and the condensation reaction repeated.

The fluorescence intensity of the standards is plotted on the per cent scale *vs.* the concentration in μg/ml of formaldehyde (Fig. 2). The curve for the standards is linear. The concentration of the sample can be determined by comparing its fluorescence intensity with the standard curve.

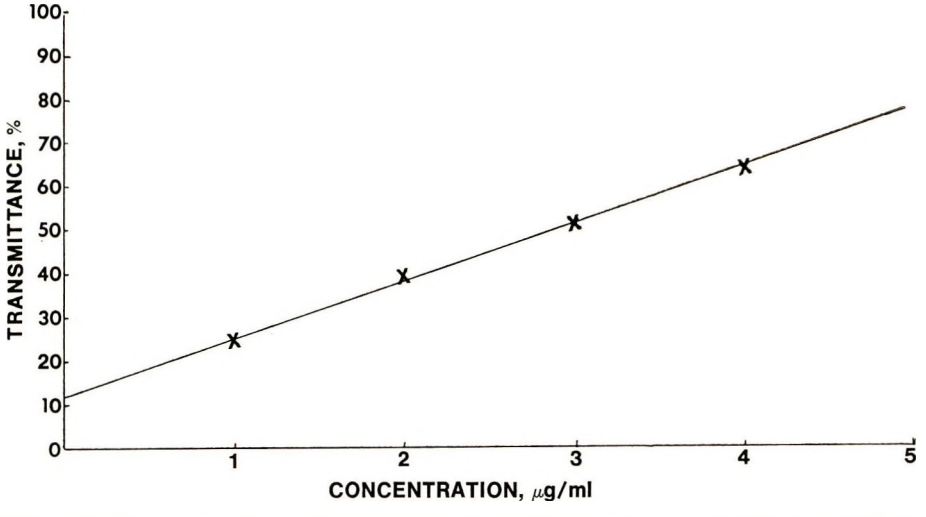

Figure 2. Fluorescence intensity as per cent transmittance *vs.* concentration in μg/ml of formaldehyde

Results and Discussion

Formaldehyde was determined by the fluorescence method on a number of shampoos not containing formaldehyde to which 1.00 mg of formaldehyde had been added by pipette. Recoveries, shown in Table I, ranged from 93 to 103%.

Formaldehyde was added to other cosmetic products in which it is sometimes used as a preservative but which did not contain formaldehyde initially. Recoveries of formaldehyde by the fluorescence method varied more than those for the shampoos; however, they were still good (Table II).

Several commercial cosmetics containing formaldehyde have been analyzed by the method with the results in Table III.

Table I
Recoveries of Formaldehyde Added to Shampoos (1 mg Added)

Shampoo	Sample (g)	Formaldehyde	
		Found (mg)	Recovery (%)
1	0.1064	0.98	98
2	0.1043	0.93	93
3	0.1029	1.03	103
4	0.1283	0.95	95
5	0.1028	1.00	100
6	0.1385	0.95	95
7	0.1122	1.00	100
8[a]	0.1398	0.98	98
9[a]	0.1568	0.90	90
	Av.	0.97	97
	Std. Dev.	0.04%	

[a]Protein shampoos.

Table II
Recoveries of Formaldehyde Added to Cosmetic Products (1 mg Added)[a]

Cosmetic Product	Sample (g)	Formaldehyde	
		Found (mg)	Recovery (%)
Bath oil A	0.2297	0.89	89
Bath oil A	0.1102	1.10	110
Bath oil A	0.1337	0.96	96
Hair conditioner A	0.1482	0.82	82
Hair conditioner A	0.2703	1.00	100
Hair conditioner A	0.1926	0.90	90
Hair conditioner B	0.2568	0.82	82
Hair conditioner C	0.1931	0.93	93
Hair groom	0.1333	1.04	104
Hand lotion A	0.1700	0.76	76
Hand lotion B	0.1615	0.97	97
Hand and body lotion C	0.1340	1.10	110
Hand and body lotion C	0.1359	0.96	96
Skin cream	0.1087	1.08	108
Hand cream	0.1082	1.06	106
Body cream	0.2033	1.00	100

[a]Bath oil A: standard deviation 0.11%. Hair conditioner A: standard deviation 0.09%. Hand and body lotion: standard deviation 0.10%

The stability of formaldehyde in shampoos was determined by adding different amounts to several shampoos, allowing them to remain several days, and determining the formaldehyde concentration by the fluorescence method. The results indicate a slight decrease in the concentration over a period of several days. The tested shampoos did not contain any materials which reacted rapidly with the formaldehyde and in such media the formaldehyde is relatively stable.

Table III
Analysis of Commercial Samples Containing Formaldehyde

Cosmetic	Formaldehyde Concn (%)
Nail hardener	6.7
Bubble bath	0.004
Nail hardener	7.0
Bubble bath	0.61
Hair rinse	0.41
Shampoo	0.01
Shampoo	0.02
Shampoo[a]	0.03

[a]This is less than the percentage of formaldehyde claimed by the manufacturer. The low result may be due to the presence of an optical brightener.

Examination of Other Aldehydes for Positive Test

Several aldehydes were treated with the acetylacetone reagent to determine if other aldehydes will condense to give a positive test. Under the experimental conditions specified, the results with *n*-butyraldehyde, citronellal, dodecylaldehyde, piperonal, benzaldehyde, and paraldehyde were negative. An aryl sulfonamide-formaldehyde resin gave a positive test, probably due to the slow release of formaldehyde by the resin.

Test of Aldehyde-Releasing Preservatives

Several preservatives known to release an aldehyde were tested with the acetylacetone reagent. The results indicate that formaldehyde-releasing preservatives give a positive test whereas dimethoxane (which releases acetaldehyde) gives a negative test. Those giving a positive test were hydroxymethyl-5,5-dimethyl hydantoin, Germall 115 (a substituted imidazolidinyl urea compound),[*] and 2-bromo-2-nitro-propan-1, 3-diol (Bronopol).[†] A quantitative determination of Bronopol and the hydantoin indicated that formaldehyde was completely released from the hydantoin but not from Bronopol.

(Received February 13, 1973)

References

(1) Sawicki, E., Hauser, T. R., and McPherson, S., Spectrophotometric determination of formaldehyde and formaldehyde-releasing compounds with chromotropic acid, 6-amino-1-naphthol-3-sulfonic acid (J-acid), and 6-anilino-1-naphthol-3-sulfonic acid (Phenyl J-acid), *Anal. Chem.*, 34, 1460 (1962).
(2) Belman, S., The fluorometric determination of formaldehyde, *Anal. Chim. Acta*, 29, 120–6 (1963).

[*]Sutton Laboratories, Roselle, N.J.
[†]Boots Pure Drug Co. Ltd., Nottingham, England.

Society of Cosmetic Chemists 1974 Officers Installed

At the December 11th luncheon session of the Society's Annual Scientific Meeting at the Americana Hotel, New York City, 1973 President Robert L. Goldemberg installed the Officers and Directors for 1974.

Left to right (seated): President-Elect Stephen G. Hoch, Treasurer Shaw Mudge, Secretary Gail J. Phillips, President Hyman Henkin, Board Chairman Robert L. Goldemberg; *(standing)* Director (East) Joseph H. Kratochvil, Director (Midwest) Rosemarie Wallisch, Director (East) Maurice L. Rosenthal, Director (Midwest) Betty Lou Day, Director (West) Horst A. Ehrhardt, and Director (East) George Pollack

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Appraisal of Efficacy of Antidandruff Formulations

ALBERT M. KLIGMAN, M.D., Ph.D., RICHARD R. MARPLES, B.M., M.Sc., M.R.C. Pathol., LARRY R. LANTIS, M.D.,* and KENNETH J. McGINLEY†

Synopsis—The EFFECTIVENESS of ANTIDANDRUFF SHAMPOOS and grooming agents can be reliably assessed in a month's time on groups as small as 10 persons. The important prerequisites are that the subjects have at least moderately severe dandruff and that estimations be made at a fixed interval after washing the scalp.

Two modes of EVALUATION are utilized: (a) a subjective one in which the amount of scaling is scored on a 0 to 10 scale, and (b) an objective one in which the quantity of horny cells produced is measured in a hemocytometer. Data are given for two widely used efficacious shampoos and for a nonmedicated control. These are valuable benchmarks which enable products to be compared on a scale of comparative merit.

Introduction

Medically, dandruff is a trivial condition; socially, it is a formidable problem for millions spend millions for alleviation. The disperser of scales has become odious.

Numerous products greet the seeker of relief from scaling. These comprise a spectrum from the worthy to the worthless. The sale of ineffective products does not necessarily reflect meretriciousness on the part of merchandisers. No shampoo can be completely ineffective; merely washing the scalp frequently enough will keep the surface scoured. Many persons obsessively concerned with cleanliness will mistake slight physiologic scaling for disease; merely washing once or twice weekly will satisfy these pseudodandruff subjects. The chief reason why good and bad products are blurred in the market place is the absence of a reliable methodology for appraising effectiveness. Procedures need to be standardized and above all the magnitude of the effects quantified.

*Postdoctoral Trainee, USPHS Grant TI AM 05261.

†Department of Dermatology, School of Medicine, University of Pennsylvania, Philadelphia, Pa. Reprint requests should be addressed to Dr. Kligman.

Others have preceded us in the search for quantification. Weighing the scales removed by brushing or by vacuuming has been proposed (1, 2). In our hands, these methods lack reproducibility. Furthermore, they sample only a proportion of the scales present; the Botwinicks found a low correlation with clinical severity (3). This inherent variability becomes extreme at the poles of high or low scaling. Gross visualization is most often employed (4–6). The reliability of the results strongly depends on the rules by which the test is conducted, especially the criteria by which subjects are selected. It should not surprise anyone therefore that different observers disagree about the very same products. Though *in vitro* screening for antimicrobial activity has its adherents, particularly for selecting potentially effective compounds, the final verdict rests with clinical performance (7).

We have been studying the nature of dandruff for the past 6 years. Though many aspects are still very puzzling, enough has been learned to establish standard techniques for appraising effectiveness. The description of these procedures and the observations on which they are grounded are presented in this paper.

Experimental Studies and Results

Methods

The subjects selected were young male prisoner volunteers, mainly black. No differences were discerned between the races.

Clincal Grading

Dandruff was graded on a scale of 0 to 10 by one observer. As with tea tasters, perfume sniffers, and other specialists, a dandruff connoisseur is indispensable for this work. The first examination was 4 days after a bland shampoo. The scalp was scraped with a wooden tongue depressor at multiple points and an overall grade was given. Free scales in the hair were ignored. Depending on the amount of scurf thus scratched up, subjects were scored as follows: 0–1, very little scaling; 2–3, mild scaling; 4–5, moderate scaling; 6–7, severe scaling; 8–10, very severe scaling. In practice, a score of 0 or 1 is never given prior to treatment, but may be achieved after highly effective treatment. Likewise, scores of 9–10 are never assigned initially. These are included to take into account the full range of potential manifestations; for example, when heavy dandruff subjects are prevented from washing for 2 weeks, scaling becomes spectacular. In our scheme, a grade of 5 designates moderately severe dandruff easily ascertainable by even the neophyte observer. Grade 6 is severe dandruff; higher grades are rarely encountered in the general population. A score of 4 signifies mild dandruff. Below this level clinical grading becomes quite unreliable; these subjects do not have dandruff. Only the expert can make appraisals in the 0 to 3 range, and not very accurately at that.

Corneocyte Counts

Originally we developed this procedure in order to recover bacteria quantitatively from the skin surface. The details have been presented elsewhere (8). The method is applicable to dandruff appraisal for it removes the desquamating portion of the horny layer. Since there is an increased production of horny cells in dandruff as shown by the accelerated migration of radiolabeled basal cells to the surface (9), corneocyte counting affords a means to determine the quantity of horny cells per square centimeter produced in a given time.

Briefly, a site on each side of the vertex was clipped so that a glass cylinder of 3.8/cm^2 area could be snugly applied to the surface. One milliliter of buffered 0.1% Triton X-100* was placed in the cup and the surface was rubbed with a blunt Teflon rod for 1 min. The wash fluid was aspirated and the procedure was repeated. The two samples were pooled. After appropriate dilution, usually 1:10 but with lesser dilutions after effective treatment, two drops of 2% crystal violet were added, the cell suspension was agitated mechanically, and the dispersed cells were counted in a Fuchs-Rosenthal hemocytometer.

Shampooing

This always consisted of two 1-min latherings with a rinse in between.

Prevalence of Dandruff

The incidence of dandruff in the healthy population is not really known. The results of different surveys are of course keenly dependent on the criteria used. Cohen examined 500 young women and graded 15% as having 2+ dandruff (10). Bourne and Jacobs evaluated 2720 soldiers and classified 2.5% as having "gross dandruff" (11). Roia and Vanderwyk considered that 70% of the population had some degree of dandruff (12). Obviously, these investigators did not employ the same rating system.

Procedure

Over a 3-year period 1,033 unselected adult males were graded as above 4 days after a nonmedicated shampoo. None were using antidandruff medications.

Results

The frequency distribution is shown in histogram form (Fig. 1). The most frequent score was 2; the median was 3. Eighteen per cent were classified as grade 5 (moderately severe dandruff) or higher. Grade 4 (mild dandruff)

*Rohm & Hass Co., Philadelphia, Pa.

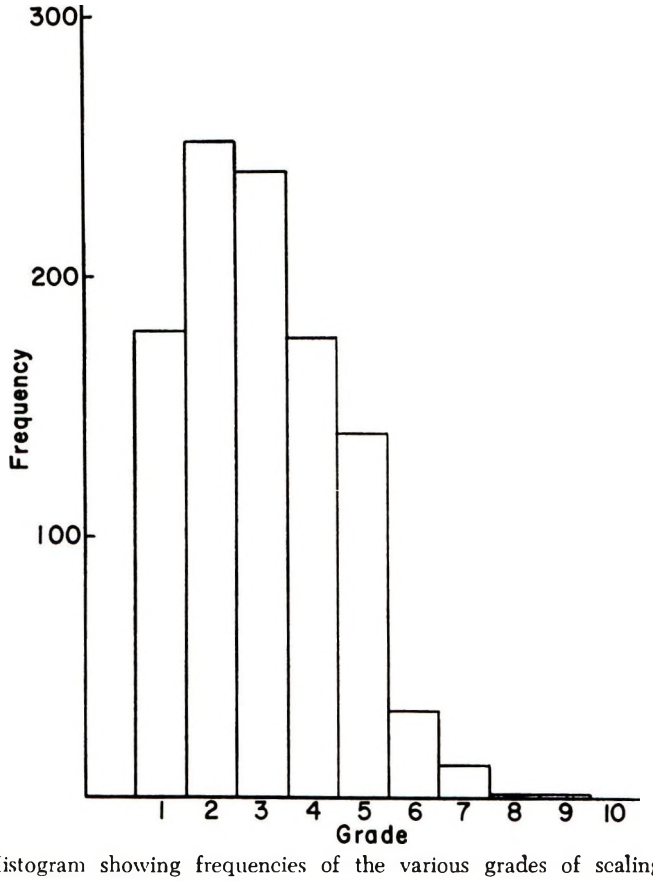

Figure 1. Histogram showing frequencies of the various grades of scaling in an unselected adult male population

included another 18%. Only 4.5% had severe dandruff (grades 6 and 7). Taking grade 4 as mild dandruff, the greatest proportion of subjects fell into the nondandruff group.

Comment

Since we do not admit subjects to clinical efficacy studies with grades of less than 5, it is clear that we reject 4 of 5 prospective candidates. We would agree with Van Abbe and Deans' assertion that it is surprisingly difficult to recruit good subjects (4).

Seasonal Variation

It is commonly supposed that dandruff declines in the summer though no clear proof has been brought forward. The sales of antidandruff products apparently decrease in that season, though this might be interpreted in different ways.

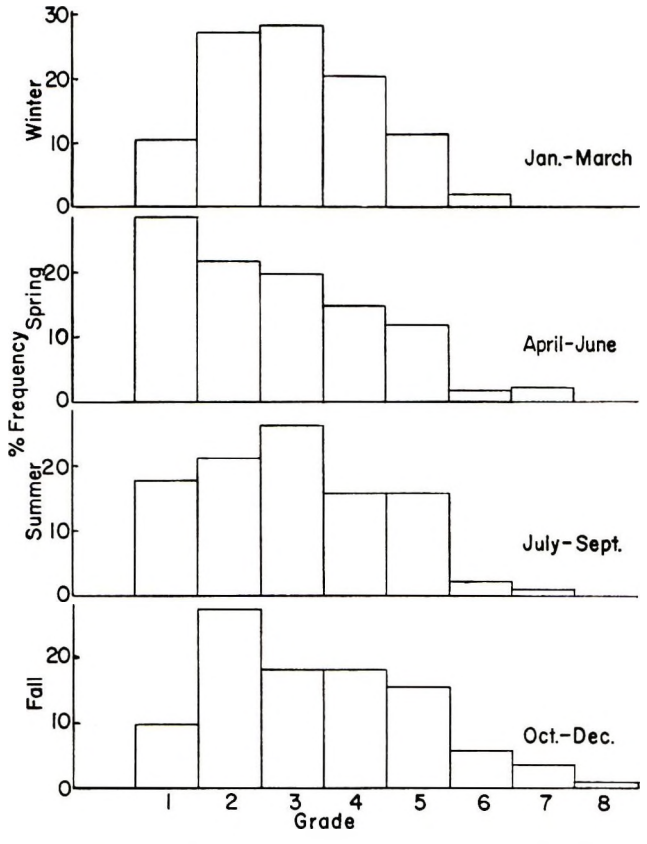

Figure 2. Distribution of grades of scaling in relation to the four seasons

Procedure

The same 1,033 individuals were distributed by grades for each month of the year. Changes in frequencies were analyzed for deviations from that expected if no seasonal effects were present.

Results

A seasonal variation of a statistically significant degree was indeed ascertainable ($p = <0.01$). For illustrative purposes, the frequencies of the various grades are shown by quarters (Fig. 2). This seasonal rhythm is very evident with regard to the frequency of grades 1; in spring, for example, nearly 30% are grade 1 while in winter the frequency falls to only 10%. The contribution to x^2 showed that the seasonal deviation could be largely attributed to an increase in grades 1 and 2 in the spring and summer while in the fall grades 6 and above were higher than at any other season.

Comment

Seasonal shifts with a summer downturn are probably greater than our figures show. We always find it more difficult to mobilize dandruff panels in the summer. This was a retrospective analysis and more subjects are represented in the winter than the summer group.

Distribution of Dandruff

It is commonly believed that dandruff is a patchy process. It has become the practice, therefore, to divide the scalp into segments, each of which is graded separately; a composite score is then calculated. Van Abbe originally evaluated 25 imaginary segments (13). Orentreich and his colleagues probably are closer to the norm, scoring 9 separate sections (14). Various devices such as fencing caps have been utilized as stencils to divide the scalp into regions of equal size (13). We, however, make one global estimate after scratching the surface at several points with a tongue blade.

We investigated the question of patchiness by doing duplicate corneocyte counts in symmetrical sites on opposite sides of the scalp. Nonconcordance would signify an unequal distribution.

Procedure

Four days after a bland shampoo, corneocyte counts were done on 148 subjects on the left and right sides of the vertex 5 cm from the midline. In another group 92 counts were done 7 days after a shampoo.

Results

Four days after the shampoo there was a high degree of correlation between duplicate samples from opposite sides ($r = 0.847$, 95% confidence limits 0.80, 0.89) (Fig. 3). This strong correlation increased in the 7-day group ($r = 0.904$, 95% confidence limits 0.85, 0.93). The variation between sides was remarkably small whether or not the subjects had dandruff. This too bespeaks validity of the method.

Comment

The results indicate that dandruff is a uniform, diffuse rather than patchy process. This accords with all our clinical observations.

We can think of two explanations for the idea of patchiness. The first arises if dislodged scales are included in the evaluation. The distribution of these through the hair will be influenced by many factors such as hair styling and brushing. Secondly, dandruff is often mistaken for seborrheic dermatitis.

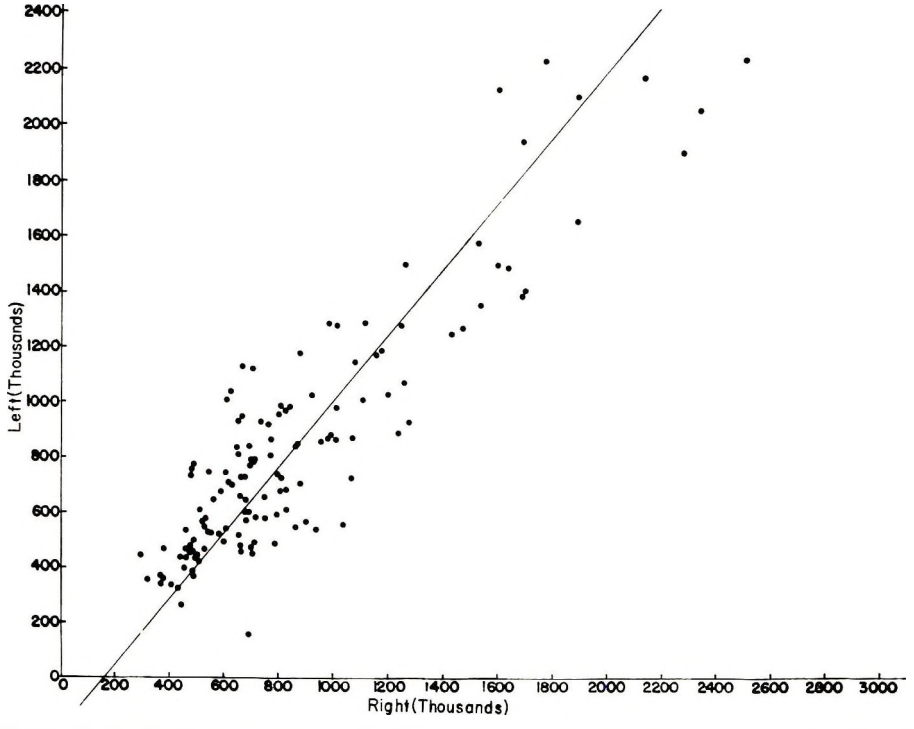

Figure 3. Duplicate corneocyte counts on opposite sides of subjects with and without dandruff

Relationship of Clinical Grade and Corneocyte Count

Clinical grades and corneocyte counts ought to be highly correlated; presumably, the greater the production of horny cells, the more visible the scaling.

Procedure

Grades and counts were done simultaneously on 141 individuals (some studied twice) giving 296 pairs of observations. The counts were duplicates from opposite sides of the vertex. Approximately half the pairs (150) were from dandruff subjects with grades of 5 and above. It is important to note that corneocyte counts in an unselected population follow a log-normal distribution; averages and statistical analysis therefore are always based on logarithmically transformed data.

Results

The orthogonal regression line was calculated from the geometric means (Fig. 4). One can perceive that higher counts tended to be associated with

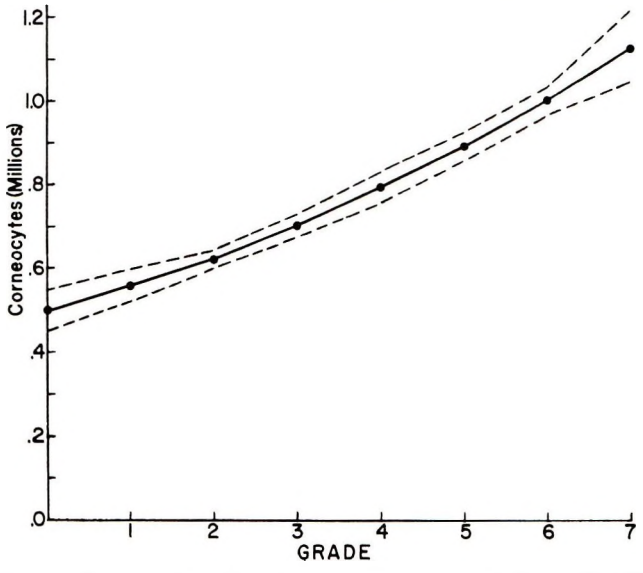

Figure 4. Orthogonal regression of corneocyte counts on grades with 95% confidence limits of the calculated line

higher grades. This correlation was significant ($r = 0.415$) but rather weak, barely satisfying tests of significance.

Comment

While this result was anticipated, the data make it necessary to introduce other considerations. Although a general parallelism was observed, individual disjunctions were quite prominent. Some persons with high counts had surprisingly low grades and vice versa. Evidently the eye sees something not measured by the count. We propose the following explanation. Dandruff is the summation of two processes; an increased production of horny cells and desquamation in larger flakes. Horny cells are not shed singly but in aggregates (15). Although there is considerable overlapping, the proportion of larger scales is much greater in dandruff than in nondandruff.

The corneocyte count is most powerful in determining the quantity of horny cells while the eye has special keenness in sensing the size of the scales. The application of irritants such as sodium lauryl sulfate and kerosene to normal scalps affords a good illustration of how the counts may be extremely high and yet there may be no gross sign of dandruff. After about 5 days there occurs a brief flurry of scaling; the scalps return to normal by 10 days.

Despite the normal appearance the counts were very high, often considerably in excess of the worst cases of dandruff ($2 \times 10^6/cm^2$). Clearly the rate of production of horny cells was being greatly accelerated by the process of irritation but this could not be detected by the eye because desquamation was

in the form of very fine scales. Visibility of scaling will mainly depend on the size of the flakes, while the corneocyte count chiefly reflects the rate of horny cell production. In any given scalp these may interact in different proportions. In consequence, the range of counts for any given grade may be quite large, especially in the nondandruff group. Some grade 2 individuals, for example, will have counts more typical of dandruff. Conversely, some grade 5 subjects will have counts in the nondandruff range. In these, cell turnover is not increased but aggregation is.

On the other hand, counts and grades were strictly correlated when scaling was conspicuous. High grades in severe dandruff were almost always accompanied by high counts.

One can imagine a product that might be effective in dandruff without in any way altering the production of horny cells. Dandruff would "disappear" if the scales were simply dispersed into smaller aggregates. Tars might be examples of ancient antidandruff medications that depend on this mode of action.

Restoration Time

The quantity of scales on the scalp at any particular time will be dependent on the interval since the last thorough washing. By shampooing daily, dandruff cannot be visualized. It is important to know how long it takes after a vigorous shampoo for scaling to reach the prewashing level. Van Abbe and Dean estimate this to be about 5 days (4). This interval is, of course, not fixed and will become proportionately shorter as dandruff becomes severer. Without knowledge of the average restoration time one cannot sensibly lay out specifications for assaying antidandruff shampoos. If bland shampooing is done at intervals less than the restoration time, scaling must diminish progressively. One could then falsely ascribe a beneficial effect to an inefficaceous shampoo. If the intervals between shampoos are unusually long, say 10 days, this permits only 3 treatments a month. Each evaluation would then take months to complete.

Effect of a Single Nonmedicated Shampooing

Corneocyte counting and grading were done on 7 dandruff subjects. The scalps were then shampooed and counts made at the following times: immediately after shampooing, and 1, 2, and 4 days afterwards.

Results—The initial grade before shampooing was 5.3. This fell to 2.0 one day later, increased to 2.8 on the second day, and reached 5.1 by the fourth.

Immediately after the shampoo the mean count was 770,000/cm^2 compared to the 1,330,000/cm^2 originally. Twenty-four hours later, the count dropped still lower to 288,000/cm^2. It rose to 1,009,000/cm^2 by the fourth day.

In a further 8 subjects, 4 with heavy dandruff (average grade 5.7) and 4 with no dandruff (average grade 2.5), counts and gradings were done every 3 days for 12 days after a single shampoo. In the nondandruff group the counts returned to the preshampoo level of 763,000 cells/cm^2 by the sixth day and did not materially increase thereafter. The clinical grades probably decreased slightly at 24 hours. It is certain, however, that the scores did not continue to rise with time, they leveled off after the third day. The final grade at 12 days was no greater than at 3.

In the dandruff group, by contrast, the pretreatment average of 1,366,000 cells/cm^2 was surpassed by day 3 with a count of 1,450,000 cells. By day 6 the count had risen to 1,880,000 cells. The counts continued to increase thereafter but only reached a final level 1,910,000/cm^2. A sharp levelling off clearly occurred after the 6th day.

The grades increased to averages of 5.6 on day 3, to 7.4 by day 6, (the original level) 8.0 by 9, and 8.4 by 12 days. One subject reached grade 9 by 9 days.

Effect of Shampooing Dandruff Subjects Every 4 Days

It was necessary to know whether bland shampooing every 4 days would bring about a steady decline in counts. Accordingly, 15 subjects, each with grade 5 dandruff, were shampooed every 4 days. Counts and grades were determined initially (4 days after a preparative shampoo) and again at 8, 16, and 24 days, each time just before shampooing.

Results—The mean initial count of 1,328,000 cells/cm^2 fell slightly to 1,270,000 at 8 days, did not change further by 16, and finally decreased a little more to 1,210,000 cells by 24 days. These reductions were not statistically significant even with a two-way analysis of variance. The grades likewise did not significantly decline throughout the 24-day period.

Effect of Shampooing Dandruff Subjects Every 2 Days

Six grade 5 dandruff subjects were shampooed every 2 days for 4 times.

Results—The counts declined from 1,450,000/cm^2 to 860,000/cm^2 2 days after the final shampoo. The signs of dandruff abated as the grades fell to 3.5 two days after the last shampoo.

Comment—A single washing of dandruff subjects disclosed some interesting matters. Immediately afterward, the count was 60% of the preshampoo level, that is to say, two, vigorous 1-min shampooings removed only 40% of the cells. The two 1-min scrubs with a blunt rod for corneocyte counting is far more efficient.

Curiously, the counts did not begin to rise immediately after shampooing. Indeed they were substantially lower 24 hours later. The effect of washing is thus somewhat more complex than one might suppose. Perhaps thorough cleansing of the scalp removes oil and debris which tends to trap desquamating material; hence, loss of scales will be facilitated for perhaps a day or so

until the oil-horn matrix is reconstituted. This may explain why bland shampoos initially lower the corneocyte counts slightly.

The contrasting behavior between heavy dandruff and nondandruff subjects after a single shampoo without further washing for 12 days is noteworthy. In dandruff, the counts approximately reached the initial level by 3 days and by 6 were 40% higher than originally. They leveled off thereafter though steadily increasing. The grades also returned to the prewash level (5.7) by the third day, reaching 7.4 by six. Clinical severity intensified further reaching grade 8 by 9 days. This represents tremendous scaling and was offensive to the subjects. In short, in heavy dandruff subjects, counts and grades were restored in less than 4 days, and continued to increase for the next 8. However, the counts leveled off rather sharply after 6 days, evidently reflecting an equilibrium between the production and loss of horny cells. The grades, however, did not really level off until day 9; the eye perceived a worsening that was not matched by proportionate increases in the counts. This discordance suggests that the larger scales are trapped and therefore easily visualized while the very small ones are shed and are therefore not sampled in the scrubbing procedure.

With nondandruff on the other hand, the counts took about 6 days to be restored to the prewash levels and leveled off thereafter at the equilibrium state. Even by the end of 12 days without washing there was not a trace of dandruff. Grades showed no tendency to increase after the first few days.

Bland shampooing of grade 5 dandruff subjects every 4 days did not significantly decrease the grades or the counts. There was a slight decrease in the counts after the first two shampoos; washing evidently has some effect initially, though limited. Four days is just about the restoration time for moderate dandruff, compared to 3 for severe dandruff. As expected, shampooing grade 5 subjects every 2 days for 4 times sharply decreased the counts and the grades. Too frequent shampooing obliterates the signs of dandruff.

Finally, we did one further test to demonstrate the contrast between dandruff and nondandruff subjects. Five grade 5 subjects and 5 grade 3 ones wore bathing caps sealed to the skin for 21 days. Disregarding squamae in the hair, dandruff did not develop in grade 3 subjects. This belies our previous assertion that nonwashing leads to signs of dandruff (16). The nondandruff subject will not convert through bad hygiene. Horrendous scaling developed in the dandruff subjects who wore caps for 3 weeks. All achieved grades of 9 or 10; malodor became great enough to create personna non grata status for the subjects.

Procedures for Assaying Antidandruff Efficacy

We propose to outline here some schemes which, based on the foregoing findings, have proved valuable for estimating the effectiveness of antidandruff shampoos and hair grooming preparations.

An important tactic has been the repeated evaluation of agents of known efficacy. This type of experience has established the reproducibility of the method and has provided benchmarks for ranking materials comparatively. The bulk of our experience is with shampoos, the most popular form.

Subjects

Institutionalized volunteers are preferable for rigorous control then becomes possible. Women are perhaps less suitable for two reasons: (a) dandruff is probably less severe in the female and hence good subjects are harder to come by; and (b) if the assay includes corneocyte counts, two sites must be clipped, a procedure not cordial to most women.

For routine assays, clinical grading alone is sufficient provided that the subjects have at least grade 5 dandruff. For more conclusive results and especially for comparing agents of differing effectiveness, a complete analysis is preferable; this entails corneocyte counts as well as clinical grading.

Procedure

The procedure for a complete analysis is given in Table I. Ten subjects are sufficient for most purposes. The scheme entails two pretreatment bland shampoos to achieve baseline levels followed by twice weekly washing with the test material for 8 applications. The test terminates on the 28th day but it is often illuminating to return to twice weekly shampooing with the bland detergent for a follow-up period of several weeks. With highly effective shampoos, it may take 4 to 6 weeks before scaling returns to the pretreatment level. Our bland shampoo is a local product* whose ineffectiveness has been established innumerable times. Most nonmedicated shampoos have little or no activity, but it is wise to determine this beforehand. Shampooing consists of two 1-min latherings with rinsing between and afterward. We find it convenient to shampoo every Monday and Thursday; that is at 3- and 4-day intervals alternately. Observations are always made 4 days after shampooing.

*Triethanolamine lauryl sulfate in a mixture of long carbon-chain amides formulated with color and perfume (Druco Shampoo, The Drug House, Inc., 1011 Butler St., Philadelphia, Pa.).

Table I
Protocol for Complete Analysis of a Shampoo

	Pretreatment		Treatment								Post-Treatment
Day	−7	−4	0	3	7	10	14	17	21	24	28
Bland shampoo	x	x									
Test shampoo			x	x	x	x	x	x	x	x	
Grade			x		x		x		x		x
Corneocyte count			x				x				x

Table II
Comparison of 2.0% Zinc Pyrithione Shampoo with the Detergent Base Alone

Material	Corneocyte Count			Clinical Grades		
	Day 0	Day 14	Day 28	Day 0	Day 14	Day 28
Detergent base	1 256 000	1 148 000	1 174 000	5.4	4.9	4.7
Zinc pyrithione	968 000	678 000	732 000	5.6	3.1	1.9

Table III
Comparative Efficacy of ZPT and Selenium Sulfide by Corneocyte Counting
(Geometric Means)

Shampoo	Subjects	Before Treatment (/cm²)	Post-Treatment (/cm²)
Selenium sulfide	16	1 056 000	214 200
Zinc pyrithione	24	904 000	622 700
ZPT detergent base	18	1 169 000	1 041 000
Druco	18	1 150 000	1 040 000

Example I—Complete analysis: A shampoo containing 2% zinc pyrithione* was compared to the detergent base in two groups of 10 men each. The results are shown in Table II. With the base, the corneocyte count decreased slightly and the clinical grade by only 0.7. This difference was not significant ($p = >0.05$). Highly significant decreases occurred with the active material. The mean grade decreased from 5.6 to 1.9 and the count fell by almost a quarter of a million cells, highly significant differences. Effectiveness was already apparent by 14 days.

Example II—Abbreviated test with corneocyte counts: The refinements provided by corneocyte counting are illustrated by the following short-term study. Dandruff subjects were shampooed twice weekly for only four times with a final count 4 days after the last shampoo. Two nonmedicated shampoos were compared to 2.5% selenium sulfide shampoo (Selsun Suspension®†) and 2% zinc pyrithione (Head and Shoulders).

The results are shown in Table III. The counts were not lowered by the two bland shampoos. Significant decreases occurred with both active materials ($p = <0.01$). The effect of the selenium shampoo was greater than zinc pyrithione; this difference was significant ($p = <0.05$). It has repeatedly been our experience that zinc pyrithione acts less rapidly than selenium sulfide. It should be noted that such rapid abatement of dandruff can only be appreciated with highly effective shampoos. Agents of lesser efficacy must be evaluated over a longer period of use.

*Head and Shoulders, Procter & Gamble Co., Cincinnati, Ohio 45224.
†Abbott Co., Chicago, Ill.

Assay of Antidandruff Grooming Agents

Procedure

The test material is applied once daily for 3 weeks; the scalp is shampooed once weekly with a bland shampoo. The control reading is made 7 days after a preparative shampoo and the final one the 28th day (7 days after the last application and shampoo). The longer interval between shampoos increases the reliability of clinical grading by allowing more time for scales to accumulate.

Example

Two per cent zinc pyrithione in Hydrophilic Ointment U.S.P. was compared with Hydrophilic Ointment U.S.P. alone in two groups of 10 men each. The agents were applied once daily for 4 weeks with bland shampooing once weekly. We now recommend 3 weeks of treatment. As a further point of interest, within each group, 5 had dandruff (grade 5) and 5 did not (grade 3). Grades and corneocyte counts were done once weekly.

Results

The corneocyte counts again provided the most eloquent evidence of the difference between treatments. In the dandruff subjects ZPT caused a great reduction from 1.75×10^6 to $4 \times 10^5/cm^2$ by 2 weeks (Fig. 5). Grades paralleled the counts falling from 5.8 to 3.8 by 2 weeks and to 2.7 by 4. These were statistically significant changes ($p = <0.01$). With hydrophilic ointment, the grades only decreased from 5.2 to 4.6. The counts decreased but not significantly so. In the nondandruff group the counts decreased modestly with both formulations. These differences were not significant.

Comment

Only tentative conclusions can be derived from such small samples. It seems unmistakable that effective grooming agents can be recognized with great confidence within 2 weeks provided that the subjects actually have dandruff. Further study is required to establish whether the mild suppressive effect of hydrophilic ointment in subjects with and without dandruff is a real phenomenon. The results suggest that unmedicated cream bases may promote desquamation of finer scales from the surface. It need hardly be questioned that antidandruff effects are obtained more promptly with daily topical application than by twice weekly shampooing with the same active agent.

Discussion

It may be well to state the conceptions which form the foundation for the methods we have described. Dandruff occurs only on the scalp and has a sin-

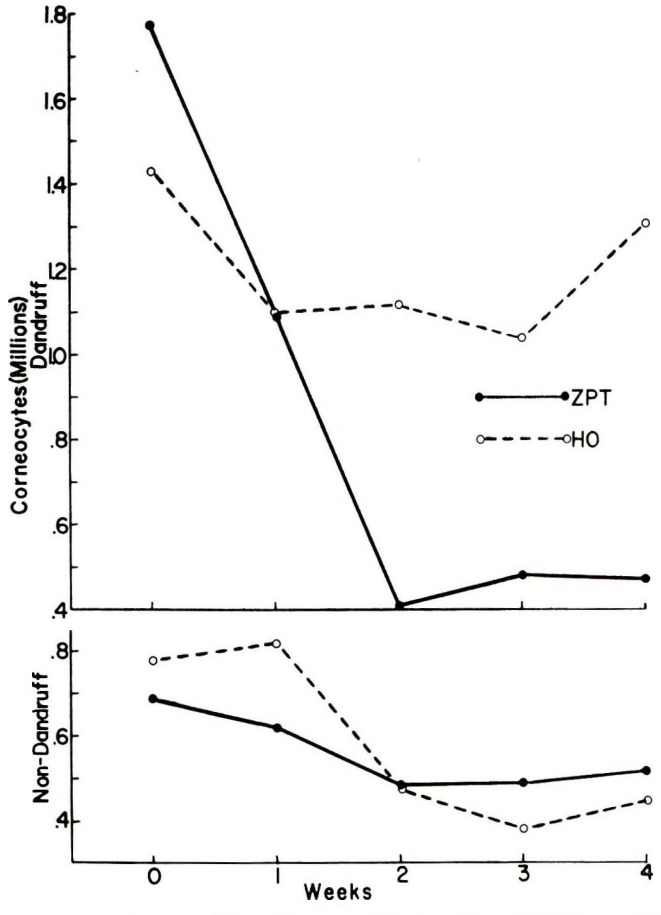

Figure 5. Comparison of nonmedicated cream (Hydrophilic Ointment U.S.P.) with an antidandruff grooming cream containing 0.5% zinc pyrithione in both dandruff and nondandruff subjects

gle manifestation, scaling. The latter is the resultant of two processes: increased production of horny material and increased size of squamae. The condition is perceived because of accelerated epidermopoiesis accompanied by desquamation in large flakes. Epidermal turnover is normally much faster on the head than on the trunk and extremities (7). The exfoliation of horny cells is, of course, a physiologic phenomenon and becomes visible on the scalp because of the protection provided by the hair. Merely shaving the scalp masks dandruff.

There cannot be a sharp division between dandruff and nondandruff since one is dealing with a continuum, a physiologic spectrum. Dandruff is merely an intensified state of desquamation; the difference is quantitative not qualitative. Dandruff is not a disease in this sense.

It is sounder to use the term nondandruff in lieu of normal. Since dandruff blends smoothly into nondandruff, the point on the scale where dandruff begins is necessarily an arbitrary choice. Individuals will view the amount of scaling they have by purely subjective criteria according to their social station, esthetic sensibilities, personal ideas of cleanliness, etc. In a popular poll one would doubtless find that self-estimates of the prevalence of dandruff would increase steadily as one proceeded up the status ladder. This accounts for the very different estimates of the incidence of dandruff. By our criteria, we would regard Roia and Vanderwyks' estimate of 70% (12) to be too high while 2.5% given by Bourne and Jacobs seems too low (11). The vast subjective element is revealed when one puts out a general call for subjects complaining of dandruff. In our experience about 60% of these will be grade 3, that is, with minimal scaling. The consumership for dandruff products probably includes many individuals in this marginal class.

By our criteria about 20% of a young male population will have dandruff of a sufficient degree, grade 5, to warrant their inclusion in panels for antidandruff assays. The mean count for grade 5 is 700,000/cm^2. It is important to appreciate that individual counts may vary from the mean by a good deal. Not all persons with counts higher than this have clinical dandruff while, indeed, some with lower counts do have dandruff. The latter circumstance is considerably more frequent than the former, that is to say, high counts almost always signify dandruff while low ones are not so well correlated with nondandruff.

More study is required of the factors which influence the size of the desquamating flakes. When horny cells separate in large aggregates the subject will have clinical dandruff whether or not the corneocyte count is higher than the average. In the last analysis, the recognition of dandruff is by clinical criteria, by grading. The special value of corneocyte counting is to follow the effect of treatment by objective means and not for classifying individuals. The counts for a given individual are highly reproducible from week to week whether or not dandruff is present.

Corneocyte counting is not only more objective but permits fine focusing beyond the resolving power of the eye. It is more discriminating with regard to judging the rapidity of the response (slope of the curve) and the magnitude of the effect. The corneocyte count has a special capability for detecting cytostatic agents. These directly suppress mitotic activity, an effect which inevitably abolishes dandruff. Topical corticosteroids and nitrogen mustards are effective for this reason (though not indicated in simple dandruff). Among conventional antidandruff agents selenium sulfide is not only antimicrobial but slows down epidermal turnover. This can be demonstrated in two ways. After treatment the counts usually fall to well below the mean for nondandruff subjects. In addition, starting with grades 1 or 2, the counts can be lowered still further to levels never exhibited by an untreated subject, that is, below "normal."

It is important to use strict diagnostic criteria in selecting the test panel. It is all too common for "antidandruff" assays to include patients with seborrheic dermatitis. This reflects the near universal belief that dandruff is merely low-grade seborrheic dermatitis. As a rule, dermatologists do not clearly distinguish between the two and the literature is completely confusing. We shall elsewhere publish observations which argue strongly against the view that seborrheic dermatitis is a severe form of dandruff. The two conditions are quite unrelated.

We pointed out in our first publication that parakeratotic foci were a histologic characteristic of dandruff (16). We now realize that this also occurs in persons without dandruff though to a lesser extent. By appropriately defatting and staining the corneocyte scrub sample one can identify nucleated cells and determine their proportion. This furnishes a simple objective means of distinguishing seborrheic dermatitis in difficult cases where the disease is limited to the scalp. It is inappropriate here to delve into details; suffice it to say that nucleocytes (parakeratotic cells) commonly make up 15 to 25% of the corneocyte count in seborrheic dermatitis and rarely exceed 5% in dandruff. Goldschmidt *et al.* (8) have recently utilized exfoliative cytology to demonstrate the high prevalence of nucleated horny cells in seborrheic dermatitis.

Unnecessarily complicated systems of clinical grading are an outgrowth of the notion that dandruff is unevenly distributed. The tactic employed to deal with this supposed geographic variability is to divide the scalp into segments each of which is separately scored; a composite index of severity is then calculated. Van Abbe and Dean have exceeded all others in inspecting every portion of the scalp. Originally they rated 25 imaginary regions; an examination of one subject took 30 min (4)! In a later "rapid" method, taking 5 min, only four areas were scored. Quite commonly the scalp is divided into 9 imaginary areas (14). We have abandoned all such approaches and form a single global estimate by throwing up some scurf in various sites with a tongue blade.

This study has confirmed what has long been suspected, namely, a distinct seasonal variation in scalp scaling. Dandruff diminishes in the summer; the frequency distributions by season showed an unmistakable increase in the higher grades in winter. We have long been aware that it is more difficult to recruit grade 5 subjects for studies in the summer. On the other hand, Van Abbe has not obtained evidence for seasonal rhythms of this kind (13). It is interesting that Orentreich has detected a seasonal pattern in the rate of scalp hair shedding; the loss is greatest in the fall (19).

Still another misconception besets the appraisal of antidandruff preparations. Laymen and physicians alike are persuaded that dandruff is a fluctuating process, subject to sudden swings in severity from week to week. The extraordinary oscillations in weekly grades portrayed by Van Abbe and Dean (4) for placebo-treated patients are alien to our experience. We consider

dandruff to be a highly stable process with oscillations of a very low magnitude. We rather think that the level of scaling is a steady state characteristic of an individual much as is hair growth or sebum output. Van Abbe and Dean have been so impressed with the fluctuating course of dandruff as to state: "It is essential to compare the progress of a treated panel with an untreated panel running concurrently" (4). This is simply not feasible. In our view, the fluctuations pertain to seborrheic dermatitis. That disease indeed does pursue an erratic course in which sudden exacerbations are a commonplace following emotional traumas, illness of various kinds, etc. The old saying of "getting one's dander up" applies to seborrheic dermatitis not to dandruff. In our experience the level of dandruff does not change appreciably from adulthood to middle age. Dandruff does not spontaneously come and go. A "cure" is impossible.

We have set rather strict time limits within which to judge antidandruff efficacy. Feasibility and economics are important considerations. In the hands of others, assays of shampoos entail about 2 months of treatment. Longer times are not unusual. A prolonged treatment period might result in a judgement of parity for two materials which were in fact different. After protracted use weaker agents may appear to be equally efficaeous in subjects with mild dandruff. As a practical consideration, an agent which has not given satisfaction after 3 weeks of use should not be esteemed.

Products of established value become useful benchmarks for assessing comparative effectiveness. Our reference products are 2.5% selenium sulfide (Selsun Suspension) and 2% zinc pyrithione (Head and Shoulders) shampoos.

In contrast to Orentreich *et al.* (14) who could not distinguish between the two (minimum treatment of 6 weeks), we regard the former as more effective. Improvement can be noted earlier, usually after the second shampoo, and the suppression of scaling is generally greater by 3 weeks. Perhaps parity could be achieved after 6 to 8 weeks of twice weekly shampooing. Since both products have been extensively used and have a known record of performance, these may serve as standards for rating novel formulations. If one has a data base it may not be necessary each time to run the reference material concomitantly.

Half-scalp applications have been utilized to compare two materials on the same individual (20). Paired comparison tests are in fact extensively used in evaluating topical therapies for skin disorders. While admirable in principle, we have shown that a drug which is very active in small amounts may be surprisingly effective at a site far removed from the area of application (21). Thus, neomycin cream to one side or even one area, may decimate the *Staphylococcus aureus* population of dermatitic skin in untreated, distant sites. Translocation of the drug is responsible for this behavior. We have observed the very same phenomenon on the scalp. We applied a 1% aqueous

solution of sodium pyrithione to one-quarter of the scalp of dandruff subjects. By 2 weeks there was a marked and equal improvement over the entire scalp. The scalp is a wet and greasy area where surface currents are certain to bring about a more or less uniform distribution of locally applied substances. We consequently inveigh strongly against half-scalp studies.

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References

(1) Vanderwyk, R. W., and Roia, F. C., The relationship between dandruff and microbial flora of the human scalp, *J. Soc. Cosmet. Chem.*, **15**, 761 (1964).
(2) Finkelstein, P., and Laden, K., An objective method for evaluation of dandruff severity, *Ibid.*, 19, 669 (1968).
(3) Botwinick, C. G., and Botwinick, I., Methods for evaluating anti-dandruff agents, *Proc. Sci. Sect. Toilet Goods Ass.*, **47**, 17 (1967).
(4) Van Abbe, N. J., and Dean, P. M., The clinical evaluation of anti-dandruff shampoos, *J. Soc. Cosmet. Chem.*, **18**, 439 (1967).
(5) Spoor, H. J., Microbiological and clinical study of anti-dandruff agents, *Proc. Sci. Sect. Toilet Goods Ass.*, **23**, 27 (1955).
(6) Alexander, S., Do shampoos affect dandruff, *Brit. J. Dermatol.*, **79**, 92 (1967).
(7) Parran, J. J., and Brinkman, R. E., The effect of human skin surface lipids upon the activity of antimicrobial agents, *J. Invest. Dermatol.*, **45**, 89 (1865).
(8) McGinley, K. J., Marples, R. R., and Plewig, G., A method for visualizing and quantitating the desquamating portion of the human stratum corneum, *Ibid.*, **53**, 107 (1969).
(9) Plewig, G., and Kligman, A. M., The effect of selenium sulfide on epidermal turnover of normal and dandruff scalps, *J. Soc. Cosmet. Chem.*, **20**, 765 (1969).
(10) Cohen, E. L., The relationship of acne with dandruff and seborrheic dermatitis, *Brit. J. Dermatol. Syph*, **57**, 45 (1945).
(11) Bourne, S., and Jacobs, A., Observations on acne seborrhoea and obesity, *Brit. Med. J.*, 1, 1268 (1956).
(12) Roia, F. C., and Vanderwyk, R. W., Resident microbial flora of the human scalp and its relationship to dandruff, *J. Soc. Cosmet. Chem*, **20**, 113 (1969).
(13) Van Abbe, N. J., The investigation of dandruff, *Ibid.*, **15**, 609 (1964).
(14) Orentreich, N., Taylor, E. H., Berger, R. A., and Averbach, R., Comparative study of two anti-dandruff preparations, *J. Pharm. Sci.*, **58**, 1279 (1969).
(15) Goldschmidt, H., and Kligman, A. M., Quantitative estimation of keratin production by the epidermis, *Arch. Dermatol.*, **88**, 709 (1963).
(16) Ackerman, A. B., and Kligman, A. M., Some observations on dandruff, *J. Soc. Cosmet. Chem.*, **20**, 81 (1969).
(17) Goldschmidt, H., and Kligman, A. M., Quantitative estimation of keratin production by the epidermis, *Arch. Dermatol.*, **88**, 709 (1963).
(18) Goldschmidt, H., and Thew, M. A., Exfoliative cytology of psoriasis and other common dermatosis, *Ibid.*, **106**, 476 (1972).
(19) Orentreich, N., Scalp hair replacement in man, *Advan. Biol. Skin*, 9, 99 (1967).
(20) Vanderwyk, R. W., and Hichemy, K. E., A comparison of the bacterial and yeast flora of the human scalp and their effect upon dandruff production, *J. Soc. Cosmet. Chem.* 18, 629 (1967).
(21) Marples, R. R., and Kligman, A. M., Limitations of paired comparisons of topical drugs, *Brit. J. Dermatol.*, **88**, 61 (1973).

Society of Cosmetic Chemists Medal Award to Sabbat J. Strianse

The Society of Cosmetic Chemists presented its 1973 Medal Award to Mr. Sabbat J. Strianse, Vice President in charge of Research and Development of Yardley of London, Inc., Totowa, N.J. The Medal Award, the Society's highest honor, was presented to Mr. Strianse in recognition of the many contributions he has made over the past 30 years to the cosmetic and toiletries industry and to the Society of Cosmetic Chemists organizations in particular.

The formal presentation was made at the December 10th luncheon during the Society's annual meeting by Mr. Robert L. Goldemberg, SCC President, and Mr. Gabriel Barnett, a long-time colleague of Mr. Strianse, acted as Eulogist.

Left to right: Medal Award Chairman Maison G. deNavarre, Medalist Sabbat J. Strianse, Eulogist Gabriel Barnett, and Society President Robert L. Goldemberg

J. Soc. Cosmet. Chem., **25**, 93–98 (February 1974)

Quantitative Aspekte der Aufnahme von Kosmetika durch die Haut

HANS SCHAEFER*

Vortrag anläßlich des VII. IFSCC-Kongresses in Hamburg vom 11.—15. September 1972

Synopsis—Quantitative aspects of absorption of cosmetics by skin.— The physico-chemical processes after application of cosmetics to the skin are related quantitatively to the SKIN'S PHYSIOLOGICAL STRUCTURE AND FUNCTION: The optimum quantity of a COSMETIC CREAM which can be applied to the skin is limited, and only part of it is absorbed by the HORNY LAYER. Beyond a certain depth of the horny layer, the individual components—including the incorporated active constituents—obey their own PENETRATION KINETICS. At the same time, the LIPID-LIKE MATERIALS applied to the skin are continuously diluted by SKIN LIPIDS and transported to the surface. Incorporated solids can also penetrate and remain in deeper layers of the horny layer. The magnitude of this process depends on the PARTICLE SIZE. After a discussion of methods suitable for quantitation of these processes, several points are noted: 1. The penetration of particles can be eliminated by selection of their particle size. 2. The DURATION OF ACTION of a cosmetic preparation on the skin normally lasts about five hours. 3. SO-CALLED "NUTRIENTS" penetrate into living cell layers in such small amounts that any influence on CELL NUTRITION is excluded. 4. It is, nevertheless, possible to influence cells cosmetically by studying the physiological regulation of cell nutrition.

Zunächst soll im Sinne des Themas definiert werden, was unter Aufnahme von Kosmetika durch die Haut zu verstehen ist.

Die Haut als Grenzorgan gegenüber der Umwelt beginnt von außen her mit der anhaftenden Lufthülle und der Behaarung. Hier ist auch das feine Lanugohaar mit einzubeziehen. Jedes Aufbringen von Kosmetika verändert diese Oberfläche, stellt also schon eine Aufnahme dar. Hinzu kommt, daß die Haut — bei entsprechender Vergrößerung betrachtet — ein stark strukturiertes Relief mit Vertiefungen, gebildet von Ausführungsgängen der Haare, der

* Prof. Dr. H. Schaefer, Hautklinik der Freien Universität Berlin im Rudolf-Virchow-Krankenhaus, D-1 Berlin 65, Augustenburger Platz 1.

Schweißdrüsen, aber auch von Mikroverletzungen, zeigt. Durch Auftragen von Kosmetika werden diese Vertiefungen ausgefüllt. Von dort aus erfolgt die Penetration eines kleines Anteils in die Tiefe.

Hier soll eine erste quantitative Angabe erfolgen. Die Frage, wieviel eines Kosmetikums, z. B. einer Creme, optimal auf der Haut verteilt werden kann, ist nicht so selbstverständlich, wie sie erscheint. In eigenen Meßreihen wurde gefunden, daß von einer normalkonsistenten Creme ca. 2 mg/cm² auf einer fettfreien Hautoberfläche verteilt und einmassiert werden können, ohne daß ein sichtbarer bzw. fühlbarer fettartiger Film verbleibt. Durch diese Menge wurden also die genannten Vertiefungen ausgefüllt. Auf die gesamte Gesichtsfläche können grob gerechnet also etwa 0,5 g verteilt werden. Das ist eine recht geringe Menge. Jeder Überschuß bleibt aber filmartig auf der Oberfläche liegen und führt so zu unerwünschten Effekten, wie Wärmestau, Feuchtigkeitsretention durch Behinderung der Abdunstung usw.

Was geschieht nun mit einer derartigen Creme beim Verreiben auf der Haut? Mit Sicherheit wird die Emulsion früher oder später brechen. Dies ist schon unter dem Mikroskop zu beobachten, wenn man Cremes zwischen zwei Objektträgern zerreibt. Das Keratin der Hornschicht wird diesen Vorgang beschleunigen, indem es der Creme Wasser entzieht. Ein Teil der fettartigen Bestandteile und auch des Emulgators wird vom Hautfett aufgenommen.

Anschließend stellt sich konsequenterweise die Frage, was mit Wirkstoffen geschieht, die einem Kosmetikum inkorporiert sind.

Innerhalb der Hornschicht findet zunächst eine physikalisch-chemische Verteilung gemäß dem Henry'schen Verteilungsgesetz statt: Der wasserlösliche Anteil verbleibt in der wäßrigen Phase und wird von dortaus an das wasserhaltige Keratin abgegeben, fettlösliche Anteile gehen von der Fettphase ins Hautfett, zum größten Teil bleibt jedoch der Wirkstoff — zumindest bis zur sogenannten Barriere — in der Grundlage bzw. deren Bestandteilen.

Hier dokumentiert sich also die Schutz-, d. h. Barrierefunktion der Hornschicht. Einerseits wird statisch das aufgebrachte Kosmetikum durch eine nach unten hin sehr kompakt und dicht werdende Hornschicht am weiteren Eindringen gehindert. Andererseits wird es dynamisch durch das Hautfett verdünnt und hierdurch und durch andere Mechanismen wieder nach oben herausgeschoben. Dieser Punkt wird später noch zu diskutieren sein.

Ab der Barriere findet eine Trennung der einzelnen Bestandteile statt. Diese ist naturgemäß nicht selektiv, so daß nur der Wirkstoff tiefer eindringen könnte, jedoch verschiebt sich das Verhältnis von Grundlagenstoffen zu Wirkstoffen, das ursprünglich z. B. 1:100 war, dahingehend, daß jeder einzelne Bestandteil gemäß einer ihm eigenen Penetrationskinetik in die lebenden Schichten der Haut einwandert. Das Verhältnis kann also 1:1 werden, so daß 99 % der

Grundlage in bzw. oberhalb der Hornschicht verbleiben, 1 % der Grundlagenstoffe sowie zwischen 0 und 1 % des inkorporierten Wirkstoffes tiefer eindringen.

Überraschende Ergebnisse werden gesehen, wenn man nun das Schicksal von Festkörpern wie kristallinen und amorphen Substanzen und als Konsequenz daraus auch von Pigmenten o. ä. verfolgt. Diese bleiben nicht etwa auf der Hornschichtoberfläche liegen, sondern dringen sehr schnell, je nach Partikelgröße und Substanz in unterschiedlichen Mengen, in die Tiefe der Hornschicht ein.

So kann man interferenzmikroskopisch noch Festpartikel in 3/4 der Gesamttiefe der Hornschicht nachweisen. Hieraus folgt, daß z. B. Puder nicht nur auf der Hautoberfläche liegen bleibt, sondern in die Hornschicht einwandern kann und auch durch intensives Waschen nur schlecht zu entfernen ist; eigentlich ist dies nur durch Bürsten, also durch mechanischen Abrieb der oberen Hornschichtlagen, möglich. Der Rest verschwindet mit der natürlichen Neubildung der Hornschicht von unten in ca. 4—6 Tagen durch den täglichen Abrieb.

Dies berührt das gesamte Problem des Waschens der Haut. Die Hornschicht kann, wie geschildert, als Reservoir auch für Feststoffe fungieren. Sind diese — wie z. B. Kristalle — nur teillöslich, so werden sie durch intensives Waschen u. U. nicht entfernt, sondern stattdessen tiefgewaschen. Maibach demonstrierte diesen Effekt auf dem letzten internationalen Kongreß für Dermatologie in Venedig. Er zeigte, daß z. B. Insekticide in der Hornschicht abgelagert werden. Wird sofort mit Seife nachgewaschen, so werden ca. 50 % dessen entfernt, was ohne Waschen in den Körper eindringen würde. Wird nach 8 Stunden gewaschen, so dringt die doppelte Menge in den Körper ein, d. h. das im Hornschichtreservoir angesammelte Material wird hierbei nicht heraus-, sondern hineingewaschen.

Was geschieht nun schließlich mit den erwähnten ca. 99 % der Grundlage, die nicht in die lebenden Schichten der Haut einwandern? Deren Schicksal ist abhängig von der hauteigenen Fettproduktion, d. h. der Talgdrüsenfunktion. Wird der Haut das gesamte Fett entzogen, so wird es innerhalb von 5 Stunden wieder vollständig ersetzt. Dieses neugebildete Fett ist auf der Stirn und auf dem Rücken am höchsten, z. B. bis zum Zehnfachen der Menge an den Extremitäten. An den letzteren ist dieser Vorgang auch verlangsamt. Die in der Hornschicht verbleibende Grundlage wird nun mit diesem Hautfett je nach Region stärker oder weniger stark vermengt, d. h. damit nach außen gedrängt. Dieser Prozeß ist im Gesicht ebenfalls nach ca. 5 Stunden abgeschlossen.

Ein zweiter Aspekt ist die starke Quellfähigkeit der Hornschicht durch Wasser und durch fettartige Stoffe beim Verreiben einer Creme. Unter normalen Bedingungen wird die einmassierte Grundlage jedoch unter Entquellen

zum großen Teil wieder herausgedrückt. Beide Prozesse führen dazu, daß der größte Teil wieder auf der Oberfläche erscheint und mit dem natürlichen Abrieb, meist durch unwillkürlichen Kontakt mit den Händen oder der Kleidung, entfernt wird.

Wie sind nun die bisher geschilderten Vorgänge quantitativ kontrollierbar?

Das Schicksal fettartiger Stoffe und damit kosmetischer Cremes kann man mit der von uns entwickelten Glasklötzchenmethode erfassen. Diese bestimmt ausschließlich Hautoberflächenfett, dessen Ab- sowie Zunahme unter natürlichen Bedingungen (1).

Das Eindringen von Wirkstoffen kontrollieren wir, mit wenigen Ausnahmen, mit Hilfe von radiomarkierten Substanzen (2).

Die Struktur der Hautoberfläche ist besonders deutlich in Aufnahmen mit Hilfe des Raster-Elektronenmikroskops zu sehen. Hiermit konnten wir größere scharfkantige Kristalle in der Hornschicht feststecken sehen.

Das Einwandern von Partikeln in die Hornschicht kontrollieren wir, indem wir sie Schicht für Schicht mit Hilfe des Tesafilmabrisses abtragen und auf jedem Abriß unter dem Interferenzmikroskop die Partikel auszählen (3).

Die Rauhigkeit der Hautoberfläche sowie auch ihre Waschbarkeit kann weiterhin sehr gut durch die Methylenblau-Methodik und weitere Methoden von Tronnier verfolgt werden (4) (5).

Aus den angeführten Beobachtungen, die im übrigen nur ausschnittweise erwähnt werden können, sollen schließlich noch einige Konsequenzen für die Kosmetik gezogen werden, zunächst für die dekorative Kosmetik:

Unsere Untersuchungen zeigten, daß nur kleine Partikel in die unteren Hornschichtlagen einwandern. Diese können über mehrere Tage dort liegen bleiben. Sie wandern vor allem dann sehr leicht ein, wenn sie in Fett suspendiert sind. Will man dies — z. B. bei Puder — verhindern, so sollte man die Partikelgröße möglichst über 50 µm, besser sogar über 100 µm halten, also z. B. möglichst kein feingefälltes Aerosil oder ähnliche mikronisierte Bestandteile verwenden und Fett als Grundlage vermeiden.

Für pflegende Kosmetika kann gesagt werden, daß die Wirkungsdauer von Fettstoffen, Wasser und Emulgator im Sinne der Aufweichung einer trocknen und spröden Hornschicht wiederum ca. 5 Stunden beträgt; fettartige Stoffe werden von ihr nicht adhäsiv gebunden. Wasserlösliche können, falls sie vom Keratin gebunden werden, unter Umständen länger verbleiben.

Hierbei gilt es aber, folgende Punkte kritisch zu bedenken: Die Hornschicht enthält normalerweise schon einen großen Anteil an bindungsfähigen Aminosäuren, Kohlenhydraten und ähnliche Verbindungen. Diese liegen im Überschuß vor und sättigen die Bindungszentren des Keratins ab. Dies ist daran zu erkennen, daß ein bestimmter Anteil hiervon leicht extrahierbar ist. Erst Stoffe

mit stärkeren Bindungsvalenzen können diese verdrängen. Eine spezifische Anlagerung, z. B. von Kohlenhydraten, kann daher nur durch physikalisch-chemische Methoden belegt werden, die diese höhere Bindungsenergie erfassen.

Zum Schluß noch einige Anmerkungen zu der sogenannten „nährenden Kosmetik": Hier muß zunächst ein vielfach mißbrauchter Begriff klar definiert werden. Eine effektive Nährstoffzufuhr im Sinne einer Nahrungsaufnahme ist für die Haut von außen nicht möglich. Denn ernährt werden können und müssen lebende Zellen, d. h., bei der Hornschicht kann und darf man nicht von Ernährung sprechen. Hauptnährstoff für die Zellen, also vor allem die Epidermiszelle, sind Glucose, Aminosäuren, organische Phosphate und Sulfate. Diese durchdringen die Hornschicht von außen jedoch nicht in einer Größenordnung, daß sie die von innen nachgelieferten Mengen relevant, d. h. mit positiven Konsequenzen, steigern könnten. Als Faustregel kann gelten, daß nur weniger als 1 % des inneren Vorrats von außen zugefügt werden kann. Selbst dieser minimale Überschuß ist in wenigen Minuten bis Stunden verbraucht.

Das Thema der externen Zuführung von Vitaminen ist noch nicht abgeklärt. Für die wasserlöslichen Vitamine ist die Wahrscheinlichkeit sehr gering, daß ihre Zufuhr von außen den natürlichen Vorrat relevant verstärken kann. Kompliziert werden die Zusammenhänge bei Vitamin C, der Ascorbinsäure. Dieses wasserlösliche Vitamin ist auf der Hautoberfläche extrem leicht oxidabel, es erhöht jedoch in der Hornschicht gleichzeitig das Reduktionspotential. Inwieweit dies Auswirkungen auf die darunterliegende Epidermis hat, müßte noch näher untersucht werden.

Fettlösliche Vitamine penetrieren mit hoher Wahrscheinlichkeit ausreichend.

In bezug auf alle Vitamine muß jedoch die Frage des möglichen Angriffspunktes gestellt werden. Hierbei ist zu bedenken, daß die Epidermis ein langsam wachsendes Organ ist und demzufolge recht träge reagiert. Schließlich sind Vitamine per definitionem keine Nährstoffe, sondern Cofaktoren für biochemische Prozesse.

Daß man hiermit auch des Guten zuviel tun kann, zeigt das Beispiel des Vitamin A. In hohen Dosen ist es toxisch für die Haut, in unterschwelligen Mengen jedoch kann es für die Therapie ausgenutzt werden. Seine therapeutische Wirkung ist dann aber von einer vitaminartigen Wirkung streng zu trennen. Im Sinne einer guten Verträglichkeit sind diese Mengen kosmetisch nicht anwendbar.

Wenn nun die Ernährung der Haut von außen nicht möglich und an sich auch nicht sinnvoll ist, so bleibt zu fragen, ob eine Beeinflussung der Ernährung vernünftig ist.

Hierbei kann man von folgenden Voraussetzungen ausgehen: Von der Biochemie der Zelle her besitzt die Haut normalerweise eine 100fache Reserve an

Enzymen, Substraten, usw. d. h., die Grundprozesse sind regulativ auf 1 % begrenzt. Bei der Altershaut als Extremfall einer kosmetisch gestörten Haut ist diese Regulation gestört. Es sind extracellulär, intracellulär und an den Gefäßen Alterungsprozesse abgelaufen, die zu Ablagerungen u. a. führen.

Regelfaktoren für die biochemischen Vorgänge sind vor allem Hormone und Stoffe mit hormonartiger Wirkung. Man sollte sich nicht durch die heute noch verallgemeinerte Auffassung irritieren lassen, daß Hormone therapeutisch verwandt werden und deshalb für Kosmetika verboten sind; denn in der Therapie werden wiederum (wie beim Vitamin A) Dosen angewandt, die weit über den zur normalen Regulation der Haut benötigten Mengen liegen und deshalb andersartige Effekte zeigen. So läßt z. B. der normale Vorrat der Haut an Hydrocortison die Entzündungsbereitschaft unbeeinflußt. Erst ein vielfacher Überschuß senkt sie. Die physiologische Regulation ist nun ein Gleichgewicht des Einflusses mehrerer Faktoren. Bei der Altershaut fallen hiervon einzelne mit Sicherheit aus. Theoretisch ist es unschwer vorstellbar, daß einerseits diese Faktoren von außen in einer solchen Quantität ersetzt werden, daß Alterungsprozesse aufgehalten werden, und daß andererseits die gesamte zugeführte Menge in der Haut quasi aufgebraucht wird, also fast nichts in den Körper eindringt. Man hätte es also mit einer Hormonsubstitution ausschließlich für die Haut zu tun. An diesem Punkt sollte eine intensive kosmetische Forschung in Zusammenarbeit mit dermatologischen Forschungsgruppen einsetzen. Die methodischen Grundlagen sind vorhanden, ein kleiner Ausschnitt hierzu konnte hier dargestellt werden.

LITERATUR

(1) Schaefer, H., und Kuhn-Bussius, H., *Arch. klin. exp. Dermatol.* 238, 429 (1970).
(2) Zesch, A., und Schaefer, H., *Arch. klin. exp. Dermatol.* (im Druck)
(3) Wolter, K., Schaefer, H., Frömming, K. H., und Stüttgen, G., *Fette, Seifen, Anstrichmittel* 72, 990 (1970).
(4) Tronnier, H., Schuster, G., und Hampe, H., *Fette, Seifen, Anstrichmittel* 72, 381 (1970).
(5) Tronnier, H., *Fette, Seifen, Anstrichmittel* 67, 512 (1965).

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The Scientific Basis for FDA Regulatory Activities in Cosmetics

ALFRED WEISSLER, Ph.D.*

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Synopsis—Increased safety for users of COSMETICS is the goal of Food and Drug Administration activities in cosmetics. In order for these activities to be effective, they must have a sound SCIENTIFIC BASIS. This paper surveys the scientific projects and capabilities at FDA in the field of cosmetics, in terms of their impingement on regulatory matters.

It deserves note that the scientific basis for REGULATORY ACTIONS may involve not only facts, but also judgments as well; the reason is that in some cases the available factual information is not complete or definitive. A brief discussion is given of recent examples, such as bubble baths, asbestos in talcum powders, and mercury preservatives in cosmetics.

Introduction

The goal here is to promote a better understanding of Food and Drug Administration's scientific work in cosmetics, as a basis for its regulatory activities. There are three broad areas that deserve discussion: the scientific resources at FDA, the operations and guidelines, and a few examples of the sometimes difficult transition from scientific knowledge to official regulations.

Scientific Resources

Approximately 1% of the overall FDA budget is allocated to cosmetics. Part of this is used to maintain about 16 people (mainly inspectors) in the regional offices. The balance is for the support of roughly 36 people plus overhead in Washington. Half of these are chemists, and there are also one medical officer (a dermatologist), 2 microbiologists, 5 secretaries, 8 people in toxicology, and 2 in the Office of Compliance. The 18 chemists are divided just about equally into three groups: the voluntary registries group, the methods

*Division of Color Technology, Food and Drug Administration, U.S. Department of Health, Education, and Welfare, Washington, D.C. 20204.

development group, and the sample analysis group. Although space is at a premium in the FDA laboratory building and there is some crowding, we have good equipment for instrumental analysis. There are adequate gas chromatographs and ir and uv spectrophotometers, as well as a fluorospectrophotometer and a mercury cold vapor atomic absorption apparatus. We are also acquiring an automated X-ray powder diffractometer and a differential thermal analysis instrument, for use in the determination of asbestos in talcum powders and for the identification of other crystalline materials. In addition, FDA cosmetics scientists have access to instruments for such specialized techniques as nuclear magnetic resonance, radioisotope counting, mass spectrometry, and high-pressure liquid chromatography when the need arises.

Operations and Guidelines

The operations, missions, and guiding philosophy in the cosmetics scientific program at FDA can be understood best by means of a historical perspective. For many years, FDA's work in cosmetic chemistry was shaped by the wording of Section 601(a) of the Federal Food, Drug, and Cosmetic Act of 1938, which states that a cosmetic shall be deemed to be adulterated "If it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or under such conditions of use as are customary or usual; Provided, That this provision shall not apply to coal-tar hair dye, the label of which bears the following legend conspicuously displayed thereon; 'Caution—This product contains ingredients which may cause skin irritation on certain individuals and preliminary test according to accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.', and the labeling of which bears adequate directions for such preliminary testing. For the purposes of this paragraph and paragraph (e) the term 'hair dye' shall not include eyelash dyes or eyebrow dyes."

Therefore, the main responsibility imposed on FDA by this law was to determine whether particular substances are present in cosmetic products, which are poisonous or deleterious in the amounts present. This led to pioneering work at FDA on the analytical chemistry of cosmetics, under such notable figures as G. Robert Clark, John H. Jones, and Sylvan H. Newburger. Dr. Newburger's "Manual of Cosmetic Analysis"(1) was published more than 10 years ago and is still the only book in its field. After having been out of print for several years, it was recently reprinted and is again available for purchase from the Association of Agricultural Chemists in Washington, D.C.

We continue to do some methods development work. For example, a well-known fluorometric method for formaldehyde (2) was adapted for use in shampoos and other cosmetic products (3). This excellent procedure consists

of reacting the formaldehyde with acetylacetone and ammonia, to yield a dihydrolutidine derivative which is intensely fluorescent. The method is highly sensitive, and can easily determine 0.001% of formaldehyde in a product. In other aspects of our methods research, we are making some use of nuclear magnetic resonance for the identification of ethoxylated compounds, and are trying to apply the highly specific techniques of enzymatic analysis to cosmetics ingredients.

As noted earlier, cosmetic chemists at FDA perform sample analyses and voluntary registries work, as well as the methods development just discussed. Parenthetically, the voluntary registries workload has grown so much that it was necessary to divert some extra manpower into it, at the expense of the laboratory projects on methods and sample analysis.

The cosmetics sample analysis work grows out of our consumer complaint system, which is based on the following rationale. In order to provide protection against unsafe cosmetics, it is not enough to monitor products for the presence of previously recognized poisonous or deleterious substances. In addition, it is necessary to identify new safety hazards which may be associated with the use of a novel ingredient, or an unrecognized toxicity of a familiar ingredient, or combinations of ingredients which may interact chemically or biologically to produce an adverse reaction in the consumer. To accomplish this objective, we maintain a central file of all cosmetics injury complaints received by FDA and we use this epidemiological data as a basis for much of our effort aimed at increased safety.

In 1970, we received 227 complaints of adverse reactions to cosmetics, and in 1971, the number increased to 314; their distribution by product category is shown in Table I. The annual number of complaints continues to increase: in 1972, there were 377, and we have already received close to 300 in the first five months of 1973. This rapid rise is probably attributable more to a growing public awareness of FDA activities in cosmetics than to any sharp increase in the safety hazard of cosmetic products. In any case, a larger number of complaints provides a broader data base and greater validity for our attempts to pinpoint safety hazards of cosmetics as reflected in actual human experience. (That is why we are looking forward to the proposed voluntary reporting by manufacturers of their own data on consumer product experience.)

Each complaint that comes in to FDA under the present system is reviewed by a panel consisting of the dermatologist and the senior cosmetics chemists. In some cases (about 120 per year) a decision is made to perform laboratory examination of a sample of the product associated with the complaint. Most often, this is a chemical analysis for the major components and for any especially significant substances, such as lead in toothpaste or mercury preservatives. In addition, some samples are examined for microbiological contamination (under Section 601c which states that a cosmetic is deemed to be adulterated "If it has been prepared, packed, or held under insanitary

Table I
FDA—Division of Colors and Cosmetics Technology Cosmetic Injury Complaints

Cosmetic Class	1970 Number	1970 Companies	1970 Per Cent	1971 Number	1971 Companies	1971 Per Cent
Baby preparations	1	1	0.4	...	...	...
Bath preparations	25	9	11.1	27	16	8.6
Creams—general	15	13	6.6	9	6	2.8
Dentrifices and mouth washes	21	6	9.4	12	7	3.8
Deodorants and antiperspirants	16	10	7.0	37	17	11.8
Depilatories	3	3	1.3	2	2	0.6
Detergent bars	4	4	1.8	4	3	1.3
Eye preparations	16	16	7.0	22	13	7.0
Facial makeup, powder, and rouge	8	8	3.5	15	15	4.8
Facial packs, masks, straps, etc.	3	3	1.3	...	...	...
Hair cosmetics:	(67)	...	(29.5)	(122)	(61)	(38.9)
Bleaches	3	3	1.3	6	4	1.9
Preparations	13	12	5.7	9	7	2.9
Dyes and color rinses	8	8	3.5	31	15	9.9
Shampoos	19	10	8.5	44	16	14.0
Straighteners	5	4	2.2	6	4	1.9
Wave sets, lacquers	12	10	5.3	18	11	5.7
Waves—cold/permanent	7	5	3.1	4	4	1.3
Hand preparations	1	1	0.4	4	4	1.3
Leg makeup	...	...	...	...	...	...
Lipsticks	5	5	2.2	6	6	1.9
Lotions	...	...	...	4	3	1.3
Miscellaneous	6	6	2.6	12	10	3.8
Nail preparations	14	11	6.2	11	10	3.6
Perfumes and colognes	2	2	.9	7	6	2.2
Shave preparations	3	3	1.3	4	4	1.3
Skin bleaches and lighteners	6	3	2.6	9	4	2.8
Skin fresheners	6	3	2.6	4	3	1.3
Sunscreens and suntan preparations	5	4	2.2	7	5	2.2
Tattoo pigments	...	...	...	...	...	...
Totals	227		100.0	314		100.0

conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health") or for toxicological properties (such as skin irritation or eye hazard) when appropriate to the nature of the complaint.

Cosmetics toxicology at FDA has of course gone hand-in-hand with cosmetics chemistry. The very wording of Section 601(a) implies the need for criteria to determine whether a given substance is "poisonous or deleterious" and if so, at what concentrations. Consequently, pioneering work on eye ir-

ritation tests and other toxicological characteristics of cosmetics ingredients was carried out by Draize and others (4); methodology in this area is still undergoing further refinements. Some other subjects of current interest in cosmetics toxicology at FDA are: sensitization phenomena, percutaneous absorption, and aerosol inhalation toxicity. In addition, one of the most important aims at this time is to define the types of safety testing for each class of cosmetics, which should be used by the manufacturer to assure himself of the safety of his product.

Science as Basis for Regulations

After this brief survey of FDA scientific activities relating to cosmetics, let us consider next the process of utilizing scientific knowledge in the establishment of official regulations or in other regulatory decisions. The transition from science to regulatory decision is not always easy and straightforward, because of any of a number of reasons, such as:

1. Incomplete factual information on toxicity.
2. Difficulty of extrapolating laboratory animal testing to humans.
3. Absence of an adequate analytical method for a suspect substance, which may be present only in traces.
4. The difficulty in setting limits in each individual case for the frequency and severity of adverse reactions beyond which corrective action must be taken. In other words, if our goal is "safe" cosmetics, quantitatively how safe is "safe"?
5. A new product will often generate a wave of complaints, which may gradually subside (Fig. 1) even if corrective action is delayed.

Inevitably, then, judgmental factors as well as factual scientific data are sometimes involved in the regulatory process. Some recent examples can illustrate this.

One example is the prohibition by FDA of the use of mercury preservatives in cosmetics, except for eye-area cosmetics where up to 65 ppm of mercury is permitted if no safe and effective substitute is available. This regulation was published in the Federal Register in January 1973, after extended consideration of the subject. The scientific informaion available as a basis for this regulatory action included data showing that some mercury compounds are absorbed through the intact skin, data on the levels of mercury preservatives used in cosmetics (typically between 5 and 50 ppm), and some data on the differential toxicity of inorganic mercury, phenylmercury, and methylmercury compounds. Further, we had the benefit of a judgment by FDA in 1970 that the safety limit for ingestion of methylmercury in fish corresponded to 30 μg of mercury per adult per day. Simple calculations showed that the use of 0.1 g of mercury-preserved eye makeup daily would not contribute more than 10% or 20% of the permissible mercury exposure, but the daily use of 10 g of a mercury-preserved body lotion could potentially far exceed the

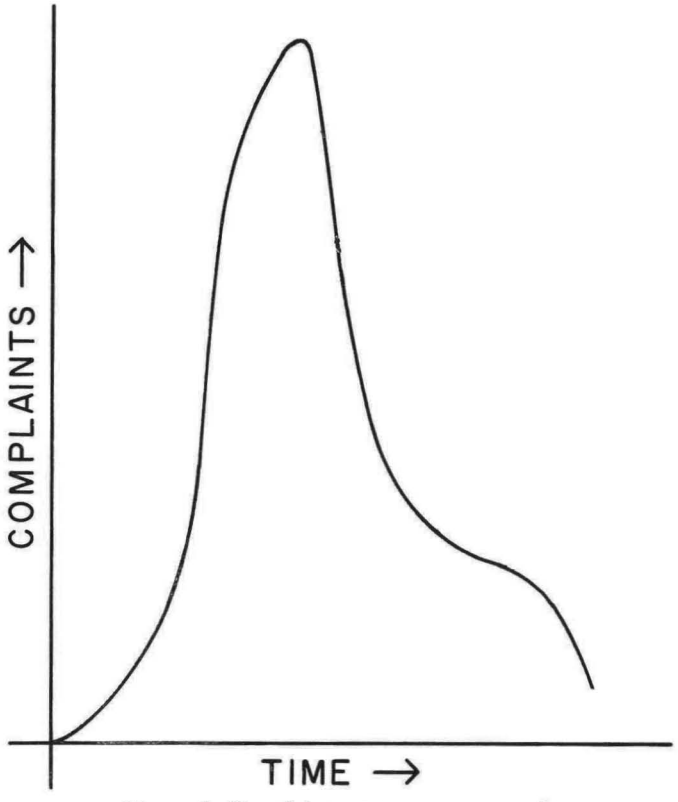


Figure 1. Complaint rate on a new product

safety limit. Even though it might have been simpler to prohibit the use of mercury preservatives in all cosmetics, we made the judgment that the outstanding efficacy of mercury against such dangerous eye pathogens as *Pseudomonas aeruginosa* conferred a benefit which greatly overbalanced the small risk of systemic mercury toxicity, in the use of mercury preservatives in eye cosmetics.

Approval was asked by one company for the use of mercury preservatives in protein shampoos and other hair preparations. It is quite possible that mercury in products applied to the hair is fixed by cystine and other sulfur compounds in hair, and becomes unavailable for systemic adsorption. However, in the absence of definitive scientific data showing this to be true, FDA was unable to give approval for the use of mercury preservatives in hair preparations.

A second example of incomplete scientific knowledge in the face of a regulatory problem has to do with the use of ionizing radiation (such as cobalt-60 gamma rays) for the sterilization of cosmetics ingredients and/or finished products. Claims were made, for example, that color additives used in cosmet-

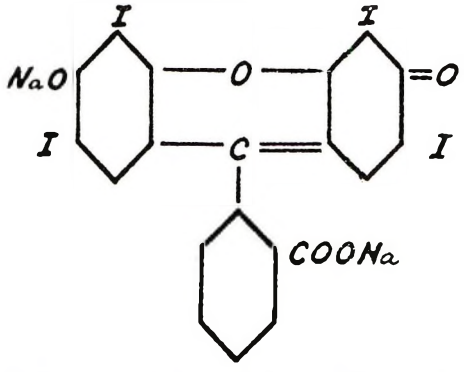


Figure 2. Structure of FD and C Red No. 3 (erythrosine)

ics could be radiation sterilized with safety. Now, it is well-known that irradiation of complex aqueous systems may cause many unpredictable chemical changes including hydroxylation, dehalogenation, or rupture of aromatic rings. In order to get more specific information, we undertook a study of the effects of cobalt-60 irradiation on FD and C Red No. 3, the structure of which is shown in Fig. 2. Doses ranging from 0.2 up to 5.0 megarad (Mr) were used. The irradiated sample and an unirradiated control were analyzed side-by-side by means of the FDA column chromatography procedure which we use regularly for the certification analysis of Red No. 3 batches.

After 30 minutes of development on a Solkafloc column, the control (unirradiated Red No. 3 solution) showed a relatively homogeneous band of color moving down the column. By contrast, a sample of solution irradiated with 5 Mr showed both a new, faster component much farther down the column and a much slower component, of deep rose color, still at the top of the column. More careful examination of the consecutive eluted fractions showed a half-dozen different color fractions in the irradiated solution.

Table II summarizes the quantitative results on the destruction of Red No. 3 by irradiation, as calculated from spectrophotometry of the column fractions shown previously. A 5-Mr dose converted all of the Red No. 3 in a 0.1% solution into unknown fractions; nothing measurable remained which has the absorption spectrum of the original tetraiodofluorescein. At a dose of 1 Mr, about half of the Red No. 3 in a 0.1% solution is destroyed. However, for Red No. 3 in the solid state, a dose of 5 Mr causes only about 1% destruction.

The results of this and related work, including irradiation of some other organic colors, did provide a portion of the scientific knowledge needed. We also have access to some physical and chemical tests on a sample of ferric oxide color additive before and after irradiation. But a large amount of further information must be obtained, regarding radiation effects on organic and inorganic color additives as well as on complex mixtures used in cos-

Table II
Irradiation of FD and C Red No. 3
Column Chromatography Fractions[a]

Fraction	Powder (as Received)		0.1% Solution				1% Soln
	Control	5 Mr	Control	0.2 Mr	1.0 Mr	5 Mr	5 Mr
Unknown	...	...	...	First 2 and last	First 2 and last	All	First 2 and last
2,4,7-Triiodo-fluorescein	0.06	0.05	...	2.04	4.05	...	...
2,4,5-Triiodo-fluorescein	2.66	2.55	2.77	3.81	6.3	...	6.4
2,4,5,7-Tetraiodo-fluorescein	85.5	84.5	85.3	72.5	36.6 1.6	...	44.7 6.5
Totals of known fractions	88.2	87.1	88.1	78.2	48.6	0	57.6

[a]Figures given as percentages.

metics, before it will be possible to make the transition from scientific knowledge to official action approving the safety of radiation sterilization.

A third case in point is provided by the bubble baths. An overwhelming weight of evidence had accumulated to show that at least two popular brands of inexpensive bubble bath powders were causing large numbers of genito-urinary rashes, inflammations, and in some cases infections or other serious conditions, especially in young girls but in others as well. Animal testing did not appear to be a useful tool for prediction of this type of human adverse reaction. We made the hypothesis that the cause was the powerful detergent action of the alkylarylsulfonates which constituted about 35% by weight of the two brands of powder bubble bath involved; the detergent action could cause removal of the normal oily protective secretions from the body surface, and open a pathway for inflammations or infections. It was of course not possible to check this hypothesis by large-scale experiments on human children. Even so, the judgment was made to request the manufacturers to cut drastically the percentage of alkylarylsulfonate used in their bubble baths. The number of bubble bath complaints was observed to drop after this reformulation, but there continue to be enough complaints to warrant some further consideration of this problem.

A fourth and last example of the distance from scientific knowledge to regulatory action is provided by asbestos in talcum powder cosmetics. There are certain facts which are well-established, as for example:

A. Asbestos occurs in a half-dozen varieties, of which two, chrysotile and tremolite, are often found as natural contaminants in talc. (All three minerals are magnesium silicates and may contain other elements as well.)

B. Asbestos workers exposed to inhalation of chrysotile asbestos fibers have a much higher risk of developing lung cancer and mesothelioma than the general population.

C. The U.S. Occupational Safety and Health Administration has established an upper limit of 5 asbestos fibers per ml of inhaled air for a 40-hour workweek of occupational exposure; this applies only to fibers longer than 5 μ. The limit is scheduled to be cut down from 5 to 2 fibers per ml of air in 1976.

D. No single analytical technique is entirely satisfactory for the determination of small amounts of asbestos in talc, at levels of 1% or less. Among the techniques which have been used are X-ray diffraction, optical microscopy, differential thermal analysis, electron microscopy, and electron diffraction, but the results are not always in agreement.

Additional relevant facts could be listed, but it is interesting also to note the large number of scientific questions for which answers are not yet available, such as:

1. Is tremolite asbestos as hazardous to inhale as chrysotile asbestos?
2. Can asbestos fibers shorter than 5 μ be ignored as a biological hazard?
3. Are nonasbestos fibers, such as glass wool, equally capable of causing lung cancer?
4. How many asbestos fibers will be inhaled as a result of each normal application of a talcum powder containing, for example, 1% of asbestos as a natural contaminant?
5. In samples which contain mineralogical species that are intermediate or transitional between talc and asbestos, what degree of biological hazard and regulatory sanctions should be associated with the transitional species?

In the face of such gaps in scientific knowledge, it is not easy to write a regulation which will apply a simple, straightforward analytical procedure to screen out those talcum powder cosmetics which contain asbestos in detectable and hazardous amounts, and thus provide the full measure of protection needed by the consuming public without imposing impossible constraints on industry. Even though this task is not easy, it is one which faces us at present and cannot be avoided. In approaching it, we must make use of the best possible scientific knowledge and judgments. That is the essence of our scientific activities in cosmetics at FDA, and the key to whatever success we hope to achieve: namely, to develop and maintain the best possible scientific knowledge and judgments.

(Received May 25, 1973)

References

(1) Newburger, S. H., *A Manual of Cosmetic Analysis*, Association of Official Analytical Chemists, P.O. Box 540, Washington, D.C. 20044, 1962.
(2) Belman, S., The fluorimetric determination of formaldehyde, *Anal. Chim. Acta.*, **29**, 120–6 (1963).
(3) Wilson, C. H., Fluorometric determination of formaldehyde in cosmetic products, *J. Soc. Cosmet. Chem.*, **25**, 67–71 (1974).
(4) Draize, J. H., and Kelley, E. A., Surface-active agents and the eye, *Drug Cosmet. Ind.*, **71**, 36–7, 118–20 (1952).

Society of Cosmetic Chemists Literature Award to Dr. John F. Corbett

The 1973 Society of Cosmetic Chemists Literature Award was presented to Dr. John F. Corbett, Director of Chemical Research at Clairol Research Laboratory in Stamford, Conn., at the Society's Annual Scientific Meeting held in New York City.

Formal presentation of the award was made to Dr. Corbett by Mr. Robert Goldemberg, the 1973 President of the Society, during the luncheon ceremonies on December 11th. The award consists of a scroll and an honorarium of $1,500. Dr. Corbett was honored for his original research work in the field of organic and dye chemistry.

Left to right: Society President Robert L. Goldemberg and Literature Award recipient John F. Corbett

Book Reviews

KOSMETIKUM FEINSEIFE, ABRISS SEINER TECHNOLOGIE, by Dieter Osteroth, Dr. Alfred Huthig Verlag GmbH, Heidelberg, 1972. × + 152 pages, illustrated and indexed.

In contrast to their American colleagues, cosmetic chemists in Europe show a great deal of interest in the production of high-grade soap toilet bars. It is not surprising, therefore, to find that the recently begun series of monographs on cosmetics includes this survey of the technology of cosmetic soaps.

Most of this volume is devoted to a description of the industrial equipment needed to produce the type of soap commonly referred to as French milled in the United States. The emphasis throughout the book is on production, not on chemistry or physics of the resulting product. A series of chapters is devoted to saponification and the production of basic soap either by the batch process or by the continuous processes developed by Mazzoni or by Lurgi, while the older Sharples process is mentioned only in passing. The equipment required for the production of the milled soap and the necessary roller mills, plodders, and presses are described in much detail.

The author's major concern are commercial European installations and flow diagrams. This booklet is expected to be of primary interest to those American readers who are involved in soap production. Only a few pages are devoted to the chemical problems which may occur during the production of toilet soaps. These few pages plus the 10–15 pages concerned with deodorants, super fatting agents, etc., comprise the portion of the book which would be of interest to typical American cosmetic chemists. It is particularly unfortunate that the book evidently went to press early during 1972 and is, therefore, already hopelessly out of date in view of Governmental regulations banning many of the additives still listed in this volume.

This book can be recommended to anyone who is interested in the production of a high quality soap by the sophisticated processes developed in recent years in Europe. To the scientist who is interested in the chemistry and the physics of soap bars this book will be a great disappointment.—MARTIN M. RIEGER—Warner Lambert

THE PHYSIOLOGY AND PATHOPHYSIOLOGY OF THE SKIN, Vols. 1 and II, edited by A. Jarrett, Academic Press Inc., New York, 1973. Vol. I, 343 pages, price 7.50 pounds; Vol. II, 805 pages, 9.80 pounds; both volumes are illustrated.

This is a remarkable new book which brings together the contents of hundreds of papers on the normal and abnormal skin. It should be especially interesting and useful to the practicing dermatologist in providing him with a sound reference source for skin diseases and their underlying causes, and in helping him solve some of his clinical problems.

The book stresses the dynamic nature of the skin as a constantly changing organ. Volume I is concerned with the anatomy and physiology of normal and abnormal epidermis in relation to its turnover and keratinization. Chapter 2, "The Biochemistry of the Epidermis," is of special interest to the cosmetic chemist. Volume II deals with the anatomy, physiology, experimental psychology, and pathology of the cutaneous blood vessels and nerves.

One of the strengths of the work is the number of good quality illustrations and photomicrographs of the normal and abnormal skin. The book is written primarily for the practicing dermatologist to give him a background in skin physiology on which to base his diagnoses, but it will also be of interest to some cosmetic scientists, especially toxicologists. A superficial treatment of allergic skin diseases, especially related to cosmetics and other environmental chemicals, is one of the chief drawbacks of the book. The other drawback is a rather brief index, which is only partially overcome by the outlines preceding each chapter. I would recommend the book for inclusion in the library of every institution where epidermal toxicity and anatomy are of primary concern.—CHARLES O. WARD,—St. John's University, College of Pharmacy and Allied Health Professions

COSMETICS: SCIENCE AND TECHNOLOGY, 2nd Ed., edited by M. S. Balsam and Edward Sagarin, Wiley-Interscience, New York, 1972. Vol. 1, xvii + 605 pages, indexed. Vol. 2, xii + 691 pages, indexed. Price $47.50 for two volumes.

The first two volumes of the long-awaited second edition of the thumb-worn Sagarin treatise that we have all used for 15 years are finally with us. In this edition, Edward Sagarin has been joined by Marvin S. Balsam as co-editor, and they have assembled a distinguished Editorial Board.

The work generally succeeds in its goal. Many chapters provide an excellent balance of history, theory, practice, prototype formulas, and exhaustive coverage of the literature. To the extent that it reflects what is in the public literature and what is in the author's experience, I am sure the information is dependable. As to whether each chapter truly reflects industry-wide practice, there is

some question. Furthermore, it should have been pointed out (where appropriate) that formulations of the type offered in many chapters are only suggested starting points for product development (like a supplier's formulary), and are not ready-to-market products. As an example, a cream formula taken from one chapter was made in our laboratory and was found to have emulsion stability measured in days rather than months or years.

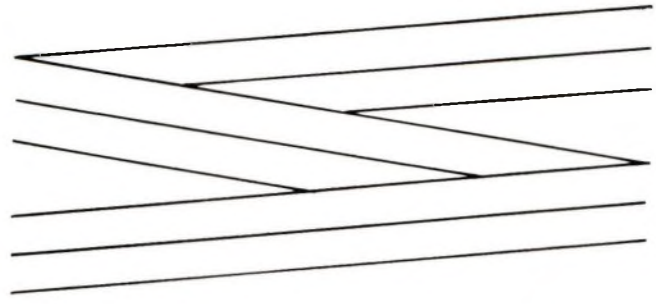
The planning and editing are to be commended. There is clear evidence of serious effort to avoid excessive repetition and overlapping. Someone has worked hard to make the language work toward straightforward communication. The trade name indexes and author indexes are valuable features, but the subject indexes are sadly deficient. The paper, printing, and binding seem to be of good quality. The proofreading is excellent, in general, though a few misspellings do occur. One chapter gives glyceryl monostearate (standard throughout the book) on p. 351 and glycerol monostearate on p. 366, illustrating the difficult problem of nomenclature.

To summarize, we are fortunate to have the benefit of the enormous effort that has gone into this major reference. We look forward to the third volume and hope that we will not have to wait as long for the third edition as we did for the second. Our industry and cosmetic science are moving too fast.—MURRAY BERDICK—Chesebrough-Pond's Inc.

Society of Cosmetic Chemists 1973 Merit Award Presentation

The 1973 Society of Cosmetic Chemists Merit Award was presented to Phyllis J. Carter of I.C.I. America, Inc., Wilmington, Del., at the December 11th luncheon during the Society's Annual Scientific Meeting in New York City. The award was given to Ms. Carter in recognition of her outstanding service to the Society through the years. She served as SCC Director in 1955, and from 1969 through 1972. She was Newsletter Chairman in 1973, Public Relations Chairman in 1966-67, and held numerous other local chapter SCC posts.

Left to right: 1974 Society President Hyman Henkin, Merit Award recipient Phyllis J. Carter, Merit Award Chairman Stanley Brechner, and 1973 Society President Robert L. Goldemberg



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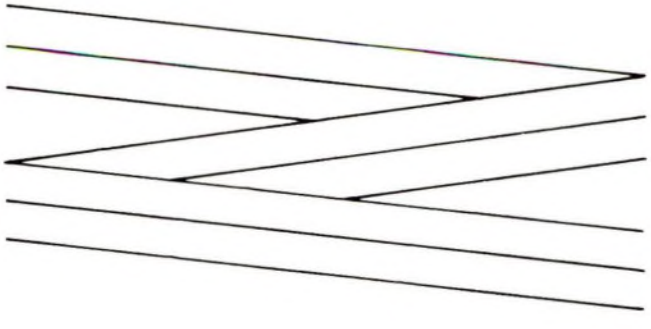

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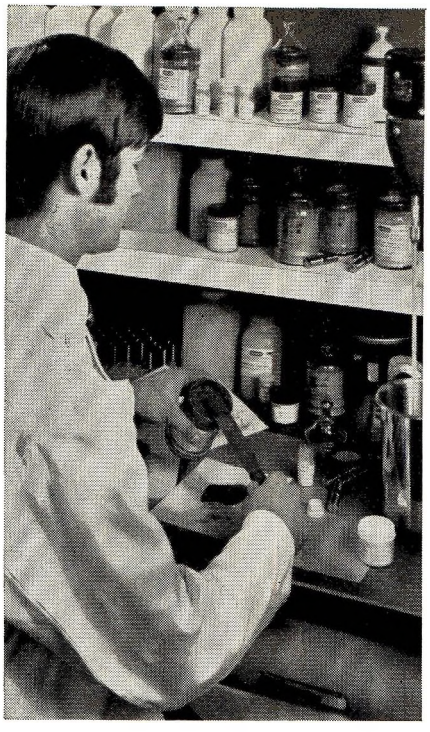

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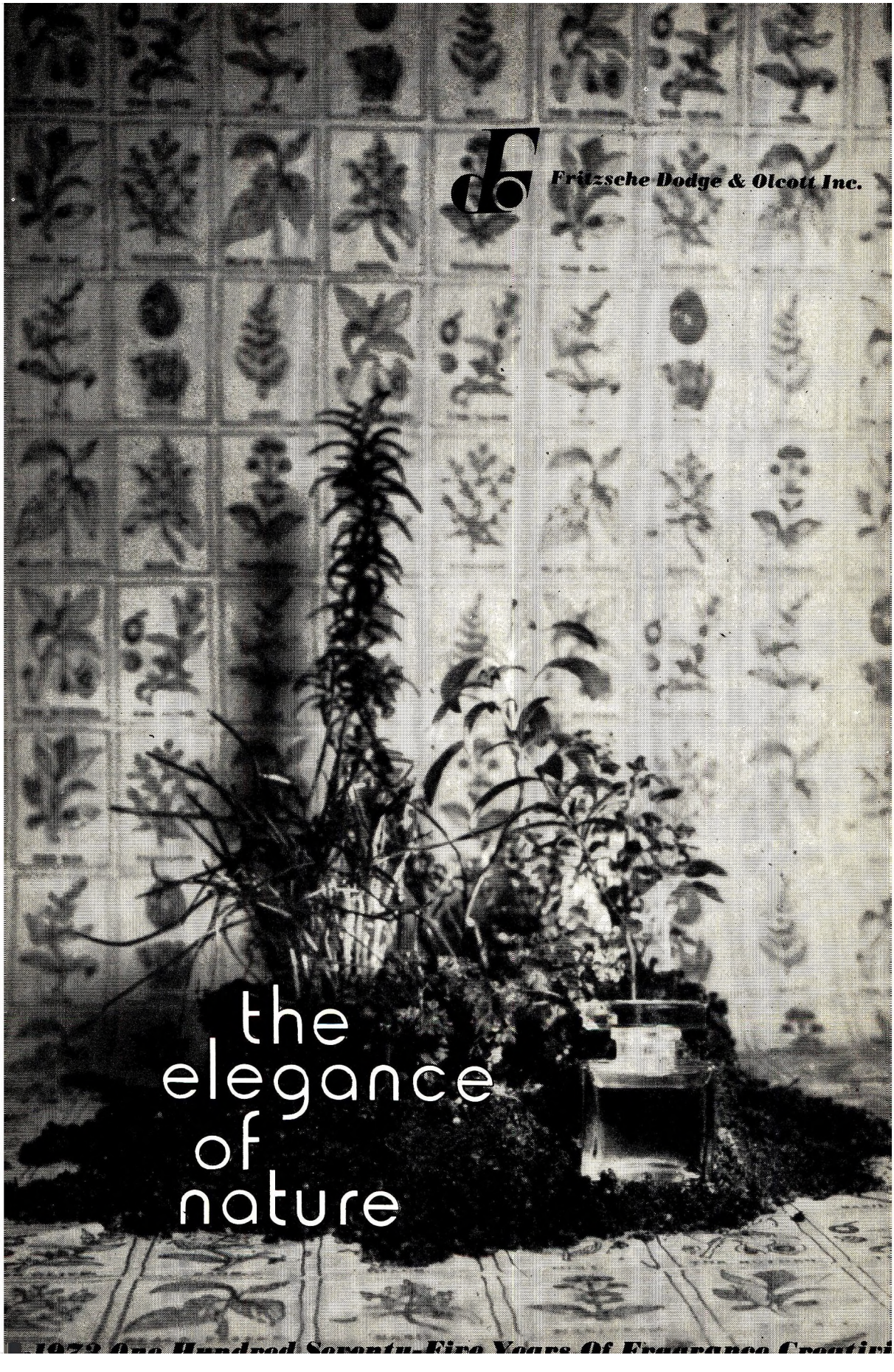
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