Vol. 28 No. 11 November 1977

Journal of the Society of Cosmetic Chemists

Contents

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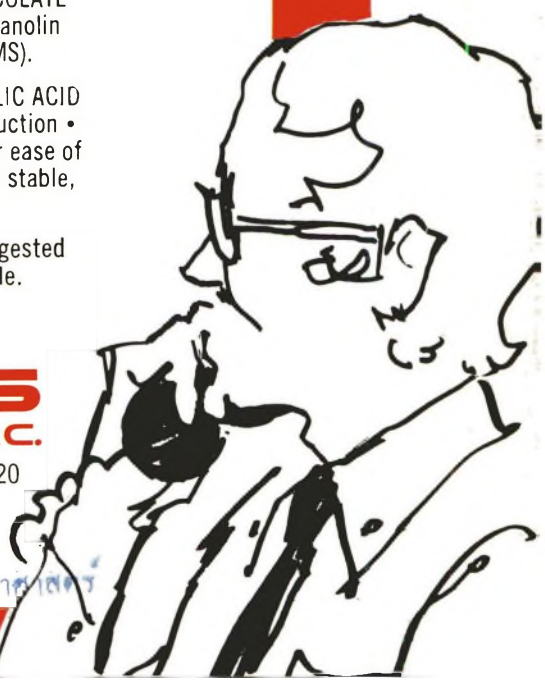

Journal of the Society of Cosmetic Chemists

VOLUME 28 • NUMBER 11

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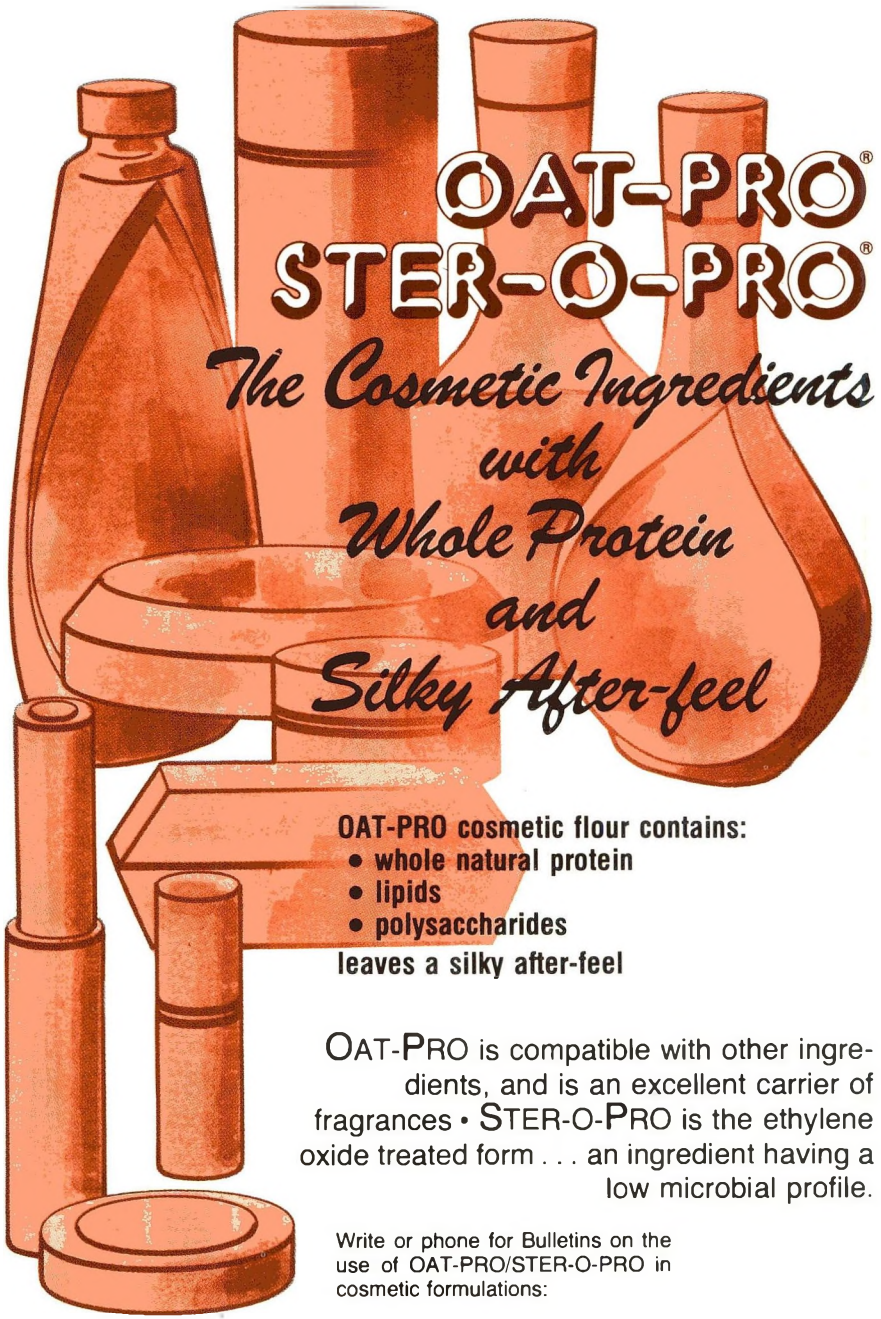

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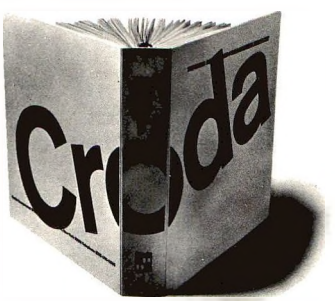

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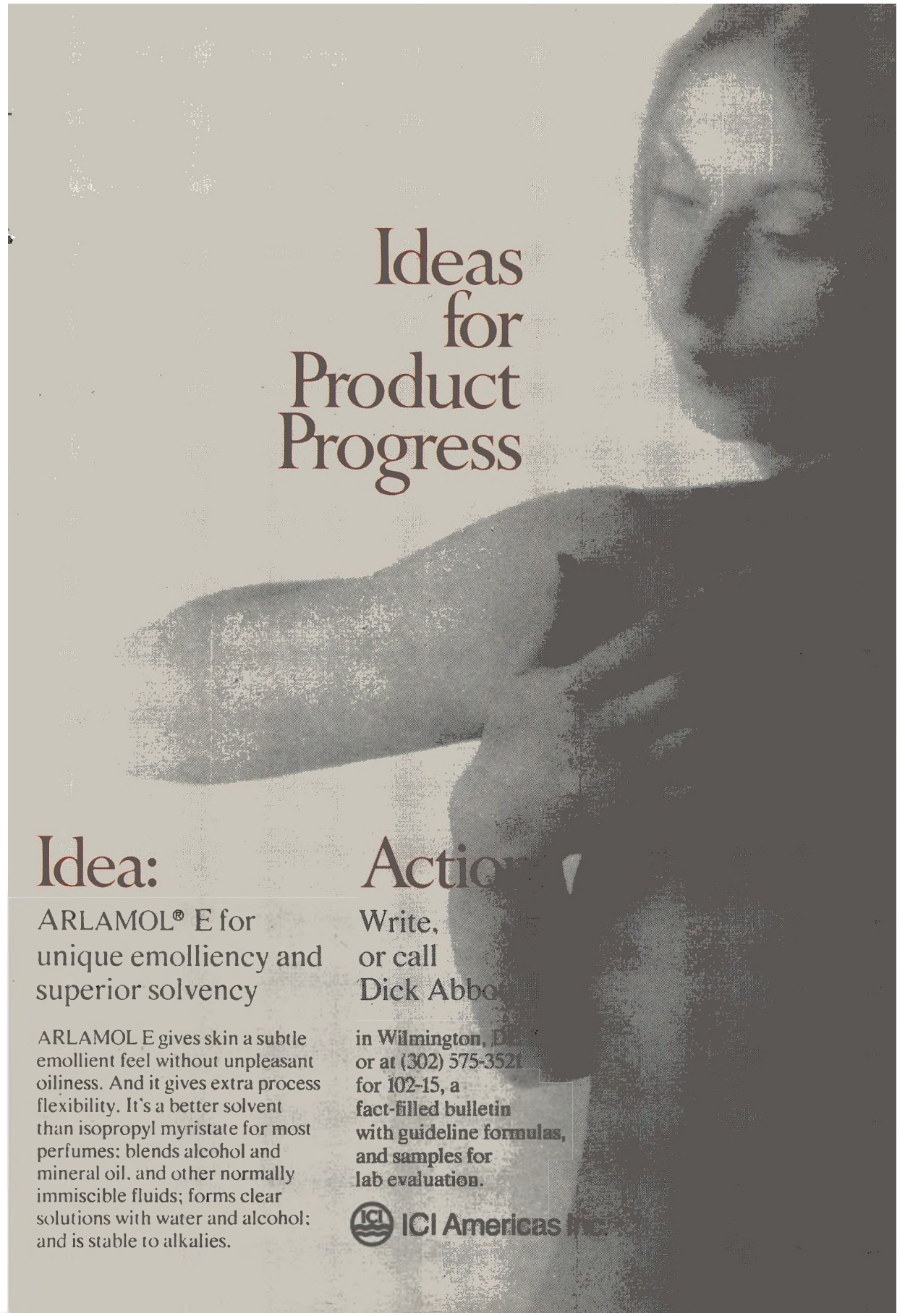
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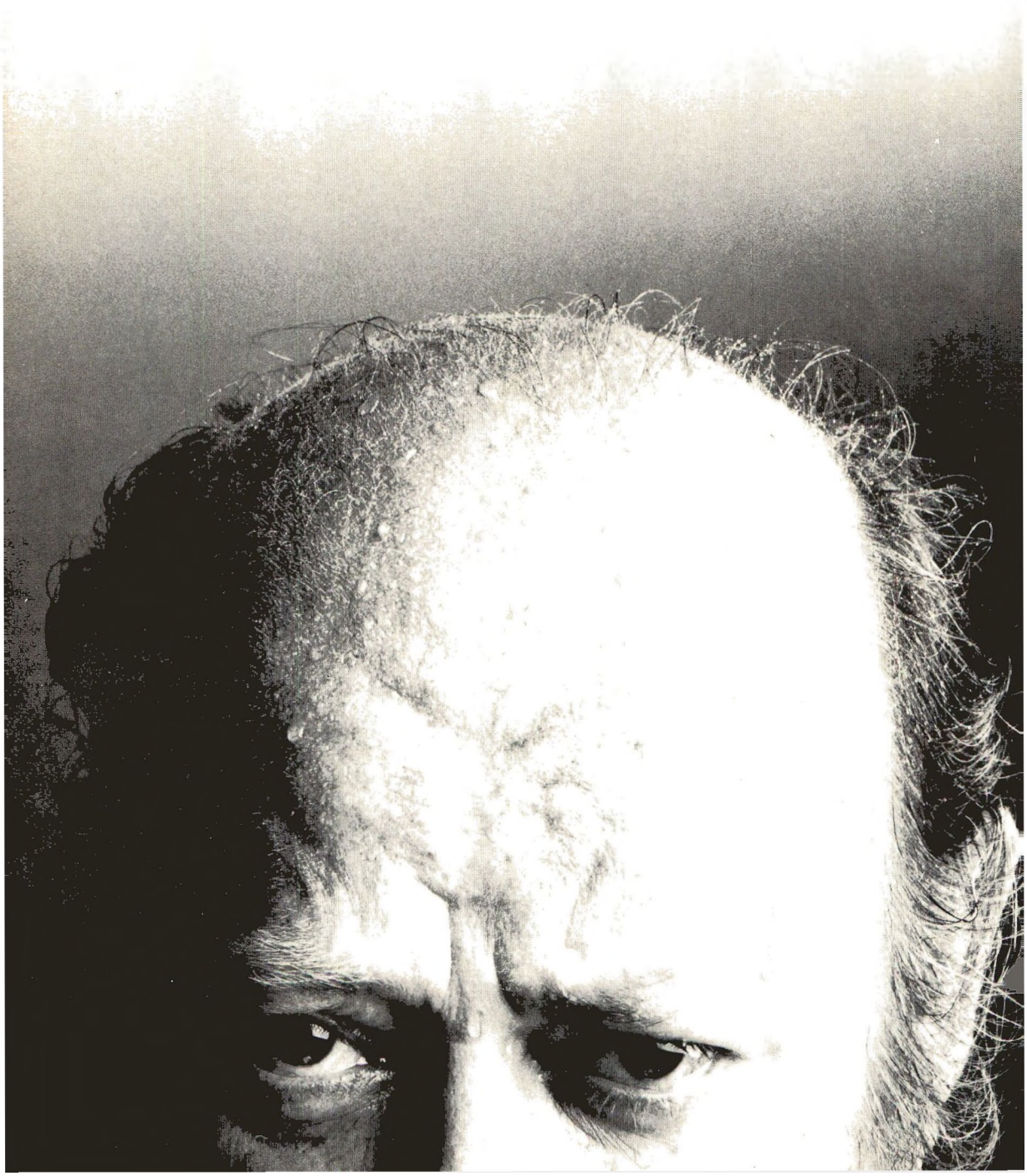

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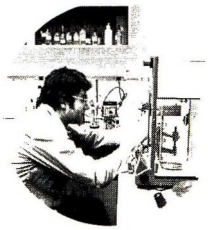

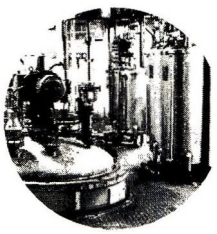

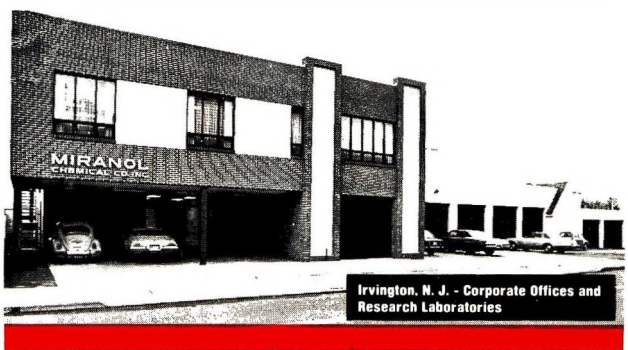

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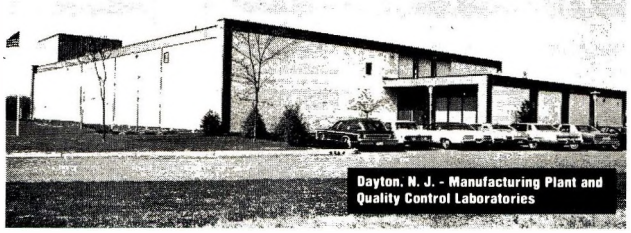

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SYNOPSES FOR CARD INDEXES

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

Antimicrobials: identification of 3,4,4′-trichlorocarbanilide and 4,4′-dichloro-3-(trifluoromethyl) carbanilide in deodorant bars: Francois X. Demers and Ronald L. Yates. *Journal of the Society of Cosmetic Chemists* **28,** 659 (November 1977)

Synopsis—The antimicrobials 3,4,4′-trichlorocarbanilide and 4,4′-dichloro-3-(trifluoromethyl) carbanilide were identified in deodorant bars by analysis of their degradation products. The antimicrobial(s) were first concentrated by solvent extraction of the deodorant bar. The extract was fused with phthalic anhydride to form mixed phthalimides, which were then hydrolyzed with hydrazine to yield a mixture of aromatic amines. Gas-liquid chromatographic analysis of the amine mixture was used to identify the antimicrobial(s) originally present in the deodorant bar. 3,4,4′-Trichlorocarbanilide when degraded yielded a mixture of 4-chloroaniline and 3,4-dichloroaniline. 4-Chloroaniline and 4-chloro-3-(trifluoromethyl) aniline were the products obtained from 4,4′-dichloro-3-(trifluoromethyl) carbanilide. The procedure was then evaluated as a method for the determination of the antimicrobials, using 3,5-dichloroaniline as the internal standard. Recoveries of added antimicrobials were 85 to 90 per cent of theoretical.

Reduction of topical irritation: Robert L. Goldemberg and Leopold Safrin. *Journal of the Society of Cosmetic Chemists* **28,** 667 (November 1977)

Synopsis—Antiirritant effects noted since 1965 are reviewed and grouped into two major chemical categories: imidazole and hydroxy compounds. Several miscellaneous types are also noted: PVP (Polyvinyl pyrollidone), quaternary ammonium complexes, and amido sulfosuccinate surfactants.

The "no tears" antiirritancy effect, which results from a combination of amphoteric surfactants with lauryl sulfates is postulated as resulting from a possible difference in sorption rates which allows the amphoteric to "occupy" the cornea's available binding sites before the anionic can do so, thus preventing "denaturing" damage to the eye by the lauryl sulfate.

The evaluation of fluoride dentifrices: Morton Pader, Lewis P. Cancro and Bernard Guillo. *Journal of the Society of Cosmetic Chemists* **28,** 681 (November 1977)

Synopsis—Four laboratory tests were investigated as indicators of the compatibility of fluoride source and abrasive system in fluoride dentifrices. These were solubility of the fluoride in water, ability to reduce the solubility of dental enamel in acid *in vitro,* uptake of fluoride from the dentifrice *in vitro,* and a rat assay for anticaries efficacy. Dentifrices were formulated with 1000 ppm fluoride (as NaF, SnF_2, or Na_2PO_3F) and with abrasives known to either interact or not interact with those particular fluorides. Also, clinically proven commercial products were examined. The assays for water-solubility of the fluoride and the rat assay clearly distinguished between the dentifrices with respect to compatibility of fluoride source and dentifrice abrasive, in agreement with the results of clinical trials reported in the literature, involving different abrasives and sources of fluoride.

The tensile properties of hair fibers in 1-propanol water mixtures: D. Lu and M. M. Breuer. *Journal of the Society of Cosmetic Chemists* **28,** 695 (November 1977)

Synopsis—The stress-strain curves of intact hair fibers immersed in aqueous 1-propanol solutions were measured as functions of 1-propanol concentration, pH and temperature. Plots of the tensile forces at given extensions against the propanol concentrations show minima at about 50 per cent propanol; these become more pronounced at low pH values and at higher temperatures.

The experimental results can be interpreted by assuming that two additive molecular processes are responsible for the elasticity of hair: conformational changes of the polypeptide chains and electrostatic interactions between the various ionic side chains. The presence of 1-propanol in low concentrations accentuates the importance of the latter process by diminishing the value of the effective dielectric constant inside the hair structure. At high propanol concentrations, however, the dehydration of the fibers increases the relative contribution of the conformational changes and brings about a strengthening of the hair.

Separation of fluoride ions in toothpastes: M. Herpol-Borremans, M. Hanocg, and M.-O. Schmitz-Masse. *Journal of the Society of Cosmetic Chemists* **28**, 705 (November 1977)

Synopsis—A method is proposed for the separation of fluoride ions in toothpastes, which contain large amounts of aluminium compounds. The method involves distillation with superheated steam in a specially designed and fabricated apparatus. This technique has been validated during the examination of all types of toothpastes.

J. Soc. Cosmet. Chem., **28**, 659–666 (November 1977)

Antimicrobials: identification of 3,4,4′-trichlorocarbanilide and 4,4′-dichloro-3-(trifluoromethyl) carbanilide in deodorant bars

FRANCOIS X. DEMERS and RONALD L. YATES, *Division of Cosmetics Technology, Food and Drug Administration, Washington, D.C. 20204.*

Received December 9, 1976. Presented October 18, 1976, Association of Official Analytical Chemists–Society of Cosmetic Chemists Meeting, Washington, D.C.

Synopsis:

The ANTIMICROBIALS 3,4,4′-TRICHLOROCARBANILIDE and 4,4′-DICHLORO-3-(TRIFLUOROMETHYL) CARBANILIDE were IDENTIFIED in DEODORANT BARS by analysis of their degradation products. The antimicrobial(s) were first concentrated by solvent extraction of the deodorant bar. The extract was fused with phthalic anhydride to form mixed phthalimides, which were then hydrolyzed with hydrazine to yield a mixture of aromatic amines. Gas-liquid chromatographic analysis of the amine mixture was used to identify the antimicrobial(s) originally present in the deodorant bar. 3,4,4′-Trichlorocarbanilide when degraded yielded a mixture of 4-chloroaniline and 3,4-dichloroaniline. 4-Chloroaniline and 4-chloro-3-(trifluoromethyl) aniline were the products obtained from 4,4′-dichloro-3-(trifluoromethyl) carbanilide. The procedure was then evaluated as a method for the determination of the antimicrobials, using 3,5-dichloroaniline as the internal standard. Recoveries of added antimicrobials were 85 to 90 per cent of theoretical.

INTRODUCTION

Deodorant bars are composed of soaps and/or detergents and fragrance oils to which antimicrobial compounds have been added to retard the growth of skin bacteria that may give rise to body odor. For many years hexachlorophene was the principal active antimicrobial agent in deodorant bar formulations. A regulation restricting the use of hexachlorophene has resulted in the use of a number of substitute antimicrobials in these preparations. Two antimicrobial compounds that are frequently used in deodorant bars are 3,4,4′-trichlorocarbanilide (TCC) and 4,4′-dichloro-3-(trifluoromethyl) carbanilide (DCTFMC). Deodorant bars commonly contain mixtures of these two compounds, making their identification by chromatographic methods difficult. Wilson (1) was unable to separate TCC and DCTFMC by thin-layer chromatography. Sheppard and Wilson (2) reported that TCC and DCTFMC were eluted in the same fraction, using partition chromatography. The ultraviolet spectra of TCC and DCTFMC are nearly identical and the compounds, therefore, cannot be characterized

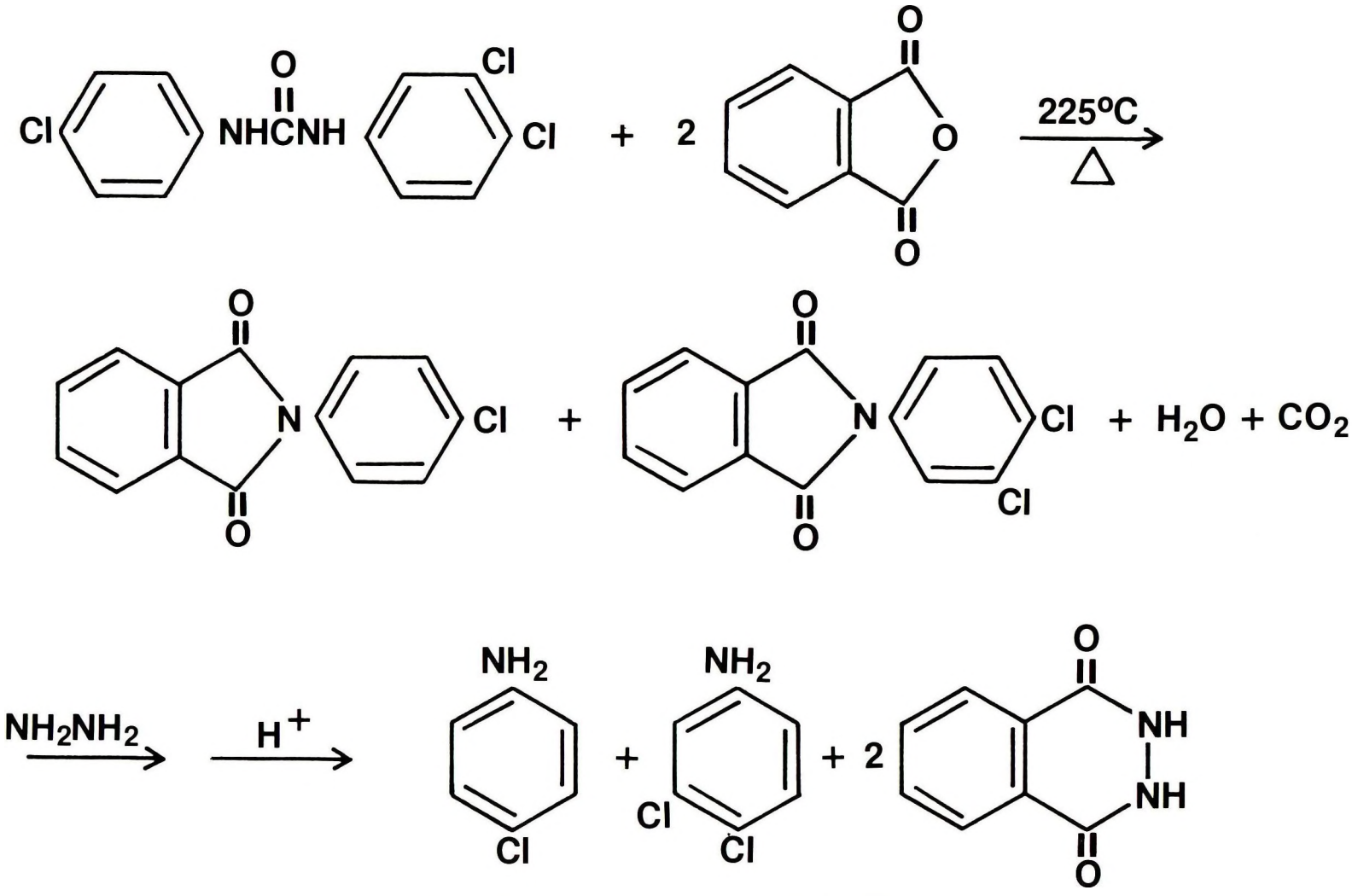

Figure 1. Degradation of TCC, using modified Gabriel synthesis

by this method. Investigations in this laboratory with high pressure liquid chromatography and gas-liquid chromatography (GLC) were likewise unsuccessful.

The primary purpose of this investigation was to develop a method for the identification of these compounds. The second part of this investigation involved evaluation of the qualitative method as a technique for the determination of TCC and DCTFMC.

Tingle and Brenton (3) reported that alkyl carbamides react with phthalic anhydride to give alkyl phthalimides in high yield. Manske (4) synthesized primary alkyl amines by hydrazine hydrolysis of alkyl phthalimides. These studies form the basis of the method reported here.

DCTFMC and/or TCC were isolated from the deodorant bars by solvent extraction. The residue remaining after evaporation of the solvent was reacted with phthalic anhydride (see Fig. 1). The reaction mass was hydrolyzed with hydrazine, and the resulting aromatic amines were analyzed by GLC. By comparison of peak retention times with those of standards, the degradation products of DCTFMC were identified as 4-chloroaniline and 4-chloro-3-(trifluoromethyl) aniline (5-amino-2-chlorobenzotrifluoride), the expected products. Similarly, TCC yielded 4-chloroaniline and 3,4-dichloroaniline. The procedure was then evaluated as a method for the quantitative estimation of DCTFMC and TCC. Known amounts of each were added to solutions of a commercial deodorant bar. Solutions were then carried through the procedure, and the resulting amines were determined by GLC, using 3,5-dichloroaniline as the internal standard. Initial recoveries of added TCC and DCTFMC varied from 25 to 29 per cent. After the method was modified to eliminate losses during evaporation of the ether extract, recoveries of 85 to 90 per cent were obtained.

METHOD

APPARATUS

A gas chromatograph (Model 810*) equipped with dual flame ionization detectors and operated under the following conditions was used: column 210° C, injection port 250° C, detector 260° C, carrier gas flow rate (helium), 80 ml/min.

The GLC column was glass, 10 ft x 4 mm i.d., packed with Chromosorb W (60 to 80 mesh)† coated with 5 per cent KOH and 4 per cent PEG 20M.‡ The column packing was prepared as follows: dissolve 8 g of PEG 20 M and 10 g of KOH in 150 ml. of warm methanol. After the solution is complete, add methanol to make the volume 200 ml. Pour methanol solution into a 1 liter round-bottom flask followed by 25 g of 60 to 80 mesh Chromosorb W. Mix well and then apply vacuum for *ca.* 1 min to remove entrained air. Release the vacuum and swirl the flask vigorously; rapidly transfer the slurry to a 500 ml sintered glass (coarse) funnel set in a side-arm filter flask. Apply suction to the funnel for 2 to 3 min. Transfer the damp support to a large crystallizing dish or stainless steel pan and dry on the steam bath. Mix (do not stir) the support thoroughly every 5 min. by shaking the dish or pan. After the odor of the solvent has disappeared, pack the dried support into the GLC column. The packed column was conditioned for 24 h at 225° C with a carrier gas flow of 10 ml/min.

An oil bath (Model 11-48)‡ was used only for reaction of phthalic anhydride with preservative.

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REAGENTS

The following reagents were used: 3,4-dichloroaniline (98 per cent, No. D5560-1);* 3,5-dichloroaniline (98 per cent, No. D5579-2);* 4-chloroaniline (98 per cent, No. C2241-5);* 4-chloro-3-(trifluoromethyl) aniline (99 per cent, No. A-4565-3);* phthalic anhydride (ACS, No. 331);† and hydrazine hydrate (85 per cent, No. H-318).†

STANDARD SOLUTIONS

Prepare separate standard solutions of 3,4-dichloroaniline, 4-chloro-3-(trifluoromethyl) aniline, and 3,5-dichloroaniline by accurately weighing *ca.* 0.2 g of each compound into separate tared 50 ml beakers. Dissolve the compounds in benzene; quantitatively transfer each solution to a 100 ml volumetric flask and dilute to volume with benzene.

PREPARATION OF SAMPLE

Using a knife or spatula, reduce 2 to 3 g of deodorant bar to powder or fine shavings. Accurately weigh *ca.* 2 g of shavings into a tared 100 ml beaker. Add 50 ml of warm water and 1 pellet of KOH, and stir to dissolve. Transfer the solution to a 125 ml separatory funnel; rinse the beaker with 1 x 10 ml and 1 x 5 ml portions of ethanol, adding rinsings to the separatory funnel. Extract the solution with 3 x 20 ml of ethyl ether. If a stable emulsion forms during the second or third extraction, add a small amount of ethanol to break the emulsion. Combine the ether extracts and wash with 50 ml of 1 per cent NaCl solution, 50 ml of water containing 1 ml of HCl, and, finally, 50 ml of 2 per cent $NaHCO_3$ solution. Dry the ether extract over anhydrous Na_2SO_4 for 30 min, transfer to a 100 ml beaker, and evaporate on the steam bath to *ca.* 20 ml. Transfer the extract to a 50 ml centrifuge tube and carefully evaporate to dryness on a steam bath. Add *ca.* 50 mg of phthalic anhydride to the residue and heat the lower portion of the centrifuge tube in an oil bath at 225° C for 15 to 20 min. Cool, and add 2 ml of ethanol:dimethylformamide (1:1) to dissolve the reaction mass. Add two drops of hydrazine hydrate, warm for several minutes, and then add 15 ml of dilute HCl (1:10). Transfer the contents of the tube to a 125 ml separatory funnel, extract with 30 ml of ethyl ether, and discard the ether layer. Make the aqueous solution distinctly basic (litmus) by adding 10 per cent NaOH solution and then extract with 2 x 30 ml portions of ethyl ether. Combine ether extracts, wash with 30 ml of water, and dry 30 min over anhydrous Na_2SO_4. Transfer this extract to a 100 ml beaker; add 0.5 to 1 ml of xylene and evaporate to 15 to 20 ml. Transfer to a 50 ml centrifuge tube and evaporate carefully on the steam bath, leaving only xylene. Stopper the tube and reserve for analysis.

If the sample is to be prepared for quantitative analysis, all of the above transfers should be quantitative by rinsing the prior container with several small portions of the appropriate solvent.

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†Eastman Organic Chemicals, Rochester, NY.

IDENTIFICATION

Using an initial range and attenuation settings of 10^2 x 8 as a starting point, inject 2 to 3 μl of a solution containing 2 to 3 μg of 4-chloroaniline/μl benzene onto the GLC column. If the initial chromatogram is unsatisfactory, adjust the injection volume and/or recorder attenuation to bring the peak on scale. If the 4-chloroaniline peak does not elute in 4–5 min, adjust the column temperature accordingly. Record the retention time of 4-chloroaniline. Similarly determine the retention times of 3,4-dichloroaniline and 4-chloro-3-(trifluoromethyl) aniline. The retention times for 4-chloroaniline, 4-chloro-3-(trifluoromethyl) aniline and 3,4-dichloroaniline relative to 3,5-dichloroaniline are 0.30, 0.48, and 1.13, respectively.

Inject 3 to 4 μl of the sample solution onto the GLC column. Record the retention values for the eluted peaks and compare with those obtained for the standards. Identify TCC by peaks corresponding in retention time to 4-chloroaniline and 3,4-dichloroaniline, and DCTFMC by peaks corresponding to 4-chloroaniline and 4-chloro-3-(trifluoromethyl) aniline.

DETERMINATION

3,4,4'-Trichlorocarbanilide (TCC): Pipet 1.0 ml of the 3,5-dichloroaniline (internal standard) solution into the sample that was previously determined to contain 4-chloroaniline and 3,4-dichloroaniline. Inject *ca.* 5 μl of this solution onto the GLC column at range and attenuation settings to keep the 3,5-dichloroaniline and 3,4-dichloroaniline peaks on scale. Measure the peak heights and, assuming a linear relationship between the concentration and peak height, estimate to the nearest 1.0 ml how much additional 3,5-dichloroaniline is needed to obtain approximately equal ($\pm$10 per cent) peak heights. Pipet the calculated amount of 3,5-dichloroaniline solution into the sample solution. Again inject the sample solution to determine if the peak heights of 3,4-dichloroaniline and 3,5-dichloroaniline are approximately equal. Adjust the volume injected and/or the attenuation to keep the peaks within 50 to 90 per cent full-scale recorder deflection. Prepare a standard solution by mixing 10.0 ml each of the 3,5-dichloroaniline and 3,4-dichloroaniline standard solutions. Using the same range and attenuation settings used for the sample, inject 3 to 4 μl of the standard solution onto the GLC column. From the chromatogram, determine the volume of either 3,4-dichloroaniline or 3,5-dichloroaniline that must be added to the standard solution to obtain peaks of approximately the same ratio as the peaks in the sample. Also determine the injection volume of standard needed to give peaks that are about the same height as those in the sample. Using these conditions, alternately inject the standard and sample solutions, making a minimum of two injections of each.

4,4'-Dichloro-3-(trifluoromethyl) carbanilide: Use the above procedure, substituting 4-cholor-3-(trifluoromethyl) aniline for 3,4-dichloroaniline. Prepare the initial standard solution by mixing 5.0 ml of 4-chloro-3-(trifluoromethyl) aniline standard solution with 10.0 ml of 3,5-dichloroaniline standard solution.

Mixtures of TCC and DCTFMC: Measure the smallest GLC peak first. Add the necessary additional internal standard to the sample and measure the second GLC peak.

Calculations: Calculate the weight of amine being determined in the sample as follows:

$$\text{Weight (mg) unknown} = (Ru/Rs) \times Ks \times (ISu/ISs)$$

where Ru is the ratio of the peak height of the unknown in the sample to that of the internal standard added to the sample; Rs is the ratio of the peak height of the known standard to that of the internal standard in the standard solution; Ks is the weight (mg) of the known standard in the standard solution; ISu is the weight (mg) of the internal standard in the sample; and ISs is the weight (mg) of the internal standard added to the standard solution.

Calculate weight of TCC or DCTFMC by using the following conversions:

$$\text{Weight (mg) TCC} = W\text{-}3,4 \times 1.95$$
$$\text{Weight (mg) DCTFMC} = W\text{-}4 \times 1.79$$

where W-3,4 is the weight (mg) found for 3,4-dichloroaniline and W-4 is the weight (mg) found for 4-chloro-3-(trifluoromethyl) aniline.

RESULTS AND DISCUSSION

Before the proposed method was applied to the analysis of commercial deodorant bars, it was necessary to determine conditions suitable for the stepwise degradation of the antimicrobial compounds. TCC and DCTFMC reacted smoothly with phthalic anhydride at 225° C; evolution of carbon dioxide and water ceased after several minutes. The reaction mass, however, was difficult to dissolve in ethanol, the usual solvent. A mixture of dimethylformamide and ethanol was suitable. Hydrolysis of the phthalimides with hydrazine hydrate and hydrochloric acid proceeded rapidly under mild temperature conditions. Aromatic amines were isolated from the reaction mixture by the usual methods.

One of our concerns was the possible interference by amines formed by the degradation of other antimicrobials used in deodorant bars. If, for example, tribromosalicylanilide reacted analogously, *p*-bromoaniline would be the expected product. This compound has approximately the same GLC retention time as 4-chloro-3-(trifluoromethyl) aniline and is, therefore, a serious interference. Tribromosalicylanilide was carried through the degradation procedure. GLC analysis of the reaction products demonstrated the absence of *p*-bromoaniline.

The GLC columns used for the analysis of primary amines are usually packed with a nonsilanized support containing several per cent of potassium hydroxide to reduce adsorption. Polyester or other liquid phases containing functional groups that react with strong bases must not be used. We found that a 10 ft glass column containing potassium hydroxide-treated Chromosorb W coated with PEG 20M gave satisfactory separation. 3,5-Dichloroaniline was selected as the internal standard because of its chemical similarity and the nearly equal specific detector response to those compounds being determined. The extraction procedure used in this study was designed to separate the neutral ether-soluble fraction from the acidic and basic water-soluble compounds present in the deodorant bar. Solvent extraction of solutions containing surfactants nearly always results in the formation of emulsions. This problem can be ef-

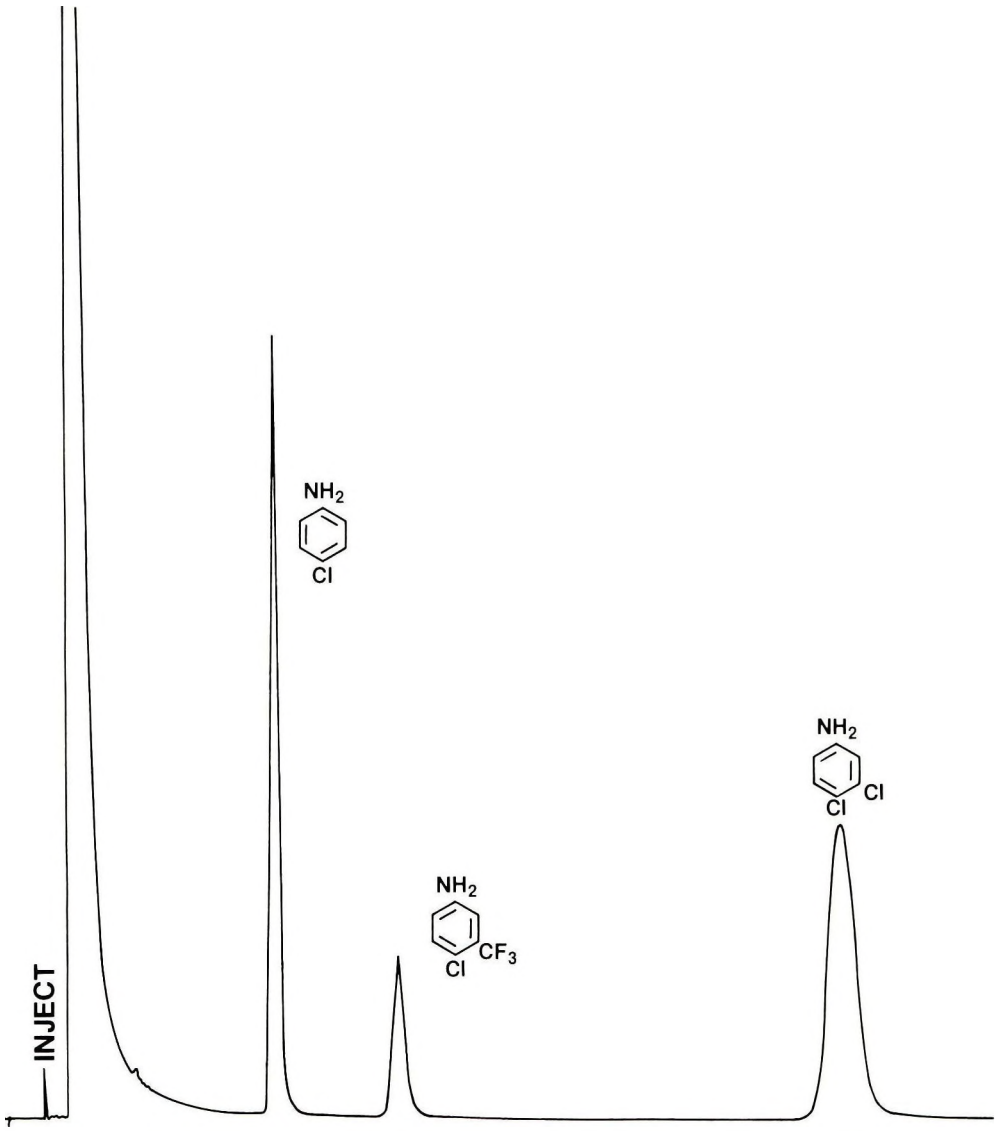

Figure 2. Gas chromatogram of degradation products of antimicrobials extracted from commercial deodorant bar: in order of elution, 4-chloroaniline, 4-chloro-3-(trifluoromethyl) aniline, and 3,4-dichloroaniline

fectively eliminated by adding ethanol. Our investigations indicate that an ethanol concentration of 20 to 25 per cent by volume is optimal. The ether-soluble fraction is usually small, generally 20 to 30 mg/g of product. Since occasionally the neutral fraction may be somewhat larger, we recommend that correspondingly larger amounts of phthalic anhydride be used for the degradation step. Likewise, the amount of hydrazine hydrate used should be increased accordingly.

Several commercial products known to contain TCC and/or DCTFMC were analyzed

Table I.
Recoveries of 3,4,4'-Trichlorocarbanilide (TCC) and 4,4'-Dichloro-3-(trifluoromethyl) Carbanilide (DCTFMC) Added to a Commercial Deodorant Bar

Preservative	Added (mg)	Recovery (mg)	Recovery Per Cent
TCC	10	9.0	90
TCC	10	8.6	86
DCTFMC	10	8.9	89
DCTFMC	10	8.5	85

by the proposed procedure. In all cases, clean chromatograms containing only those peaks corresponding to the expected products were obtained (see Fig. 2).

To evaluate the qualitative method as a procedure for the determination of TCC and DCTFMC, known amounts of each antimicrobial were added separately to solutions of a commercial deodorant bar and the solutions were analyzed by the described procedure. The isolated amines were determined by GLC, using 3,5-dichloroaniline as the internal standard. Initial recoveries were 25 to 29 per cent of theoretical, much lower than expected. A step-by-step evaluation of the procedure indicated substantial losses of the aromatic amines when the ether extract was evaporated to dryness. The procedure was modified by adding 0.5 to 1.0 ml of xylene to the extract to keep the sample from evaporating to dryness. This modification resulted in recoveries of up to 90 per cent (Table I). Other minor modifications in the procedure were not effective in increasing recoveries. Because we did not consider recoveries of 90 per cent sufficiently accurate for a quantitative method, further studies were not done. Therefore, it is recommended that the procedure be used only to identify the antimicrobials present.

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Reduction of topical irritation

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Synopsis

ANTIIRRITANT effects noted since 1965 are reviewed and grouped into two major chemical categories: IMIDAZOLE and HYDROXY compounds. Several miscellaneous types are also noted: PVP (Polyvinyl pyrollidone), quaternary ammonium complexes, and amido sulfosuccinate surfactants.

The "no tears" antiirritancy effect, which results from a combination of AMPHOTERIC surfactants with lauryl sulfates is postulated as resulting from a possible difference in sorption rates which allows the amphoteric to "occupy" the cornea's available binding sites before the anionic can do so, thus preventing "denaturing" damage to the eye by the lauryl sulfate.

INTRODUCTION

Some 12 years ago Goldemberg (1) presented a paper to the Third IFSCC Congress on the use of antiirritants in cosmetic formulations. Its major thesis was that the topical irritation potential of cosmetic ingredients depends as much on their extrinsic "formulation environment" as on intrinsic properties of the ingredients themselves.

That initial paper, plus several subsequent ones touching peripherally on this subject, proposed three possible mechanisms of action by which antiirritants may function: (1) *via* complexation of the irritant; (2) by blocking otherwise chemically reactive sites of skin keratin; and (3) by preventing complete physical contact with the skin.

We have no reason to change this overall view today, and in fact, we provide in this paper a considerable expansion of the original reference section of that 1965 paper, thus bringing the subject to date. We have now had time to explore many of these phenomena in depth. Many clear cut accomplishments have been achieved in this area during the past decade—including a number of newly issued patents covering antiirritant activity of various compounds. The "desensitization" (of perfume components) *via* nonimmunologic processes is now also being actively explored (23, 59).

It is the purpose of this paper to summarize such recent developments in the field of antiirritancy, and to offer theoretical considerations linking together as many of them as possible.

GENERAL

The basic concept first enunciated in 1965 still holds: it is possible to change the irritation potential of topically applied raw materials by varying their "formula environment." Materials, which *per se* are soothing to the skin, occasionally reverse their roles and increase topical or eye irritation levels in certain types of formulations. On the other hand, strong irritants can frequently be rendered totally innocuous by combining them with precise (usually small) percentages of other ingredients. It is such other ingredients which we herein define as "antiirritants."

There are several probable mechanisms by which some compounds are able to reduce topical or eye irritation of other ingredients. Some of these processes are more or less mechanical, depending primarily on physical factors for their "activity" in this respect. However, we must not confuse such physical effects with specific antiirritancy of a chemical nature. To avoid later confusion between these two phenomena, we shall first briefly review recently noted *physical* effects, to preclude them from later discussion of antiirritancy operating *via* mechanisms of chemical reactivity.

PHYSICAL ANTIIRRITANCY

The simplest physical effect is diminution of skin contact by the irritant—applying oily substances to the skin prior to application of aqueous irritants (such as greasing the forehead and temples before applying caustic hair straighteners); and gelling (or otherwise thickening) products to reduce intimate skin contact. Gelled shampoos and bubble baths frequently are not irritants when tested "as is." Once diluted to the point where they flow readily, however, they often become primary skin and eye irritants (56). Perhaps related to viscosity and consequent skin penetration are the well known phenomena that light mineral oils (40 *visc.* and under) are irritants, medium weight (70 *visc.*) oils are neutral, and heavy mineral oils are antiirritants.

The rate of sorption of surfactants onto keratin surfaces has been shown by Garrett (2) to relate directly to their irritation potential. Another rather purely physico-chemical factor affecting irritation response is the loosening of hydrophobic bonds, discussed at length recently by both Dominguez (3) and Hall (4) at the Ninth IFSCC meeting. At this same meeting, Suzuki pointed (5) to the correlation between skin irritancy and rate of penetration (into sebaceous glands by isopropyl myristate, glyceryl trioleate, etc.). The partition coefficient between pharmaceutical vehicles and skin fat has been discussed by both Rabinowitz (6) and Goldemberg (7) as a probable factor determining substantivity and the associated irritation potential of certain active ingredients. Various proteins and partially degraded collagens have been cited for their "protective colloid" and other inactivating effects (8,9,10,11,12,13,20), while partially depolymerized chitin and/or pulverized egg shells appear to promote wound healing (14,15,16,47), perhaps simply by acting as foci for epithelial granulation. Note that Chitin contains D-Glucosamine as a major constituent.

Reduction of pH is probably the sole reason that addition of ammonium carbonate reduces irritation of thioglycolate permanent waves (17). Several authors have also pointed out (18,19) that climatic influences should not be ignored when judging the results of human irritation testing, especially large scale tests such as the Food and

Drug Administration's recent study of the cosmetic use habits and skin irritation responses of 10,000 typical American families.

Inhibition of polymerization (and/or oxidation) perhaps explains the observed usefulness of Vitamin E (30), of the reduction of lanolin sensitizations over the years (21), of the value of Na_2SO_3 in Paraphenylene diamine (PPD) hair dyes (24), and the reduction of uv-induced skin cancers *via* ingestion of antioxidants (25). The "quenching phenomenon" (22,23,27,61) has also been connected with prevention of the formation of oxidative resins in perfume aldehydes.

Keratin substantivity of compounds also affects their irritation, sensitization and/or antiirritant potential, as pointed out by Goldemberg (7,26,27) in regard to Ni^{++} and other materials. Scheuplein and Ross (28) showed that irritancy of sodium lauryl sulfate (SLS) and other surfactants correlates to their keratin denaturing ability, to their effect on its water binding capacity, and to their ability to liberate (SH) groups from keratin. Bettley (29) showed similar effects for sodium laurate, while Dominguez *et al.* (3) recently tied much of this data to the peak sorption (onto keratin), which occurs as the surfactant approaches the C_{12} chain length.

Finally, the shape of the molecule (its size and the molecular location of irritating moieties) affect the degree and type of irritancy produced. Dominguez *et al.* (3) gave us an excellent discussion of the effects of moving the SO_3 group from the first to the third carbon position in C_{12} alkyl sulfates. When the sulfonate is in the "normal" (No. 1) position, lauryl sulfate surfactants have a much smaller molecular configuration, are much more irritating, sorb more strongly onto keratin, and extract more soluble protein than do lauryl sulfates whose SO_3 group is attached to carbon No. 3. Other workers have also shown the frequent association between keratin sorption, protein extraction capability, and irritation reactions caused by alkyl sulfate surfactants.

By contrast, sucrose ester surfactants (claimed by Croda, Inc. to have almost no denaturing effect on skin proteins) apparently do not disrupt the skin's lipid layer. They are not only nonirritating *per se*, but have been shown to distinctly reduce irritation of lauryl ether sulfate formulations (Table I).

Table I
Effect of Two Ethoxylated Nonionics on an Amphoteric Shampoo Base
(Average Draize scores, 6 rabbits)

I. 30 Per Cent Shampoo base, 70 Per Cent water

24 h	7 days
18	6.5

II. 30 Per Cent Shampoo base, 5 Per Cent POE 20 sorbitan monolaurate, 65 Per Cent water

24 h	7 days
19	5.0

III. 30 Per Cent Shampoo base, 5 Per Cent sucrose monolaurate, 65 Per Cent water

24 h	7 days
18	3.0

	SHAMPOO BASE
20.0	Amphoteric-10
7.0	Na lauryl ether sulfate (1 mol Et0)
1.0	Coconut DEA superamide (1:1)
2.0	Propylene glycol
30.0	

CHEMICAL ANTIIRRITANCY

During the past decade, many observed antiirritancy effects resulting from both planned investigations and fortuitous formulating practices appear to cluster around two major types of chemical compounds: *imidazole* derivatives and various *hydroxy* compounds. Investigators reporting such results have not generally appeared to be aware that their work falls into the following two major groupings.

I. IMIDAZOLE COMPOUNDS:

Kawakami (31) claims "antiphlogistic and antihistaminic" activity from use of 0.08 to 10 per cent hydroxyethyl-4,5 diphenylimidazole. His data (Table II) clearly show such an effect. Libby (33) reacted imidazoline with methyl acrylate and various acrylamides, forming compounds which (at 2 per cent levels) reduce the eye irritation of shampoos and hair grooms containing ethoxylated amides and/or quaternary ammonium compounds.

Imidazolidinyl urea ("Germall 115") is an active bactericide which Lanzet (34) showed to distinctly reduce the primary irritation of a liquid make-up (*via* 48-h closed human patch testing) when added at 0.2 per cent levels (Tables III & IV). Other urea compounds, clathrates of various cosmetic oils in combination with inorganic pigments, are currently being investigated for their antiirritant properties (52). A recent Canadian patent (48) describes the use of 3 per cent imidazol-3-oxyalcanoic acid (and its metal salts) in cosmetic preparations for this purpose.

The antiirritant effects of imidazoline amphoteric surfactants are also well-known, due to their current common use in baby and "no tears" shampoos. Originally produced under Hans Mannheimer's "Miranol" patents (32), they are now offered by several other firms as well.

Of particular interest in this amphoteric surfactant series is the fact that C_{10} and C_{12} mono- and di-carboxylic imidazoline surfactants (those of major commercial interest) show the least irritation *per se* and (frequently) show the most potent antiirritant properties. If keratin sorption of amphoterics eventually turns out to peak at the C_{12} chain length (as has already been demonstrated for the alkyl sulfates), one can only conclude that in this particular case, sorption is *good*. Perhaps, keratin sorption of imidazoline amphoteric surfactants occurs preferentially to that of the lauryl sulfates and similar anionics, thereby preventing denaturation *via* blocking the limited number of binding sites available on the cornea. Perhaps such preferential sorption is responsible for the well-known "no tears" effect, which results when amphoterics (plus polysorbate 20) are added to typical anionic shampoo formulations. Another possibility is that such amphoterics (and the Polysorbate?) form a complex with lauryl sulfates via hydrogen bonding, and that this complex (a new entity) simply has different irritational properties.

Manufacturers of such amphoteric compounds would be well advised to run studies designed to measure relative sorption rates of the amphoteric and anionic alone, and of combinations thereof. Such studies would tell us a great deal about the mechanism by which certain imidazoline derivatives provide antiirritancy.

Table II
1-Hydroxyethyl-4, 5-Diphenylimidazole
(Antiphlogistic and Antihistaminic Composition)

Control Scores (No Imidazole)		With Imidazole Per Cent Imidazole	Score
10	Cold cream	0.08%	1
2	Vanishing cream	0.03%	0
10	Face "milk" lotion	0.10%	0
5	Face lotion	0.04%	0

Primary skin irritation (10 skin-sensitive humans). Results reported in U.S. Pat. 3,504,090 to Iwao Kawakami (1970).

Table III
Antiirritant Effect of Imidazolidinyl Urea Preservative
(48 h Closed Patch Test of a Liquid Make-up on 100 Humans)

I. Liquid make-up (control):
94 persons showed (0) reaction
4 persons showed (+) reaction
2 persons showed (++) reaction
II. Same liquid make-up + 0.25 per cent Germall 115:
98 persons showed (0) reaction
2 persons showed (+) reaction
0 persons showed (++) reaction

Table IV
Antiirritant Effect of Acetamide MEA on SLS

	Ratio (MEA/SLS)	Conjunctival Scores* (Mean Value)
3 Per cent SLS	0	14.7
3 Per cent SLS + 0.35 per cent MEA	0.16	11.3
3 Per cent SLS + 3 per cent MEA	1.0	8.7
3 Per cent SLS + 7 per cent MEA	2.5	9.3
3 Per cent SLS + 15 per cent MEA	5.0	2.6

*Draize eye irritation scores.

II. HYDROXY COMPOUNDS

The many recent reports of antiirritant properties attributed to diverse hydroxy compounds suggest that perhaps a general principle is operating here, a broad reaction mechanism.

We summarize these reports very briefly: Polysorbate 20 has been patented for shampoo use by Bollch *et al.* (35). Esters of branched chain fatty alcohols with hydroxystearic acid have been patented by Jacobi (36,37) to reduce skin irritation and defatting of the dermis (Table V). Sucrose esters (with HLB ranges as high as 14.5) are claimed by Croda, Inc. to be nonirritating to the skin and eyes, to have no denaturing

Table V
Irritation-Reducing Effects from Topical Use of C_8 Fatty Alcohol Esters of Hydroxy Fatty Acids*

		Primary Irritation Score (Skin)
1.4 Per cent	Na lauryl sulfate	4.28
5.0	Na lauryl sulfate	3.56
4.5 0.5	Na lauryl sulfate 2,6-dimethyl-octyl-hydroxy stearate	3.06
4.5 0.5	Na lauryl sulfate a-ethyl-hexyl-ricinoleate	2.73
4.5 0.5	Na lauryl sulfate 2,6-dimethyl-octyl-ricinoleate	2.57
4.5 0.5	Na lauryl sulfate a-ethyl-hexyl-12-hydroxy stearate	2.45

*(U.S. Patent 3,906,106 to Otto K. Jacobi (9/16/75).

effect on cutaneous proteins, and to act as antiirritants with effects substantially similar to those shown by Polysorbate 20 (Table I)(CTFA label designation).

Work previously reported by Goldemberg (1) demonstrated two such hydroxy compound effects: Polysorbate 20 (in combination with an acetylated monoglyceride) reduced the eye irritation of an aluminum antiperspirant preparation, and Pluronic F68, a polypropylene/polyethylene block polymer, totally nullified primary irritation otherwise produced by an alcoholic cologne. Edlich *et al.* (38) later singled out this same block polymer as having particular interest, demonstrating that the ethylene oxide content of such polyols is the determinant of tissue toxicity. It has also been found to detoxify iodine (57), as does PVP. Henkel Inc. (39) has shown that "higher ethoxylated lauryl sulfates" significantly reduce the eye irritation of shampoo formulations based on fatty alcohol sulfonates.

Riso (60) pointed out that the 7 mol EtO lauryl sulfate is completely nonirritating to the eye, but unfortunately foams poorly. It can be "boosted" with up to 5 per cent triethanolamine dodecyl benzene sulfonate, a good foamer which is very mild in the eye (up to this level.) Use of this alkyl aryl compound is restricted in the United States in bubble baths, however, due to its potential for vaginal irritation when applied in concentrated solutions.

As mentioned above, Kawakami (31) demonstrated antiirritancy for hydroxyethyl-4,5 diphenylimidazole. Peck and Spoor (40) have each confirmed that topically applied dihydroxy-phenylamine (ℓ-DOPA) reduces the number of sensitization reactions among PPD-sensitive hair dye users. They worked with formulations made according to Feier's 1972 patent (41) on PPD/ℓ-DOPA hair dye combinations.

Similar claims, though with less positive documentation, have been advanced for galacturonic acid (in aloe Vera gel), glycolic (hydroxyacetic) acid, glyceryl triacetate, allantoin polygalacturonate (42), and for the glucose trimer, "Pullulan" (44). Opdyke (45) once reported a curious phenomenon: the only discernable chemical difference in skin which has "accommodated" (to the insult of continuous immersion in SLS) is the

Table VI
Kelley-Ritter "Mildness Additive" Patents*

	Total Score, 12 Persons (24 hr Skin Patch)
6 per cent SLS (sodium lauryl sulfate)	15
6 per cent SLS + 6 per cent TEA oleate	15
6 per cent SLS + 6 per cent TEA dimerate	5
Use of Dimer Acids *via* Following U.S. Patents:	
US 3,538,009—11/3/70	US 3,798,182—3/19/74
US 3,630,934—12/28/71	US 3,813,350—5/28/74
US 3,769,242—10/30/73	US 3,947,382—3/30/76

*Tests were run with dimer and trimer acids (of oleic and linoleic), and with their esters and amides (in 1:1 ratios, at 0.15 per cent) with various detergents such as ABS, SLS, lauryl ether sulfate, and TEA laurate.

presence of glycogen, another hydroxy compound. Lipkin (8) recently reported on the use of a glycoprotein obtained from normal human epidermis to inhibit *in vitro* growth of malignant cells. *Glucan*, a yeast-derived polysaccharide, stimulates macrophage activity (and subsequent immune response) when injected directly into active tumors, according to Smith's review (46) reporting on Dr. Peter Mansell's experiments at McGill University. Zviak patented the use of thiodiglycollic acid (50) to reduce scalp irritations, while thioglycerol has also been claimed as an epithelial cell growth stimulant (51). There also exists a gluconamide quat which can be tolerated in the eye at 100 times the levels at which benzalkonium quats are tolerated.

Are all of these hydroxy compound effects just coincidence? *It seems most unlikely.*

Finally, Kelly and Ritter (43,62,63,64,65,66,67) have clearly demonstrated (Table VI) *via* guinea pig immersion and human patch testing that hydroxy derivatives (-OH and -COOH) of oleic and linoleic dimer and trimer acids are potent antiirritants.

All of these reports are highly suggestive of a prophylactic effect deriving from the presence of the hydroxyl group in topically-applied materials.

CARBOXYL COMPOUNDS

Kelly and Ritter also reported (43) that dimer acids themselves (containing 2-4 carboxyl groups) are "mildness additives which prevent or reduce skin irritation" of many surfactants. When carboxyl groups of dimer acids are replaced by weaker polar groups (such as hydroxyl) the antiirritant effects do not appear until such hydroxyl groups are separated by at least 15 atoms. Here was the first attempt at quantifying the hydroxyl ion antiirritant effect.

Kelly and Ritter's observations are most interesting in light of LeVeen (49), who patented the use of traumatic acid (1-decene-1,10-dicarboxylic acid) for its pronounced favorable effect on the ingrowth of new epithelial tissue into burned areas. LeVeen reports that the presence of traumatic acid increases ingrowth rate by 40 per cent (Table VII), whereas sebacic acid (a saturated acid with eight central carbons separating two carboxy groups) does not affect such growth rate at all, and adipic acid (having two

Table VII
Traumatic Acid
(1-decene-1,10-dicarboxylic acid)
"Ingrowth" on 1 cm^2 Human Burn Blisters (as Per cent of Control)

Control (PEG 6000)	0	(Base line)
Sebacic acid (2 per cent in PEG 6000)	0	(No change in healing rate)
Adipic acid (2 per cent in PEG 6000)	−50 per cent	(Decrease in healing rate)
Traumatic acid (2 per cent in PEG 6000)	+40 per cent	(Increase in healing rate)

*Ref: Brit. 1,013,109 to H. H. LeVeen (1965).

Table VIII
Chronic Toxicity (IP) of Phthalate Esters (Mouse)

Phthlate Ester	Acute LD_{50} (g/Kg)	Chronic LD_{50} (g/Kg)
Dimethyl	3.98	1.40
Diethyl	3.22	1.56
Dibutyl	3.57	0.89
Diisobutyl	3.99	1.94
Di-n-Octyl	65.70	3.02
Di-2-Ethylhexyl	37.77	1.35
Butyl Carbobutoxymethyl	6.88	3.34
Bis (2-Methoxyethyl)	4.18	1.65

(Lawrence *et al.*, *Environ Res.*, 9, 1–11 (1975)).

carboxy groups separated by four central carbons) actually *decreases* ingrowth by 50 per cent. The apparent chain-length relationship shown in this series of examples is unfortunately clouded by the unsaturation of traumatic acid, whose carboxyls are at either end of a 10-carbon chain. Pacini (58) claimed that traumatic acid (and especially its cobalt salts) reduce the skin irritation of detergent compositions when used at levels as low as 0.0005 per cent.

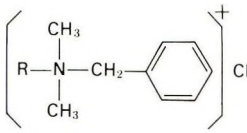
III. MISCELLANEOUS OTHER CHEMICAL IRRITANTS

Several other "chemical" antiirritant effects have been observed, which do not fall into either Imidazol or Hydroxy Compound categories.

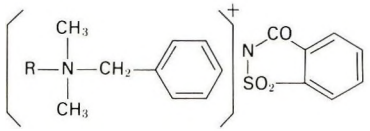
The phthalate esters, for example, were recently discussed by Lawrence of the University of Tennessee (Table VIII). It is fascinating how an apparently innocuous switch in the alcohol portion of an homologous series of esters can make such a difference in their toxicity. All of us know of similar examples, such as the sunscreen PABA-ester series, which differ drastically in the "sting" produced on mucous membranes of certain individuals.

The prime example of detoxification is PVP, perhaps the classic antiirritant and detoxicant of all time. Although its effects were noted long before the development of current theories of antiirritant mechanisms, we still do not know how or why PVP works. Yet, no one can doubt the antiirritant potency of this unique polymer.

TWO ALKYL DIMETHYL BENZALKONIUM QUATS



Chloride



Saccharinate

Table IX
Alkyl Dimethyl Benzalkonium Quats
(Comparison of Properties)

	Chloride	Saccharinate*
Taste	bitter	sweet
LD_{50} (g/Kg)	445	1130
Primary skin irritation	moderate	0
Draize eye irritation (non-irritating level)	0.1 per cent	1.0 per cent
Phenol coefficient	580	525

(*Onyxide 3300 or Hollichem HQ 3300).

The basic patent for detoxicant PVP uses was issued in 1956 to Shelanski (53), who modestly only claimed a "method for reducing the vapor pressure of free halogens." The substantial detoxification of iodine and chlorine—although clearly recognized in the introductory portion of his patent—was not claimed.

Pointing out that the PVP iodine "complex" was more active than free iodine itself, Shelanski described how its irritation and sensitization effects were now completely absent and that its oral toxicity had been reduced tenfold by formation of this "complex" with PVP. This was an astounding discovery, the basis for many commercial products in the years to follow. Imagine gargling with iodine, a material known only as a potent poison until then, carrying the skull-and-cross-bones label!

As early as 1954, Shelanski and Cantor (54) reported on the reduction of irritation of sodium alkyl sulfates *via* addition of 1 per cent PVP. Many other examples of detoxification and antiirritancy were later discovered for this material, summarized in Wood's excellent review (55) which lists 148 references.

Scher Chemical Co. recently reported that Acetamide MEA demonstrates (eye) antiirritant properties in conjunction with sodium lauryl sulfate (Table IV). This unusual material may, therefore, be of interest in shampoo formulations.

Two other major examples of antiirritancy do not fall into "simple" chemical categories: the quaternary ammonium saccarinate complexes and certain sulfo-succinate amido surfactants. In a manner reminiscent of the behavior of PVP, cationic saccarinate complexes are more effective than the "parent" benzalkonium quats from which they are derived, yet their oral toxicity is so low as to allow their use in mouth washes. Their

Table X

Ricinoleic Acid Sulfosuccinate Monoethanolamide (SS/RAM)

(Antiirritant Effect on Addition to Typical Foaming Agents *via* "Repeated Insult" Skin Testing)

I. Addition of SS/RAM to Sodium Dodecyl Benzene Sulfonate (SDBS):

10 per cent SDBS alone (control)									10 per cent SDBS + 0.5 per cent SS/RAM									10 per cent SDBS + 1 per cent SS/RAM								
Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total
	1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4	
1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
2	1	0	2	1	0	0	2	0	6	2	1	0	1	1	0	0	2	0	5	2	2	1	0	0	0	0	0	0	3
3	1	1	3	2	0	1	3	3	14	3	2	1	2	1	0	0	2	1	9	3	2	1	0	1	1	1	0	1	7
4	1	1	4	3	0	1	3	2	15	4	1	0	2	2	0	0	2	2	9	4	2	2	1	1	1	1	0	1	10
Control									35										23										20

II. Addition of SS/RAM to Sodium Lauryl Ethyl Sulfate (SLES):

10 per cent SLES alone (control)									10 per cent SLES + 0.5 per cent SS/RAM									10 per cent SLES + 1 per cent SS/RAM								
Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total
	1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4	
1	1	0	0	0	0	0	0	0	1	1	1	0	0	1	0	0	0	0	2	1	1	0	0	0	0	0	0	0	1
2	1	1	2	3	1	0	2	1	11	2	2	2	2	2	0	0	1	1	10	2	1	1	1	1	0	0	1	1	6
3	1	2	2	4	0	1	1	2	13	3	2	2	2	3	1	0	1	2	13	3	1	1	2	2	0	2	0	3	11
4	2	2	3	4	1	1	2	3	18	4	2	2	3	3	2	1	0	1	14	4	1	2	2	3	0	0	0	3	11
Control									43										39										29

III. Addition of SS/RAM to Sodium Lauryl Sulfate (SLS):

10 per cent SLS alone (control)									10 per cent SLS + 0.5 per cent SS/RAM									10 per cent SLS + 1 per cent SS/RAM								
Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total
	1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4	
1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
2	1	2	3	1	0	0	2	0	9	2	1	2	1	0	0	0	0	0	4	2	0	0	0	0	0	0	0	0	0
3	1	3	2	3	0	1	0	2	12	3	0	2	1	1	0	0	0	1	5	3	1	1	0	1	0	0	0	0	3
4	1	3	2	4	0	0	1	3	14	4	1	2	1	2	0	0	0	1	7	4	1	1	0	0	0	0	0	1	3
Control									35										16										6

5 per cent Primary Irritation index is zero, their 1 per cent solutions safe in the eye (Table IX). Formation of the saccarinate complex, whatever its mechanism, clearly reduces the normal toxicity and irritation of benzalkonium quaternary compounds.

Amido-sulfosuccinate surfactants have also recently received considerable publicity for their apparent ability to reduce the eye irritation of shampoo formulations. One such product, disodium monoricinoleamido MEA sulfosuccinate, has been shown to reduce Draize eye irritation scores by 32 to 54 per cent when added at 1 per cent to 10 per cent alkyl sulfate solutions (Table X).

CONCLUSIONS

Quite clearly, hydroxy compounds (and their related carboxy derivatives) have a special interest to those seeking topical antiirritant effects. In particular, hydroxyl compounds demonstrating keratin substantivity ("sorption") appear to be of particular interest.

A second major category, imidazole and imidazoline compounds, also repeatedly demonstrated activity in this respect—perhaps *via* preferential sorption to keratin binding sites. It is proposed that this mechanism may explain the "no tears" effect obtained from mixing amphoteric surfactants (plus Polysorbate 20) with typical anionic shampoo ingredients.

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The evaluation of fluoride dentifrices

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Synopsis

Four laboratory tests were investigated as indicators of the compatibility of FLUORIDE SOURCE and ABRASIVE SYSTEM in FLUORIDE DENTIFRICES. These were solubility of the fluoride in water, ability to reduce the solubility of dental enamel in acid *in vitro*, uptake of fluoride from the dentifrice *in vitro*, and a rat assay for anticaries efficacy. Dentifrices were formulated with 1000 ppm fluoride (as NaF, SnF_2, or Na_2PO_3F) and with abrasives known to either interact or not interact with those particular fluorides. Also, clinically proven commercial products were examined. The assays for water-solubility of the fluoride and the rat assay clearly distinguished between the dentifrices with respect to compatibility of fluoride source and dentifrice abrasive, in agreement with the results of clinical trials reported in the literature, involving different abrasives and sources of fluoride.

INTRODUCTION

Fluoride dentifrices, as opposed to purely cosmetic dentifrices, now account for approximately 80 to 85 per cent of the United States' market, and are becoming increasingly important in dentifrice markets throughout the world. The anticaries efficacy of dentifrices containing fluoride with compatible toothpaste excipients has been proven in numerous clinical trials. (Most of those which have been reported in the literature up to 1972 are summarized by Gershon *et al.* (1)). These trials demonstrated that a properly formulated fluoride dentifrice containing 1000 ppm fluoride incorporated as stannous fluoride, sodium fluoride, or sodium monofluorosphosphate can be expected to reduce the caries rate by some 15 to 30 per cent over the course of 2 to 3 years when used in normal dentifrice fashion by populations susceptible to caries.

Fluoride dentifrices in the United States, Canada, and elsewhere are categorized as drugs. As such, their formulation poses unique and difficult problems. Both safety and efficacy must be firmly established before marketing. There are only a few who at this time question either safety or efficacy of fluoride combined with a compatible cleaning system, but there is still no unanimity with respect to the means for proving compatibility and efficacy. Views have ranged from simply the presence of a prescribed amount of fluoride in a soluble form as adequate evidence of efficacy to the requirement of several clinical trials to prove such efficacy. One of the more important reasons for such a divergence of views is the lack in the literature of virtually any correlations between the results of chemical and animal assays for efficacy and those of clinical tests. The former types of tests have in some instances given results not subsequently satisfactorily confirmed by clinical test when applied to agents other than fluoride. On the other hand, caries clinical tests are far from precise, and they, too, have suffered from

lack of reliability, frequently not showing positive results for established fluoride products. But perhaps the greatest dilemma is that caries clinical trials on fluoride dentifrices are not undertaken unless the formulation has passed several laboratory tests; clinical testing of dentifrices is too consuming of time, financial resources, and personal effort for it to be undertaken on a purely exploratory basis. The consequence is that virtually all clinical trials conducted during the past decade or two employed fluoride systems which, on the basis of laboratory data, were expected to give positive results when tested clinically. More often than not, these expectations were realized, and in a sense, this provided evidence for the validity of laboratory tests as a predictor of clinical efficacy of fluoride dentifrice systems. But very few publications have appeared which present the other side of the coin, *viz.*, negative clinical findings, and it is only when studies are conducted to establish dose-response curves for fluoride in dentifrice, the effects of altering the excipients, and the role of other dentifrice properties (e.g. abrasion) can a scientifically cohesive and complete concept emerge for fluoride dentifrice formulation. It is doubtful that this ideal situation will ever be achieved; the costs and frailties of clinical trials are too great. Nonetheless, there is a substantial body of work, already available, from which one can draw upon to shed light on the problem.

Fluoride dentifrices have been formulated with abrasives and other excipients which result in minimal insolubilization of the fluoride ion because it is considered essential for efficacy that some minimal amount of "free" fluoride be present to react with the dental substrate, *viz.*, that availability of the fluoride depends on its being in soluble form.

Hefferren (2) pointed to the need for analyzing fluoride dentifrices for water-soluble anticaries species, and presented procedures for the assay of fluoride in solution. Hefferren (3), Cooley (4), and Gershon *et al.* (5) discussed and presented methodology for the assessment of the ability of fluorides to reduce the solubility in acid of dental enamel. König *et al.* (6) and others presented animal assays designed to evaluate the anticaries value of a fluoride preparation. Brudevold *et al.* (7) suggested that uptake of fluoride by dental enamel can be an important aspect of fluoride efficacy. In the current studies, several of these laboratory tests were conducted with dentifrices in which the fluoride was added at a level of 1000 ppm, but in which interaction of fluoride and abrasive reduced the amount of fluoride soluble in water to varying degrees. Thus, any differences in response in the assays could be attributed with reasonable assurance to differences in the amount of fluoride in soluble form. Appropriate responses, i.e., decrease in effect with decrease in water-soluble fluoride species, whether fluoride ion or monofluorophosphate ion, would lend support to the concept that availability of the fluoride species, i.e., its water solubility, is the prime requisite to dentifrice efficacy. The results are also discussed in relationship to the value of tests for bioavailability of the fluoride species in predicting the clinical efficacy of a dentifrice containing any of the three commonly used sources of fluoride—stannous fluoride, sodium fluoride, or sodium monofluorophosphate.

METHODS

EXPERIMENTAL DENTIFRICES

Dentifrices were prepared employing conventional abrasives, humectants, and foaming agents. They were packed into appropriate tubes and equilibrated at room temperature

before being subjected to assay. In some instances, where the assay required several weeks, the state of solubility of the fluoride was determined at the beginning and end of the assay period. The fluoride sources studies were SnF_2, NaF, and Na_2PO_3F. The abrasives examined were dicalcium phosphate dihydrate (DPD), chalk, calcium pyrophosphate, insoluble sodium metaphosphate (IMP), and silica gel. A commercial dentifrice was used as the calcium pyrophosphate product to be assured that the abrasive had the correct properties; this introduced an uncontrolled factor which did not appear to confuse the results of the study. Similarly, a commercial dentifrice was used as the IMP product. The compositions of these products have been reported (8).

ESTIMATION OF AVAILABLE FLUORIDE

Soluble or available fluoride was determined essentially as described by Hefferren (2). This involved dilution of the dentifrice 1:10 with water, centrifugation to obtain a clear supernatant solution, and analysis of the solution for fluoride by electrode or chemically, as appropriate. The major deviation from Hefferren's procedure was use of a 1:10 dilution; Hefferren recommended a 1:3 dilution. The higher dilution gave higher values for available fluoride, but in all instances the two methods ranked available fluoride content of the various products in the same way.

ESTIMATION OF ABILITY OF DENTIFRICE TO REDUCE SOLUBILITY OF DENTAL ENAMEL IN ACID (RES)

The RES method reported by Hefferren (3) was employed. Six enamel crowns were mounted in acrylic and placed in a vessel. The susceptibility of the enamel to dissolution was measured by exposing the teeth to a lactic acid-lactate buffer solution at pH 4.5, under standardized conditions of temperature, time, concentration, solution volume, pH, and stirring rate. The amount of phosphate dissolved by the buffer solution was determined. The same teeth were then exposed to a 25 per cent (W/W) slurry of fluoride dentifrice in water for a specific period of time. The teeth were then rinsed with water, and a second measurement of enamel dissolution was made. The amount of phosphate present in the initial and final buffer solutions provided the RES value:

$$\text{RES per cent} = \frac{\left[PO_4^{-3}\right]\text{ initial} - \left[PO_4^{-3}\right]\text{ final}}{\left[PO_4^{-3}\right]\text{ initial}} \times 100$$

FLUORIDE UPTAKE IN TOOTH ENAMEL

The degree of incorporation of fluoride into tooth enamel was evaluated using a modification of the procedure reported by Brudevold *et al.* (7). Noncarious enamel crowns were mounted in wax at the base of small glass vials. The crowns were then subjected to several successive etchings with 0.5 *M* $HClO_4$ until a constant amount of fluoride was removed at each etching. The fluoride concentration per million parts of surface enamel removed by etching was determined by analyzing the etching solutions for calcium, phosphorous, and fluoride. The teeth were then exposed to 25 per cent (W/W) slurry of fluoride dentifrice in water for 15 min. Following this exposure, the teeth were rinsed in dionized water and etched again with 0.5 *M* $HClO_4$. The post-

treatment etch solution were analyzed. The difference between the fluoride content of the treated tooth surface and that of the untreated tooth surface gave the amount of fluoride incorporated into the enamel.

ANIMAL MODEL SYSTEM FOR ASSESSING CARIES REDUCTION BY FLUORIDE DENTIFRICES

The animal assay system employed was essentially that of König *et al.* (6). It gave an excellent dose-response curve with aqueous fluoride solutions containing fluoride at levels occurring in dentifrices. (The method will only be outlined here; details will be reported elsewhere.) Osborne-Mendel albino rats were employed. They were maintained under conditions generally observed for specific pathogen-free animals. Females were fed a balanced vitamin-supplemented diet from mating to the end of the suckling period. Trials were started on the day of weaning. Weanlings were randomly distributed to the various treatments, the animals being distributed among the cages so as to equalize the stresses of weaning, treatment, and cariogenic diet. A cariogenic diet was fed *ad libitum*. It consisted of sucrose (56 per cent) plus milk powder and other essential nutrients. About 24 animals were subjected to each treatment. Twenty-second applications of the materials to be tested were applied to the lower jaws by means of a marten-hair brush, using about 15 to- and fro- motions of the brush. The rats were deprived of food and water for 1 h after treatment. The treatments were applied twice daily during the first 2 weeks and once daily during the third week (no treatment on Sundays). The rats were sacrificed, and the lower jaws were removed and prepared for sectioning and evaluation of carious lesions after staining. The severity of carious lesions in the first and second molar teeth was assessed by the method of König *et al.*, which grades carious lesions in terms of the stages of the carious process from start (in the enamel) through the next stage (in the dentin) to the conclusion (cavitation). In essence, 4 stages are recognized after staining: *A* lesions (limited to enamel, no staining of the adamantine border), *T* lesions (early dentinal lesion, involving color reaction at the adamantine border), *B* lesions (moderate dentin lesion, comprising progression of the lesion with decalcificiation of dentin bordering on the pulp), and *C* lesions (severe dentin lesion, involving destruction in the direction of both the pulp and occlusal surfaces, loss of enamel in the sulcus, and first signs of cavitation). In calculating the reduction of incidence of carious lesions produced by the test products compared to nonfluoride products in the current study, only the more severe lesions (B and C) were considered. These values were combined, and reduction in carious lesions calculated as:

$$\text{Per cent reduction lesions} = 100 \times \frac{(\text{B + C lesions on nonfluoride dentifrice}) - (\text{B + C lesions on fluoride dentifrice})}{(\text{B + C lesions on nonfluoride dentifrice})}$$

Of course, the values obtained by this procedure are valid for only within-trial comparisons. Also, it should be recognized that the magnitude of the reduction in numerical terms can depend on the value attributed to the various lesions; in this study it was found advantageous to base the calculatons of fluoride effect in the rat on only the B and C lesions.

Table I

	A	B	C	D	E	F	G	H_1	H_2	I[a]	J[b]
Abrasive	DCPD 47 per cent	DCPD 47 per cent	DCPD 47 per cent	DCPD 47 per cent	$CaCO_3$ 37.5 per cent	$CaCO_3$ 37.5 per cent	Silica gel 21 per cent	Silica gel 21 per cent	Silica gel 21 per cent	IMP+DCP 42 per cent 5 per cent	$Ca_2P_2O_7$ 39 per cent
Fluoride	None	NaF 0.22 per cent	SnF_2 0.40 per cent	MFP 0.80 per cent	NaF 0.22 per cent	MFP 0.80 per cent	—	SnF_2 0.41 per cent	MFP 0.80 per cent	MFP 0.76 per cent	SnF_2 0.4 per cent
Other ingredients											
Humectants	27 per cent	27 per cent	27 per cent	27 per cent	21 per cent	21 per cent	72 per cent	72 per cent	72 per cent	22 per cent	30 per cent
Miscellaneous formulating ingredients	3.6	3.6	3.6	3.6	4.0	4.0	4.0	4.8	4.8	[a]	[b]
Water to 100 per cent	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

[a]Colgate toothpaste; composition taken from *Accepted Dental Therapeutics*, 36th Edition, American Dental Association.
[b]Crest toothpaste; composition taken from *Accepted Dental Therapeutics*, 36th Edition, American Dental Association.

RESULTS AND DISCUSSION

In these experiments, model toothpaste systems were formulated in which the abrasive and the fluoride were either compatible or incompatible. Compatibility was shown by a high proportion of the added fluoride remaining in a water-extractable form, and incompatibility was shown by the fluoride being complexed with the abrasive and being insolubilized thereby. Separate experiments (not reported here) demonstrated very clearly that the humectants (glycerol and sorbitol), binding agent, and foaming agent, and flavor did not influence the interaction between the fluoride and the dentifrice abrasive in formulations typical of those investigated in this study. Other trials, with the silica-SnF_2 system, gave results which demonstrated that the nature of the nonfluoride ingredients other than the abrasive did not detectably affect the response to the fluoride in the assays for fluoride solubility, reduction of enamel solubility, or rat caries inhibition.

DENTIFRICES STUDIED

Table I shows the compositions of the dentifrices investigated in terms of abrasive, fluoride source, and other ingredients such as humectant and miscellaneous formulating ingredients, the latter including binding agent, flavor, and foaming agent. The compositions of the dentifrices were selected (1) to provide a basis for a placebo, i.e. nonfluoride paste, to be used for the animal caries trials, and (2) to provide compositions which would reveal differences in response between dentifrices containing different dentifrice abrasives and different sources of fluoride. The dentifrices were assayed in groups, the number of products per group being limited by the logistics of the rat caries test. Thus, for example, dentifrices A through F were tested in the rat caries test alongside each other in order to achieve maximum comparability of results and statistical validity.

Dentifrices A through F represent products with either (1) no fluoride, (2) abrasives which are known to interact with free fluoride ion, or (3) sources of fluoride ion which have been shown to be reactive with calcium-containing dentifrice abrasives on one hand and nonreactive on the other hand.

Dentifrice A is the placebo in the A-F series. It contains as abrasive dicalcium phosphate dihydrate, and contains no fluoride. Dentifrice B comprises dicalcium phosphate dihydrate and, as fluoride source, sodium fluoride. Sodium fluoride is known to interact with dicalcium phosphate dihydrate. Dentifrices C and D both contain dicalcium phosphate dihydrate as the abrasive; C contains stannous fluoride while D contains sodium monofluorophosphate. Dentifrices E and F contain calcium carbonate as the abrasive, E containing sodium fluoride as source of fluoride ion and F containing sodium monofluorophosphate.

Dentifrices G through I represent a group of dentifrice compositions in which the fluoride source and the abrasive are known to be compatible. In this series, dentifrice G represents the placebo. The last test series of dentifrices is represented by dentifrices G, H_1, H_2, and J. Both H_1 and J contain stannous fluoride and a compatible abrasive. Dentifrice G, again, represents the placebo.

Table II
Evaluation of DCPD and $CaCO_3$ Dentifrices

Product	Abrasive/ Fluoride[a]	Available Fluoride Initially ppm	Available Fluoride After 7 Weeks ppm	Reduction in Enamel Solubility Per Cent	Reduction in Carious (B + C) Lesions in Rat Trial Per Cent
A	DCPD/–	—	—	−4.2	—
B	DCPD/NaF	155	143	15.6	6
C	DCPD/SnF_2	130	111	23.0	4
D	DCPD/MFP	864	888	16.9	44
E	$CaCO_3$/NaF	378	354	8.5	27
F	$CaCO_3$/MFP	856	844	6.4	51

[a]All dentifrices formulated with 1000 ppm added fluoride, as NaF, SnF_2, or MFP.

"COMPATIBLE" VERSUS "INCOMPATIBLE" SYSTEMS

The results with dentifrices A through F are given in Table II. Data are given for water-soluble fluoride at the beginning and at the end of the rat caries trial (which covered a period of 6 weeks), reduction in enamel solubility, and reduction in carious lesions in the rat trial.

Water-solubility of the fluoride:

The incompatibilities of certain of the fluoride sources and the dentifrice abrasive are clearly demonstrated. In each instance (except for the nonfluoride control, dentifrice A), fluoride was added at a level of 0.10 per cent (fluoride basis). Substantial interaction and insolubilization of the fluoride occurred very rapidly as demonstrated by lowered values for water-soluble fluoride. Both sodium fluoride and stannous fluoride reacted with the dicalcium phosphate dihydrate, and over 85 per cent of the fluoride was insolubilized within 1 week after manufacture of the dentifrice. Sodium fluoride showed less reactivity with calcium carbonate than it did with dicalcium phosphate dihydrate, but even in this instance, almost 60 per cent of the fluoride was insolubilized by the abrasive. Sodium monofluorophosphate, in contrast to sodium fluoride and stannous fluoride, showed excellent compatibility with the dicalcium phosphate dihydrate and calcium carbonate, and not more than about 15 per cent of the fluoride ion contained therein was rendered insoluble over the course of the trial.

Reduction in enamel solubility (RES):

The RES test, the ability to so affect dental enamel as to make it more resistant to attack by acid, has been a valuable criterion for assessing the utility of potential anticaries compounds. It is not the intent here to explore in depth relations between the RES test and other anticaries agent assays. They do not necessarily measure the same parameters. For example, the RES test involves a single parameter, *viz.*, attack by acid on dental enamel, while the rat caries assay involves multiple parameters related to the carious process. Factors which quantitatively affect one test markedly may be less important in another. A case in point is the nature of the cation associated with the fluoride. The RES value is markedly affected by the presence of the stannous ion in an ac-

tive form. Hefferren (3) showed that the rate and extent of dissolution of dental enamel in acid varied with the treatment (SnF_2, NaF, $SnCl_2$), and that the $SnCl_2$ was a very effective inhibitor of dissolution when the time of acid attack was limited to a few minutes, but not when it was extended to 2 h. SnF_2 produces greater reductions in RES than an equivalent amount of MFP. The mechanism whereby MFP influences resistance of enamel to acid differs from that of the simpler fluorides.

Table III
Reduction of Enamel Solubility by SnF_2 Dentifrices

Dentifrice Type	Abrasive	Available Fluoride ppm	Reduction of Enamel Solubility Per Cent
C	DCPD	130	23.0
H_1[a]	Silica gel	Average 790 Range 750–880 n = 8	64 54–72 n = 20
J[a]	$Ca_2P_2O_7$	Average 710 Range 640–750 n = 8	38 14–60 n = 4

[a]Commercial products, selected randomly for analysis. J reportedly contains stannous pyrophosphate in addition to stannous fluoride.

In Table III, the SnF_2 dentifrices C (DCPD/SnF_2), H_1 (silica/SnF_2), and J ($Ca_2P_2O_7$/SnF_2) show the importance in the RES test of having the active ions in water-soluble form. The response to the test was directionally in proportion to the amount of fluoride ion available. However, strong conclusions cannot be drawn, since the data are limited and the role of tin, whether soluble or insoluble in the dentifrice, was not assessed.

In Table II it can be seen that MFP-containing dentifrices (D and F) yielded only relatively small reductions in enamel solubility compared to SnF_2 containing dentifrices despite the high levels of available active ion(s) in the former. In Table II it is also apparent that on a strictly numerical basis the results of the RES test did not correlate with the rat caries assay results. It can be concluded that results of the RES test should be examined independently of those of the rat caries assay, as evaluating different parameters of activity of anticaries agents.

Rat caries trials:

Of greatest significance are the results of the rat caries trials. Here, a definite relationship was established between the ability of a dentifrice to reduce the incidence of carious lesions and the level of water-soluble fluoride or fluorophosphate ion. In Table II are the results of a series of trials in which NaF, SnF_2, and MFP were combined with abrasives which are incompatible with NaF and SnF_2 but compatible with MFP. A key finding was that fluoride ion bound to the abrasive was inactive in protecting the rat against caries. This effect has been hypothesized on many occasions, but it is believed that the series of tests reported here provides the first published clear cut evidence for

Table IV
Rat Caries Trial Number 1

Dentifrice	Type	Reduction in Carious Lesions (Per Cent)	Available Fluoride (as F) (ppm)
G	Silica, no F	—	Nil
H	Silica/SnF_2	50	880
I	IMP + DCP/MFP	70	950[a]
J	$Ca_2P_2O_7/SnF_2$	73	730

[a]Not determined specifically for this trial. The water-soluble content of this commercial dentifrice has been found on several occasions to be about 950 ppm.

Table V
Rat Caries Trial Number 2

Dentifrice	Type	Reduction in Carious Lesions (Per Cent)	Available Fluoride (as F) (ppm)
G	Silica, no F	—	Nil
H_1	Silica/SnF_2	37	790[a]
H_2	Silica/MFP	37	960
I	IMP + DCP/MFP	31	950[a]
J	$Ca_2P_2O_7/SnF_2$	29	710[a]

[a]Available fluoride contents of the commercial dentifrices (H_1, I, J) were not determined specifically for this trial; the available fluoride values are average values for the commercial products (cf. Table III).

Table VI
Rat Caries Trial Number 3

Dentifrice	Type	Reduction in Carious Lesions (Per Cent)	Available Fluoride (ppm)
G	Silica, no F	—	Nil
H_1	Silica/SnF_2	42	820
H_2	Silica/MFP	34,30	950,990
I	IMP + DCP/MFP	36	950

differentiation of soluble and bound fluoride in a dentifrice using an animal system. Dentifrices D (DCPD/MFP) and F($CaCO_3$/MFP), both containing MFP at a level of 0.8 per cent (1000 ppm fluoride) produced significant reductions in caries. Dentifrices B (DCPD/NaF) and C (DCPD/SnF_2), representing pastes with sodium fluoride and stannous fluoride in an incompatible base gave negligible reductions in carious lesions despite the fact that they, too, contained 1000 ppm fluoride. It must be concluded that their low order of efficacy was attributable only to the low amount of available fluoride. Dentifrice E, which contained sodium fluoride in a calcium carbonate base, did yield a modest reduction in rat caries. However, the level of available fluoride at the time of the test was reasonably high, i.e. intermediate between that of the DCPD/NaF dentifrice and DCPD/MFP dentifrices. Presumably, it would decrease on aging, as reaction between the fluoride and abrasive progressed.

Table VII
Fluoride Uptake After 5 Min Exposure

Group Treated with Product J				Group Treated with Product H_1			
Sample Numbers	Pretreatment ppm F	Post-Treatment ppm F	Uptake ppm F	Sample Numbers	Pretreatment ppm F	Post-Treatment ppm F	Uptake ppm F
III-1	147.4	253.8	106.4	IV-1	69.4	136.7	67.3
III-2	81.9	126.6	44.7	IV-2	51.5	181.0	129.5
III-3	98.4	142.8	44.4	IV-3	75.9	148.7	72.8
III-4	34.0	97.6	63.6	IV-4	75.5	167.5	92.0
III-5	62.0	162.0	100.0	IV-5	46.5	147.9	101.4
III-6	34.0	120.4	66.4	IV-6	87.2	241.5	154.3
III-7	56.2	152.4	96.2	IV-7	233.6	336.0	102.4
III-8	113.5	348.8	235.3	IV-8	195.6	460.3	244.7
III-9	37.7	158.1	120.4	IV-9	42.7	151.2	108.5
III-10	40.8	106.5	65.7	IV-10	79.7	171.4	91.7
III-11	79.5	176.6	97.1	IV-11	45.8	159.0	113.2
III-12	52.8	105.5	52.7	IV-12	118.3	225.7	107.4
III-13	53.4	75.0	21.6	IV-13	70.7	307.5	236.8
III-14	151.8	240.3	88.5	IV-14	103.0	261.4	158.4
III-15	69.7	121.3	51.6	IV-15	125.9	351.2	226.3
III-16	72.7	144.1	71.4	IV-16	67.7	230.9	163.2
III-17	80.0	123.0	43.0	IV-17	135.1	556.6	421.5
III-18	186.1	184.7	Nil	IV-18	42.1	168.1	126.0
III-19	180.5	180.6	Nil	IV-19	59.3	276.6	217.3
III-20	55.0	116.8	61.8	IV-20	45.2	767.3	722.1
III-22	83.5	165.6	82.1	IV-21	77.1	180.7	113.6
III-23	45.6	169.1	123.5	IV-22	328.1	339.8	11.7
III-24	132.9	221.6	88.7	IV-23	57.2	287.7	230.5
				IV-24	63.3	154.3	91.0
Average			75.0	Average			171.0
N			(23)	N			(24)
S.D.			48.4	S.D.			144.2

"COMPATIBLE" SYSTEMS

Tables IV, V, and VI give data on additional trials with compatible abrasive/fluoride systems. The data are organized according to products assayed simultaneously in a single rat caries trial. All of the reductions in carious lesions over the nonfluoride product were significant at $p < 0.05$. Comparison of data from trial-to-trial was not statistically valid. The results given in Tables IV to VI show: (1) compatible abrasive/fluoride systems respond positively in the rat caries test; (2) the response is positive regardless of whether the fluoride source is SnF_2 or MFP; and (3) the response is positive regardless of the abrasive when the abrasive is compatible with the fluoride. The results confirm those of Table II, and in conjunction with the latter results support current concepts which require that clinical fluoride efficacy in a dentifrice critically depends on the fluoride and abrasive being compatible.

Uptake of fluoride by dental enamel:

Only limited data were obtained on the uptake of fluoride by human tooth enamel. This technique is difficult to carry out for many reasons, the major one being the large number of tooth samples required to assure statistical confidence. There is, as would be expected, great variability from tooth to tooth, even within teeth from the same

person. Soundness of the tooth surface, history of exposure to fluoride, and other factors come into play.

The results of a comparison of dentifrice H_1 and J are given in Table VII. They reveal that fluoride can be taken up *in vitro* from dentifrice slurries containing a substantial amount of available fluoride. Further studies will be necessary to determine the extent to which this uptake is dependent on the availability of the fluoride and/or other factors; the data in Table VII suggest that such may be so, but are far from adequate to establish a case with any degree of confidence. The data in Table VII clearly demonstrate the extreme variability in fluoride uptake from tooth sample to tooth sample, and thus the importance of conducting studies of new formulations with sufficient numbers of teeth and appropriate controls.

DISCUSSION

The foregoing results help evaluate the utility of 3 tests used to assess the anticaries activity of a fluoride dentifrice, *viz.*, reduction in enamel solubility (RES), uptake of fluoride by enamel, and animal caries assay.

The RES test gave results which cannot be interpreted readily. The values failed to correlate well with either the water-soluble fluoride content or the rat assay values. The RES values in Table II seem to reflect more an abrasive effect than a fluoride effect. At this time, it is probably safest to conclude that the RES test as applied to a fluoride dentifrice can show whether that dentifrice exerts an effect on the substrate (tooth enamel), but that this may not be translated to a positive anticaries effect.

The ability of the enamel to take up fluoride has been investigated extensively as a tool to evaluate fluoride treatments. Insufficient data are presented here to draw firm conclusions. What results are shown certainly do not point to a quantitative correlation between the amount of fluoride taken up from a dentifrice and the degree to which that dentifrice inhibits the development of carious lesions in the rat on a cariogenic diet. Additional investigations are required before the results of fluoride uptake *in vitro* can be interpreted with confidence.

The rat caries assay as conducted in our laboratories (details to be published elsewhere) gave results which are consistent and readily interpretable. They show a correlation with available fluoride, and do not seem to show a response to fluoride which is insolubilized by the abrasive. Of greater importance is the observation that the rat assay exhibits a positive response to all fluoride dentifrice systems which have been reported in the literature to be clinically effective, such as $Ca_2P_2O_7/SnF_2$ and IMP + DCP/MFP, and $CaCO_3$/MFP. Furthermore, the magnitude of effect of such clinically tested dentifrices such as $Ca_2P_2O_7/SnF_2$ and IMP + DCP/MFP is about the same when determined by the rat assay and about the same when determined by human clinical trial; thus, the rat assay has shown the equivalence of certain formulations which has been shown clinically.

More extensive and exact experiments than those reported here are needed to establish quantitative correlation between the RES and fluoride uptake tests on one hand and the rat caries assay on the other. The RES test and the fluoride uptake test measure the effect of fluoride dentifrices on specific parameters involved in the fluoride effect on caries. The rat caries assay, on the other hand, measures efficacy of a fluoride denti-

frice in terms of the totality of the carious process. The RES and fluoride uptake tests are extremely important in showing ability of an agent to interact beneficially with the tooth substrate; they are limited as an evaluative tool in providing less than a full picture. The rat assay can be criticized on the same basis that all animal systems can be criticized, i.e., differences between human and animal systems. But compared to the other, *in vitro.* tests which involve only an enamel substrate, it alone gives a complete assessment of efficacy which is compatible with current concepts of fluoride dentifrice formulation and the results of human clinical trials.

The carious process is extremely complex. Hefferren (3) has summarized more recent thinking on the carious process and on the design of anticaries agents. He has also pointed to the incompleteness of our knowledge on the mechanism of fluoride action. And he has indicated the need for greater reliance on definitive laboratory studies, the basis for which is correlation of experimental data on the new product with the clinically established product. The studies reported above clearly define such a correlation.

It is becoming increasingly apparent that caries is a specific disease state, caused by specific disease organisms. The route to cure of this disease is not unlike that of any other disease–eliminate the causative microorganisms(s), combat the microorganism(s) by making the environment unfavorable, and/or increase the resistance of the substrate to the action of the microorganism(s). The mechanism of anticaries activity for a fluoride, while not totally understood, is generally considered to involve, at a minimum, the incorporation of fluoride into the dental enamel and strengthening of the enamel thereby against acid attack, which acid is generated by specific microbial populations under favorable environmental conditions. A direct effect of fluoride on the microbial metabolism has not been ruled out as another route of fluoride action. Other mechanisms may be involved, such as interactions of effects of fluorides and effects of variations in substrate (tooth) characteristics.

The tests described above follow the pattern commonly used in the assessment of drug efficacy when formulating products containing drugs of established efficacy. Fluoride "availability" assures that the drug is in an active (noncomplexed) state. Reduction in enamel solubility (*in vitro*) and fluoride uptake (*in vitro*) give further assurance that the drug is in a state wherein it can act on the substrate, and the animal assay gives final assurance that the drug is active against the disease process *in vivo.*

The ideal situation in correlating the results of *in vitro* and animal assays with the human assay is a series of studies in which dose-response curves are available for all the test situations. Such is not feasible in the fluoride arena, and only one real attempt to establish a dose-response to fluoride in a (compatible) abrasive system appears to have been reported. Reed (9) conducted two-year clinical trials with calcium pyrophosphate dentifrices containing 0, 250, 500, or 1000 ppm added fluoride (as NaF). All 3 fluoride products resulted in a significant reduction of the parameter "decayed, missing, and filled teeth." Only the product with 1000 ppm fluoride, however, gave a significant reduction in the more relevant parameter, "decayed, missing and filled tooth surfaces" (DMFS). Trends, however, pointed to a dose-response relationship with both parameters. DMFS reductions, for example, were: 7.5 per cent for 250 ppm F, 8.5 per cent for 500 ppm F, and 20.0 per cent for 1000 ppm F. Extension of the study to a third

year might have established a good dose-response curve. With the exception of Reed's work, no clinical trials have been found in the literature to establish a dose-response in fluoride dentifrices.

Lacking totally appropriate experimental clinical data on which to base judgments of the effect of fluoride in a dentifrice on dental caries, i.e., lacking dose-response clinical data of the type available for most drugs, one can assess the value of *in vitro* and animal data for fluoride dentifrices in relationship to clinical efficacy only by reference to the treatment of comparable data for other drug products. This has already been done in a sense by fluoride dentifrice investigators; it is universally accepted that a prime prerequisite for formulation of any fluoride dentifrice is that the fluoride source must not interact excessively with the abrasive and thereby become insolubilized. The experimental data presented above, particularly the data in Table II, support this view in its entirety. No thinking dentifrice formulator today would, for example, incorporate sodium fluoride into a DCPD dentifrice, or SnF_2 into a DCPD dentifrice.

The results in Table II are especially important in that they point out definitively that *in vitro* and animal data disclose compatibility relationships between fluoride source and abrasive which do tend to qualitatively correlate with clinical trial data reported in the literature. Thus, for example, MPF is shown to be compatible with every abrasive tested (DCPD, $CaCO_3$, IMP + DCP), and clinical results have been reported establishing the clinical efficacy of MFP not only in dentifrices containing these abrasives (e.g. 10, 11), but also with another compatible abrasive, *viz.*, alumina trihydrate (12). On the other hand, there are reports of negative findings with NaF in dentifrices containing DCPD as the abrasive (13). This type of correlation should not be overlooked in assessing the significance of the *in vitro* and animal tests reported here.

SUMMARY

Four laboratory assays were applied to dentifrices formulated with a variety of abrasives and fluoride sources. These were: (1) fluoride availability; (2) reduction in enamel solubility (RES), (3) fluoride uptake by human dental enamel; and (4) rat caries assay. The assays for fluoride availability and the rat assay very clearly distinguished between the dentifrices based on compatibility of the fluoride source with the abrasive. The results of the RES and fluoride uptake assays gave valuable information on the ability of a fluoride in a dentifrice to interact with the dental enamel. The results clearly support current views of fluoride dentifrice formulation, i.e., that the fluoride must not be insolubilized by the abrasive if it is to have anticaries activity. They also correlate qualitatively with results of clinical trials reported in the literature, involving different abrasives and sources of fluoride.

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The tensile properties of hair fibers in 1-propanol water mixtures

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Synopsis

The stress–strain curves of intact hair fibers immersed in aqueous 1-propanol solutions were measured as functions of 1-propanol concentration, pH and temperature. Plots of the tensile forces at given extensions against the propanol concentrations show minima at about 50 per cent propanol; these become more pronounced at low pH values and at higher temperatures.

The experimental results can be interpreted by assuming that two additive molecular processes are responsible for the elasticity of hair: conformational changes of the polypeptide chains and electrostatic interactions between the various ionic side chains. The presence of 1-propanol in low concentrations accentuates the importance of the latter process by diminishing the value of the effective dielectric constant inside the hair structure. At high propanol concentrations, however, the dehydration of the fibers increases the relative contribution of the conformational changes and brings about a strengthening of the hair.

I. INTRODUCTION

Alcohols are extensively used in the formulation of hair care products. Although many of the technologically important properties of keratin fibers have been known to be affected by exposure to alcohols (1, 2) (e.g., the elastic modulus and the temperature of supercontraction both change when hair is immersed in aqueous alcoholic solutions (3)), the mechanisms responsible for these processes are still unclear. Essentially, two hypotheses have been formulated to account for these phenomena. Blankenberg and Zahn (2) suggested that the alcohols break hydrophobic bonds and thus, weaken the keratin structure. Breuer (4), on the other hand, postulated that the presence of alcohols in the keratin fiber alters the transition equilibrium between the organized and amorphous regions of keratin and, therefore, affects the stress–strain characteristics of the fibers.

Neither of these hypotheses allowed for the possibility that the absorption of alcohols by hair might also affect the electrostatic interactions within the fibers and, thus, could affect their mechanical properties.

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Recently, we have obtained experimental data suggesting that, indeed, this might be the case. The present communication reports these findings.

II. EXPERIMENTAL

A. MATERIALS

Intact hair was obtained from the DeMeo Company.* Before use, it was shampooed once with an anionic shampoo-pH 4.3,† rinsed and dried in air. Reagent grade 1-propanol was used for preparing the solutions. The buffers used were pH 7.0, pH 7.4 phosphate buffers (0.05 *M*), and pH 2 HCl solution, respectively.

B. METHODS

One-in. long hair fibers were mounted onto plastic tabs using an epoxy glue‡ and soaked overnight in pH 7.0 buffer. First, a reference stress–strain curve was obtained for each fiber; i.e., the fiber was stretched to 20 per cent extension (at 1 in./min) while immersed in pH 7 buffer at 20°C (Reference curve No. 1). A table model Instron Extensometer was used with standard procedures being employed.

Subsequently, the fiber was relaxed in pH 7.4 buffer for 24 h, equilibrated in the appropriate proponal-water mixture and the stress–strain isotherm measured while the fiber was immersed in the solution at the appropriate temperature. A 24-h period was allowed for equilibration of each fiber in the appropriate water-alcohol mixture, since previous work has ascertained that this time period was sufficient to reach equilibrium (5). After completion of the measurements, the fibers were again relaxed in pH 7 buffer at 20°C for 24 h and a second reference stress–strain curve obtained using identical experimental conditions to those employed during the determination of the first calibration curve (reference curve No. 2).

III. RESULTS

Although ethanol is the most widely used alcohol in cosmetic and toiletry products, we chose 1-propanol for our investigations. Our choice was motivated by the finding of previous investigators who showed that immersion into 1-propanol/water mixtures have the largest effects, among the alcohols, on the properties of keratin fibers (1–4).

In order to eliminate, as far as possible, errors which were due to fiber to fiber variations, the forces were normalized, i.e., divided by the force obtained on the same fiber at the corresponding extension during the first reference cycle. The symbol f′ denotes the normalized force (i.e., the ratio f/fo) where f and fo are the two forces measured on the same fiber at a given strain level under the given experimental conditions and dur-

*DeMeo Brothers, New York®.

†Earth Born Green Apple Shampoo®, Personal Care Division, the Gillette Co., Boston, MA.

‡Twoton glue®, Descon Corp., Danvers, Mass.

Table I
Ratios of the Tensile Forces of Hair Fibers in pH 7 Buffer Solutions Before and After the Experiments

Treatment Exposure to W/W per cent Propanol	f_0'/f_0*				T°C
	pH 2.0		pH 7.4		
0	0.89	0.92	—	1.05	60
30	0.86	0.89	1.02	0.92	60
50	0.94	0.99	0.87	0.95	60
80	0.89	—	0.97	0.93	60
0	0.94	0.98	1.03	1.02	40
30	1.00	1.04	1.00	1.00	40
50	1.03	1.05	0.98	1.00	40
80	1.00	1.00	1.00	1.00	40
0	0.98	0.90	0.95	0.93	20
30	0.93	0.97	0.93	0.93	20
50	0.93	0.95	0.89	0.94	20
80	0.95	0.96	0.92	0.93	20

*f_0 and f_0' denote the values of the elastic forces in the first and second reference cycles, respectively.

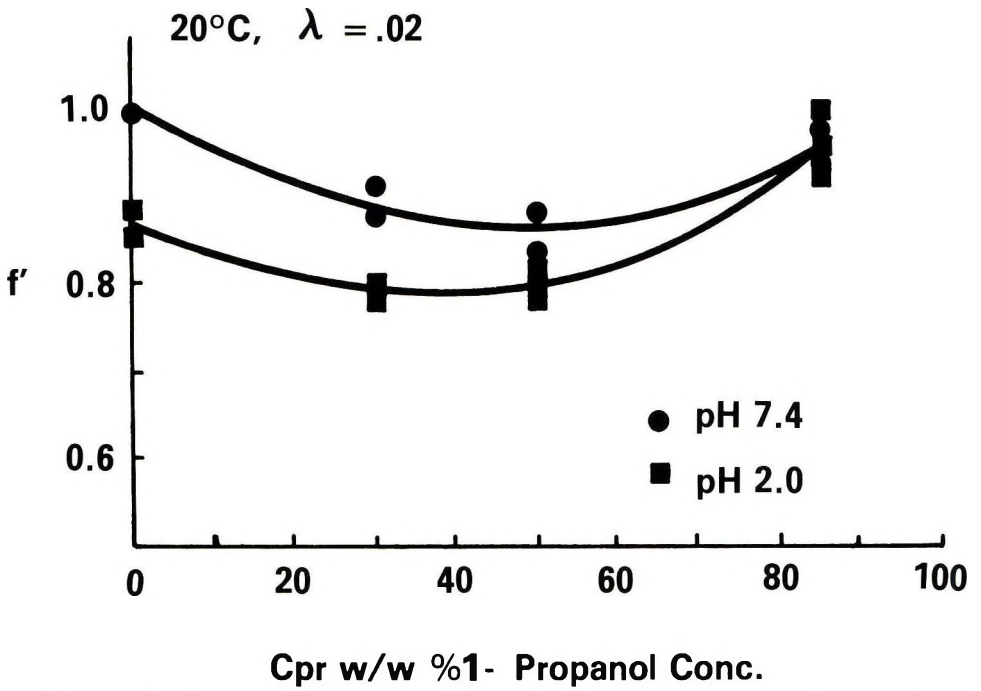

Figure 1. Plot of normalized force f' of intact hair fibers against 1-propanol content of immersion liquid at 20°C and extension λ = 0.02

ing the first reference cycle, respectively. The values of the normalized forces were reproducible within an error of ±4 per cent.

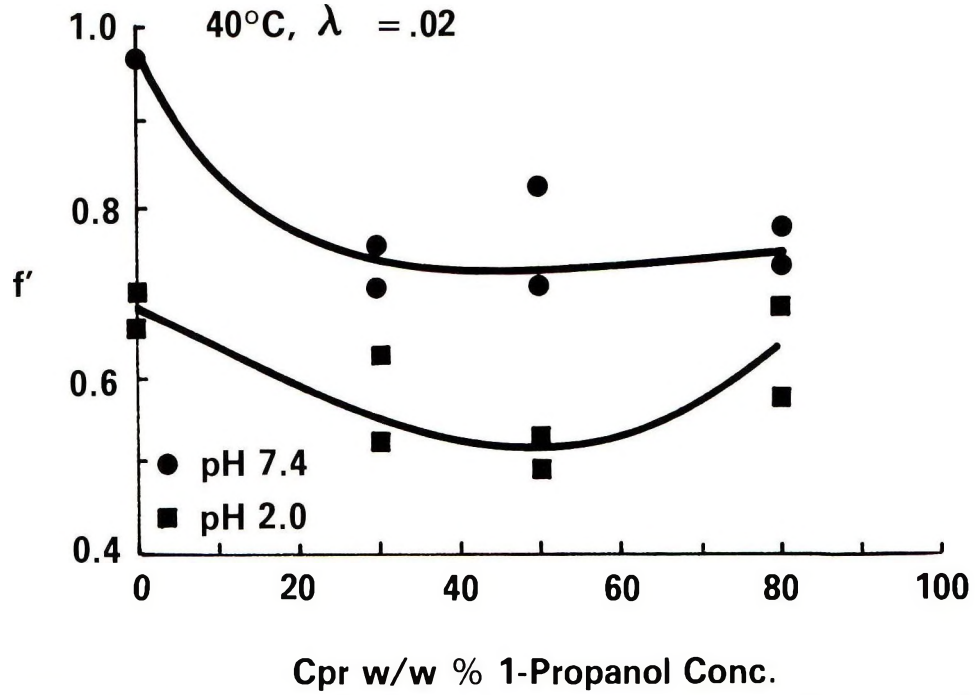

Figure 2. Plot of normalized force f′ of intact hair fibers against 1-propanol content of immersion liquid at 40°C and extension λ = 0.02

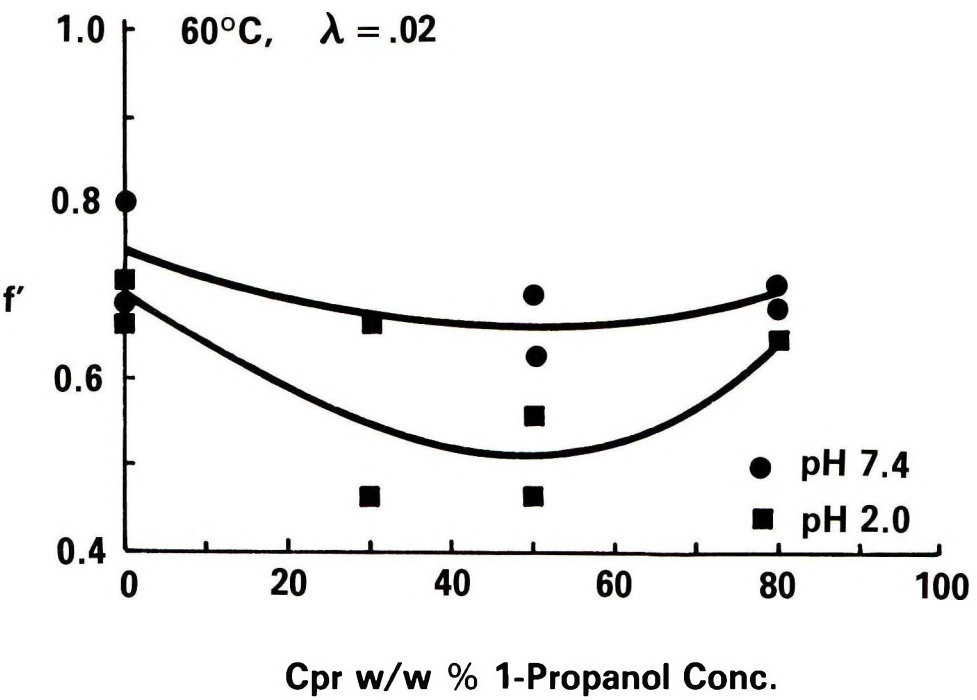

Figure 3. Plot of normalized force f′ of intact hair fibers against 1-propanol content of immersion liquid at 60°C and extension λ = 0.02

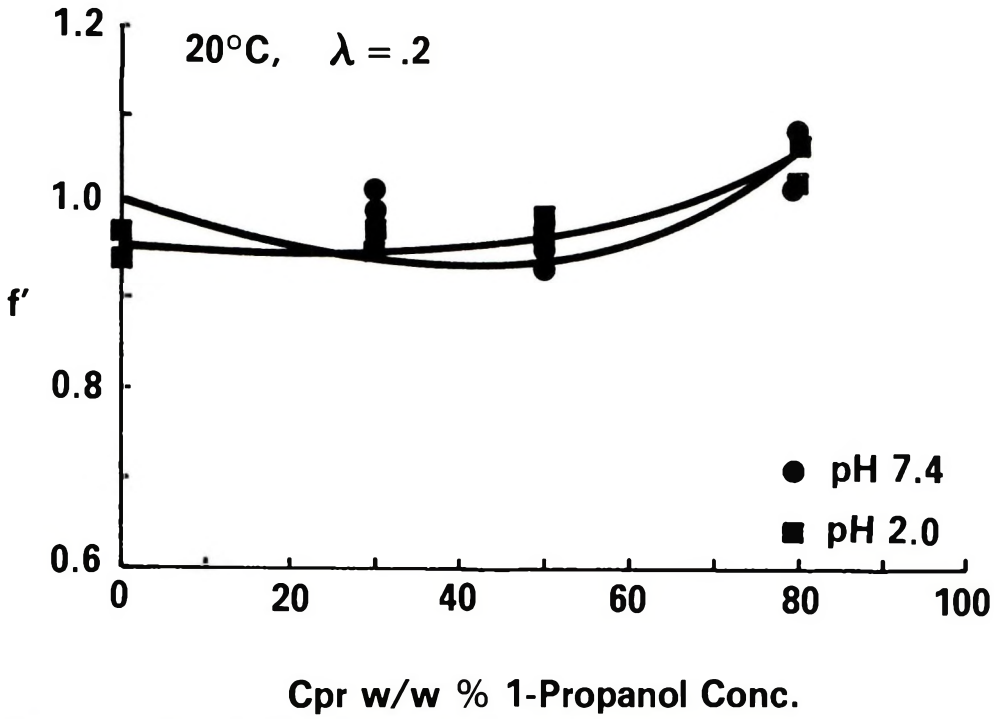

Figure 4. Plot of normalized force f' of intact hair fibers against 1-propanol content of immersion liquid at 20°C and extension λ = 0.2

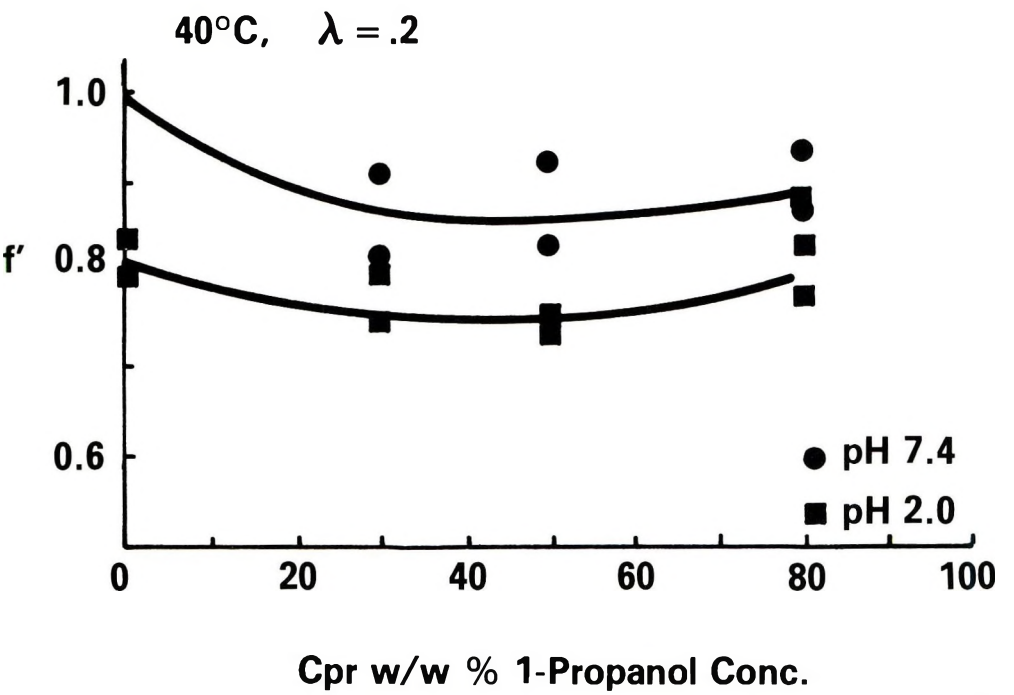

Figure 5. Plot of normalized force f' of intact hair fibers against 1-propanol content of immersion liquid at 40°C and extension λ = 0.2 (This figure is reproduced with permission of John Wiley & Sons where it originally appeared in the Interpretation of the Mechanical Properties of Wool, *Appl. Polym. Symp.*, 18, 775–94 (1971), by J. W. S. Hearle, B. M. Chapman and G. S. Seniov.

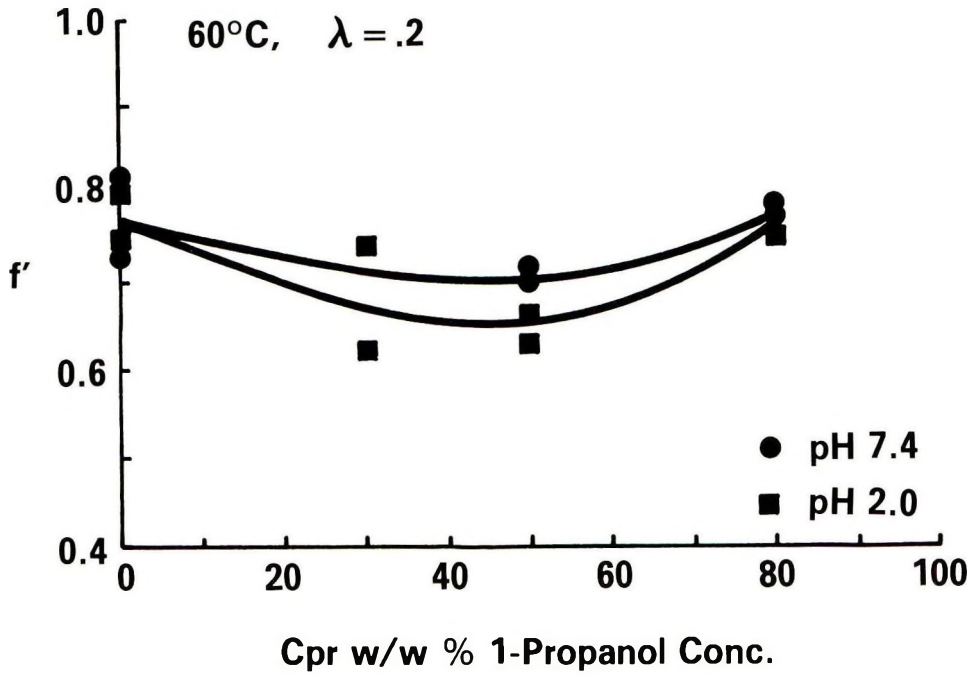

Figure 6. Plot of normalized force f′ of intact hair fibers against 1-propanol content of immersion liquid at 60°C and extension λ = 0.2

None of the treatments caused any irreversible changes in the fibers. We ascertained this fact by comparing the forces measured during the first and the second reference cycle at the same strain level. Allowing for the experimental error of the technique, no differences were found (Table I). In view of the high reproducibility of f′ values, the use of a limited number of fibers for each experimental condition appeared justified to us.

In three series of experiments, we determined the values of f′ as respective functions of temperature, pH and 1-propanol concentration. The results are shown in Figs. 1–6, where the values of f′ are plotted against C_{pr}, the propanol concentration for two pH values (pH 2.0 and pH 7.4) at three temperatures (20, 40, and 60°C).

For a given temperature and pH, increasing the propanol concentration initially reduces the value of f′. As the propanol concentration is further augmented, however, the value of f′ passes through a minimum (at about C_{pr} = 50 per cent) and then again increases.

For a given propanol concentration, the values of f′ are considerably lower at pH 2.0 than at pH 7.4. Raising the temperature from 20° to 40°C enhances the pH effects, i.e., the differences between the values of f′ at pH's 7.4 and 2.0. Finally, all the effects described are more pronounced at low extensions than at higher strain levels.

IV. DISCUSSION

An interpretation of these experimental results can be best considered in the context of a model previously suggested for hair structure (6, 7) (Fig. 7). Accordingly, keratin

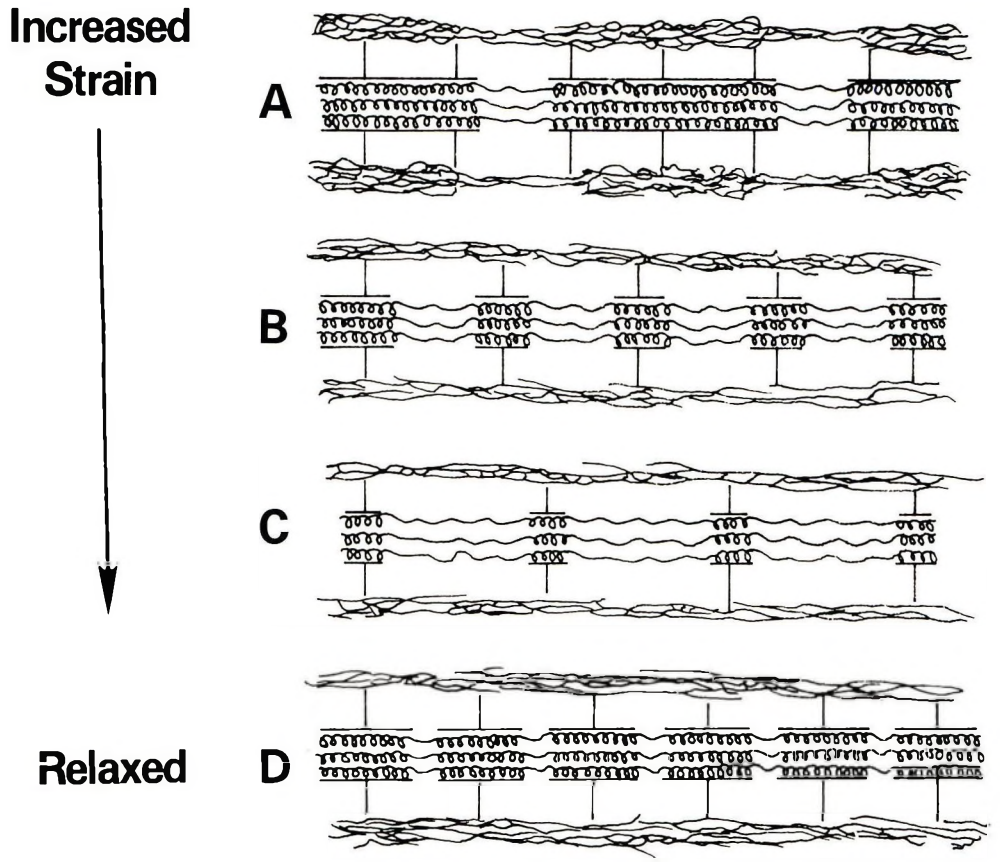

Figure 7. A Keratin structure at various points of stress–strain curve. A → C represent stages of fiber structure at increasing strainings; D shows situation after fiber has been allowed to relax to lower strain level. Spirals, "wiggly" lines, and fuzzy regions denote α-helices, unwound polypeptide chains and matrix, respectively (reproduced with permission from ref. 7)

fibers are regarded as crosslinked polyelectrolyte gels consisting of partially crystalline (α-helical) polypeptide chains, which carry both positively and negatively charged groups attached to the main chains.

Application of an axial stress extends the network, resulting in conformational changes of the polypeptide chains (8), and in increased distances between the various charged groups attached to the polypeptide chains. In most instances, depending on the pH of the surrounding medium, either an excess of positive or negative groups is present in the hair fiber. Consequently, straining of the fiber decreases its electrostatic energy (6).

In accordance with this model, G_t the free energy of an unstrained fiber can be expressed as the sum of two terms: G_{st} the structural and G_{es} the electrostatic free energies (8).

$$G_t = G_{st} + G_{es} \tag{1}$$

Since f_{sr} the structural and f_{es} the electrostatic contributions to the total force, are defined as (9)

$$f_{st} = \frac{1}{l_0}\left(\frac{\partial G_{st}}{\partial \lambda}\right)T, P$$

$$f_{es} = -\frac{1}{l_0}\left(\frac{\partial G_{es}}{\partial \lambda}\right)T, P \tag{2}$$

where f_t the total forces resisting the straining of hair, is

$$f_t = f_{st} + f_{es} \tag{3}$$

and λ denotes the extension ratio

$$\lambda = \frac{l}{l_0} \tag{4}$$

and l and l_0 represent the length of the fiber in the strained and unstrained state, respectively.

Using statistical mechanics, the values of f_{st} and f_{es} can be expressed in terms of molecular quantities. Thus, assuming that the structural contribution of the elastic force is due to a change of the polypeptide chains from α to β conformation, the value of f_{st} is given by (9)

$$f_{st} = \frac{\Delta G_0}{\Delta L_0} \quad \frac{kT}{\Delta L_0} \ln r \tag{5}$$

where ΔG_0, ΔL_0 are the standard free energy and the fiber length change involved when a unit weight of fiber changes from α to β conformation. The function r depends on the extent of change; its value has been previously calculated as a function of extension (10).

The value of f_{es} can be derived from the polyelectrolyte model of hair and can be expressed as (9)

$$f_{es} = n\frac{\gamma^2 \epsilon^2 \kappa}{D\lambda}\left[\frac{1}{1 + \lambda A} - \frac{1}{\lambda A}\ln(1 + \lambda A)\right] \tag{6}$$

where n equals the number of molecular chains in unit weight of fiber: γ equals the net charge of an average molecular chain; ϵ equals the electronic charge; D equals the dielectric constant; κ equals the Debye parameter (i.e., the reciprocal of the radius of the ionic atmosphere); λ equals the extension ratio; A equals $l_0\kappa$; and l_0 equals the average contour length of an unstrained molecular chain in the network.

When hair samples are immersed in aqueous solutions of propanol, limited amounts of propanol (up to about 2 mol/1000 g) are absorbed by the hair fiber (5). At the same time, due to the lowering of water activity, the fibers gradually dehydrate (5). These two processes affect the values of f_{st} and f_{es}, but to different extents. The increase in the propanol content and the simultaneous decrease of water in hair diminishes D, the effective dielectric constant inside the fiber (11) and, thus, increases the value of f_{es}. This process is expected to be more pronounced at pH 2 than at pH 7, since the net charge of the fibers is greater at the lower pH value (for titration curves of keratin, see (12)).

On the other hand, dehydration of the hair fiber shifts the α–β conformational equilibrium towards the α form and thus, increases the force required for straining the fiber (13), i.e., increases the value of f_{st}. The pH of the solution should not affect this latter process.

It is also instructive to consider, in light of this model, some of the X-ray data which have been obtained on keratin fibers containing increasing amounts of propanol. Feughelman and Snaith (14) and later Heideman and Halboth (15) measured the changes occurring in the spacing of the interhelical distances in keratin fibers and found that the spacing of 9.3 Å increases when the propanol concentration is augmented in the immersion liquid. According to these authors, the 9.3 Å spacing corresponds to the distances between the helices in the protofibrils. The increases in this spacing, therefore, suggests that the propanol penetrates the protofibrils and, in doing so, pries the polypeptide helices apart. A similar explanation was suggested by Nemetschek (16) when interpreting the low angle X-ray data of collagen treated with various alcohols.

The findings that neither an increase of alcohol concentration beyond 50 per cent nor the changing of the pH from 6 to 1 affect the 9.3 Å spacing (15) suggest that most of the ionic groups are situated on the surfaces of the protofibrils and in the interior of the protofibrils electrostatic effects do not exert any serious influences.

Raising the temperature from 20 to 60°C affects the absolute values of f′, but does not change the overall shape of the f′ versus C_{pr} curves. This result is in agreement with previous data which indicated that propanol absorption is hardly at all affected by temperature (10).

V. CONCLUSIONS

The force resisting straining of hair is governed essentially by two types of molecular processes: (a) structural changes (α–β transition); and (b) changes in the electrostatic energy of fiber as a consequence of the increase in the interionic distances. These two processes depend differently on environmental factors (i.e., temperature, pH, propanol concentrations).

Our experimental results, presented in this paper, suggest that exposure of hair to aqueous propanol solutions of increasing concentrations first weakens the fibers by increasing the electrostatic repulsion forces between the similarly charged side chains. At higher propanol concentrations (> 50 per cent w/w), however, hair becomes stronger, owing to the dehydration of the fiber which makes the structural conformational changes of the polypeptide chains more difficult.

The experimental results can be explained, at least in qualitative terms, by a molecular model which regards keratin as a partially crystalline crosslinked polyelectrolyte gel.

A quantitative interpretation of the forces in terms of this model necessitates the assignments of arbitrary values to many molecular quantities (e.g., the effective dielectric constant in hair, its dependence on water and propanol uptake, the value of κ inside the hair structure). Since none of the quantities are known to any degree of reliability at this time, this exercise does not seem profitable. Similar conclusions were obtained by Wolfram and Milligan when investigating the tensile properties of esterified and acylated wool (17).

VI. ACKNOWLEDGMENTS

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Methoden zur Bestimmung von Fluorid-Ionen in Zahnpasten

III. Trennung der Ionen in Gegenwart großer Mengen von Aluminium-Verbindungen.

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Synopsis: A method is proposed for the separation of fluoride ions in toothpastes, which contain large amounts of aluminium compounds. The method involves distillation with superheated steam in a specially designed and fabricated apparatus. This technique has been validated during the examination of all types of toothpastes.

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Einleitung

Im Verlauf einer früheren Arbeit haben wir gezeigt, daß die Bestimmung von Aluminiumfluorid, nach der Abtrennung des Anions durch Mikrodiffusion, nicht quantitativ ist (1). Daraufhin haben wir eine Methode zur Bestimmung von Fluor-Ionen in Zahnpasten erarbeitet, die für alle Arten von Fluor-Verbindungen anwendbar ist (2). Hierfür empfehlen wir die Methode von Willard und Winter (3), die bei Gegenwart von Perchlorsäure in einer erprobten Spezialapparatur von ganz bestimmter Bauart ausgeführt wird (2). Ziel der vorliegenden Studie ist es, eine neue Methode der Trennung vorzuschlagen, die allgemeiner anwendbar ist als die vorhergehende, da sie von der Zusammensetzung des Präparates nicht beeinflußt wird und selbst in Gegenwart großer Mengen von Aluminiumoxid anwendbar ist; eine Substanz übrigens, die als Schleifmittel bei bestimmten Typen von Zahnpasten gebraucht wird. Obwohl zwei Bestimmungs-Methoden — eine potentiometrische (Lanthan-Fluorid-Membran-Elektrode) und eine spektrofotometrische (Komplex des Cer-III-alizarinkomplexon) — beschrieben wurden, die sich hinsichtlich ihrer Empfindlichkeit, Reproduzierbarkeit und Genauigkeit als gleichwertig erwiesen haben (2), entschieden wir uns für die zweitgenannte bei den folgenden Untersuchungen.

Experimenteller Teil

Apparaturen und Reagenzien

Apparatur

Sie ist bereits früher beschrieben worden (2).

Reagenzien

Außer den Reagenzien, die im Verlauf der beiden ersten Teile (1,2) gebraucht wurden, werden noch folgende angewendet:
Phosphorsäure Merck P. A. mind. 85%.
Antischaum Nalco 40-BO-3 Benelux Chemicals.

Die verschiedenen Ergebnisse, die man nach der spektrofotometrischen Bestimmung der Ionen im Destillat erhielt, sind auf der Tabelle I dargestellt. Deren Analyse zeigt klar, daß die Zersetzung des Musters durch die Perchlorsäure zu deutlich niedrigeren als den theoretischen Resultaten führt (~ 50%). Da der Fehler bei etwa 8% liegt, sind die Ergebnisse kaum reproduzierbar.

Tabelle 1

Microdestillation von Fluorwasserstoff in Gegenwart von Aluminiumoxid. Einfluß der verwendeten Säuren.
(Die Zusammensetzung des untersuchten Gemisches steht im Anhang.)

Verwendete Säure: $HClO_4$				Verwendete Säure: H_3PO_4			
g Versuchs-probe	Theorie $\mu g\ F^-$	gefunden $\mu g\ F^-$	gefunden % F^-	g Versuchs-probe	Theorie $\mu g\ F^-$	gefunden $\mu g\ F^-$	gefunden % F^-
1,0032	450,7	244,6	54,3	0,9939	446,5	441,5	98,9
0,9949	446,9	222,2	49,7	1,0081	452,9	444,5	98,1
1,0065	452,2	269,3	59,5	0,9765	438,7	420,5	95,9
1,0423	468,3	244,9	52,3	0,7405	332,7	330,0	99,2
$\bar{\%}$ F^- gefunden 53,9 $S^* = 4,1$				$\bar{\%}$ F^- gefunden 98,0 $S^* = 1,2$			

S^*: Standard-Abweichung

Anders verhält es sich, wenn man Phosphorsäure verwendet: unter diesen Bedingungen sind die Resultate befriedigend, die Messungen genau und wiederholbar. Unsere Arbeit hat sich daraufhin mit der Bestimmung von Fluor in zwei Zahnpasten befaßt, die wir selbst hergestellt hatten (siehe Anhang). Die eine enthielt 20%, die andere 50% Aluminiumoxid. Die Ergebnisse der beiden Versuche sind in der Tabelle II zusammengefaßt. Ihr Studium erweist, daß die Phosphorsäure-Methode völlig den Erwartungen entspricht, und bestätigt, daß die Trennung auch in Gegenwart großer Mengen von Aluminium quantitativ bleibt. Allenfalls könnte man noch anmerken, daß bei Anwesenheit von 50% Oxid der gefundene Prozentsatz von Fluor gegenüber der Theorie leicht erhöht ist: die Standard-Abweichung erreicht 2%; diesen Unterschied erklären wir mit den Schwierigkeiten, die wir bei der Zubereitung einer solchen Paste hatten, da deren feste Konsistenz die Homogenisation behinderte.

Die Verwendung von Phosphorsäure stellt dennoch ein Problem dar, und zwar in Bezug auf die Wahl der Antischaummittel, die dem Reaktionsgemisch zugesetzt werden. Im allgemeinen empfehlen die meisten Autoren, wie übrigens wir selbst in den vorangehenden Arbeiten (1, 2), die Anwendung entweder von Octanol oder auch von Oleyl-Alkohol. Nun werden aber in Anwesenheit der verwendeten Säure die Phosphor-Ester, die sich im Verlauf der Reaktion bilden, durch den Wasserdampf mitgerissen; sie verstopfen das zentrale Ablaufrohr des Kühlers und behindern so den gleichmäßigen Weitergang der Analyse. Um diesen Übelstand zu beseitigen, schlagen wir die Anwendung des Anti-Schaummittels vor, das unter dem Namen NALCO 40-BO-3 im Handel ist, dessen genaue chemische Zusammensetzung uns aber nicht bekannt ist.

Tabelle II

Bestimmung von Fluor-Ionen in einer Zahnpasta mit hohem Aluminiumoxid-Gehalt
(Microdestillation in Gegenwart von H_3PO_4; Spektrophotometrie.)

Zahnpaste I* 50% Al_2O_3; Theorie 127,2 mg F^- % g			Zahnpaste II* 20% Al_2O_3; Theorie 126,4 mg F^- % g		
Versuchs-probe in g	mg F^- % g gefunden = x	x-Theorie mg F^- % g	Versuchs-probe in g	mg F^- % g gefunden = x	x-Theorie mg F^- % g
0,9360	134,9	+ 7,7	0,5471	128,1	+ 1,7
	135,4	+ 8,2		128,9	+ 2,5
1,0214	138,8	+ 11,6	0,5253	127,5	+ 1,1
	138,8	+ 11,6		126,6	+ 0,2
0,5496	131,0	+ 3,8	0,6194	126,6	+ 0,2
	130,5	+ 3,3		127,5	+ 1,1
0,6080	133,1	+ 5,9	0,7153	126,2	− 0,2
	134,4	+ 7,2		126,9	+ 0,7
0,5372	134,6	+ 7,4	0,6266	124,5	− 1,9
	135,9	+ 8,7		124,9	− 1,5
0,6309	130,4	+ 3,2	0,6372	127,9	+ 1,5
	130,4	+ 3,2		127,9	+ 1,5
Ergebnis	$\bar{m}g$ F^- % g : 134,0 S** = 2,9		Ergebnis	$\bar{m}g$ F^- % g : 126,9 S** = 1,4	

* Die genaue Zusammensetzung der untersuchten Zahnpasten steht im Anhang.
** S = Standard-Abweichnung

Zusammenfassung

Die Methode der Abtrennung von Fluor-Ionen durch Mikrodestillation in Anwesenheit von Phosphorsäure in einer Apparatur bestimmter Bauart eignet sich besonders gut zur Auffindung und Bestimmung dieser Ionen in einer Zahnpaste, die viel Aluminiumoxid enthält.

Anhang

Zusammensetzung der von uns hergestellten Mischung und der zwei analysierten Zahnpasten.

Hergestellte Mischung

Natriumsulfat, wasserfrei 50,0050 g — Aluminiumoxid 50,0043 g — Natriumfluorid 0,0995 g — Indigocarmin 0,0931 g.

Zahnpaste I

Natriummonofluorphosphat (95,71%) 1,0071 g — Aluminiumoxid 50,01 g — Sorbit (Subst.) 17,53 g — Natriumdodecylhydrogensulfat 2,30 g — Natriummonohydrogenphosphat, Dihydrat 0,59 g — Natriumbenzoat 0,84 g — Natriumsaccharinat 0,02 g — Phenol 0,01 g — Carraghen 1,29 g — Indigotine 0,02 g — destilliertes Wasser ad 100,0 g.

Zahnpaste II

Natriummonofluorphosphat (97,71%) 1,008 g — Aluminiumoxid 20,00 g — gefällte Kreide 16,00 g — Sorbit (Subst.) 17,53 g — Natriumdodecylhydrogensulfat 2,06 g — Natriummonohydrogenphosphat, Dihydrat 0,49 g — Natriumbenzoat 0,97 g — Natriumsaccharinat 0,01 g — Phenol 0,02 g — Carraghen 1,32 g — Indigocarmin 0,02 g — destilliertes Wasser ad 100,0 g.

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Book Reviews

CONTINUOUS FLOW ANALYSIS: THEORY AND PRACTICE (CLINICAL AND BIOCHEMICAL ANALYSIS SERIES VOLUME 3) by William B. Burman, Marcel Dekker, Inc., New York 1976, 352 Pages. Price $24.50.

This is a reference book for analytical chemists already familiar with the use of the Auto Analyzer for quality control and research applications. The author is Chief of the Methods Research Branch of the National Center for Drug Analysis of the Food and Drug Administration in St. Louis. In compiling the book, the author reviewed 3,000 papers in continuous flow analysis. The book contains 941 references to literature on this subject. Chapter 1 describes briefly the development of the Auto Analyzer and its application to analytical determinations with extensive reference to the literature. Chapter 2 deals with a description of the Auto Analyzer modules which have been developed and the problems associated with their use. Chapter 3 describes the use of other laboratory instruments in conjunction with the instrument, such as; atomic absorption, spectrophotometers, Redox systems, flame photometers, gas chromatographs, etc. Chapter 4 deals with the selection and assembly of tubings and fittings for separation of immiscible liquids and the tubings used for various materials. Chapter 5 describes various uses of continuous flow manifolds with liquid column chromatographic systems having off and on line modes. Chapter 6 deals with the use of automatic data processing in conjunction with the instrument. Chapter 7 is written by Dr. W. H. C. Walker of McMaster University in Canada and discusses the theoretical aspects of a continuous flow system from the standpoint of factors influencing peak characteristics and practical steps that can be taken to improve peak quality and analytical performance.—ROBERT T. CONNER—Consultant

FILTRATION: PRINCIPLES AND PRACTICES (IN TWO PARTS), PART I. (Chemical Processing and Engineering Series, Volume 10) Edited by Clyde Orr 1977, Marcel Dekker, Inc., New York, 1977, 544 Pages, 700 References, 160 Figures, 26 Tables, 501 Equations, bound, Illustrated. Price $45.00.

This, the first part of a two volume edition, focuses on a variety of filtration topics related in part to cosmetic processing of waste chemicals and maintenance of environmental air quality standards. Earlier chapters present a rigorous mathematical treatment of Gas and Liquid Filtration models. Medium, Depth, and Cake Liquid Filtration methods are supported by discussions on various well-known filtration aids and pretreatment techniques. Filter media strength, stability, and chemical resistance are classified according to trapped particle size, permeability, solids holding capacity, and longterm media efficiencies.

The review of industrial gas filtration techniques in Chapter 4 is particularly relevant to the treatment of airborne powders, pigments, and fumed cosmetic thickeners. Also pertinent in this and later chapters is the discussion of solid-liquid separation as a function of batch, semi-continuous, and continuous operations. Selection of most suitable equipment for filtration needs is aided by worked through problems and detailed schematics of familiar industrial equipment.

A final chapter on Ultra filtration centers on the separation of 10 to 100 Å particles and Tubular Membrane Configurations, Thin-Channel Membrane Modules, and Hollow Fiber Systems are shown. Application of Ultra Filtration to water purification is offered as an alternative to other less feasible means.

An excellent listing of filtration references is given after each chapter.—JAMES KINNEY—Clairol Inc.

ANALYSIS OF ESSENTIAL OILS BY GAS CHROMATOGRAPHY AND MASS SPECTROMETRY, Vol. I, 1st Ed., Edited by Yoshiro Masada. John Wiley & Sons, Inc., New York, 1976, IX + 334 pages. Price $37.50.

The book consists of two parts. The first part is the subject of this review. The second part (32 pages) printed only in Japanese, describes basic information on the components and methods for analysis of an essential oil as well as basic information concerning gas chromatography and mass spectrometry.

Part I, contains the botanical description, physical and chemical constants, gas chromatograms, mass spectrum, and recent bibliography for sixty-four essential oils.

The Gas Chromatograms are supplemented by peak identifications as well as instrumental conditions. The mass spectrums of major components of the oils also have peak identifications. There are 156 figures.

The book is a useful guide for anyone conducting research concerned with perfumes, flavors, and spices.

It is a guide in that the representative samples of oil used for analysis do not represent, in all cases, the actual material of commerce available in the U.S.—WINTHROP E. LANGE—The Purdue Frederick Company

SURFACTANT SCIENCE SERIES, VOLUME 7: ANIONIC SURFACTANTS, PART I, Edited by Warner M. Linfield, Marcel Dekker, Inc., New York, 1976, XI + 314 Pages. Price $35.00.

This two-part volume deals primarily with the organic chemistry of anionic surfactants, a class of surfactants which is probably the one of greatest importance from both an economic and a scientific perspective. The literature on this class of compounds is voluminous: consequently, each major type of anionic surfactant is covered in a separate chapter; the lipid and petrochemical antecedents of these surfactants are each treated in a separate chapter; also, there is a chapter on the

mechanisms of sulfonation and sulfation reactions, since so many synthetic routes to anionic surfactants include either of these reactions.

Part I included an introductory chapter on soap and lime-soap dispersing agents, which is as comprehensive and thorough treatment on the subject as can be found anywhere in the literature. This is followed by a chapter on "Petroleum-based Raw Materials for Anionic Surfactants" and another on "Lipid and Other Nonpetrochemical Raw Materials." The fourth chapter deals with the previously cited "Mechanisms of Sulfonation and Sulfation." Successive chapters deal with "Alcohol and Ether Alcohol Sulfates," "Sulfated Monoglycerides and Sulfated Alkanolamides," "Sulfated Fats and Oils," and "Alkylarylsulfonates." The separate chapters are written by experts in each individual field.

Each chapter is extremely well done and thoroughly covers the area of its scope and contains a pertinent list of references at the end. The general format for each chapter contains: an introduction, a section on the preparation of the compounds, a section on the physical or general properties of the compounds including an analysis, a section on applications of these particular compounds, and a list of products in this class by tradenames. Typical of this format is Chapter 5 on "Alcohol and Ether Alcohol Sulfates" which is comprehensive in its scope and thorough in its preparation and execution.

This is an excellent book and would be of great use to both beginners and experienced practitioners in the field of surfactant technology, particularly in the cosmetic field. However, there are some minor criticisms: Part I does not have an index of its own—there is a cumulative index in Part II of this volume; also, considering the price of this book, this reviewer is less than impressed by the quality of the print and the cover (too soft for a "hard" cover and some variation in the intensity of the print).—ROBERT MARCHISOTTO—Biosciences Information Service.

METHODS IN OLFACTORY RESEARCH, Edited by D. G. Moulton, Amos Turk, and J. W. Johnston, Jr., 497 pages. Price $28.50

Although this volume owes its conception to the NATO sponsored Summer School of 1970 which was held in the Netherlands; thanks to its three experienced editors, it has achieved more than a publication of the proceedings of the meeting. Rather, the editors have succeeded in offering a substantial text on the multidisciplinary approach to olfactory research.

The text is comprised of fourteen chapters, each one contributed by a different author from a roster of eighteen distinguished scientists.

As would be expected, the overview of Olfactory Research is treated by such widely differing contributions that one wonders how the separate contributions in any multidisciplinary research program can be brought to work in concert, in order to reach an investigative goal.

However, this problem with multidisciplinary research is not at all a shortcoming of the volume, since do doubt each reader will find the chapters that interest him or her, even if other chapters do not.

While all of the chapters are written on a scholarly level, this reviewer was particularly impressed by the comprehensiveness of chapter 5, entitled, "Applications of Scanning Electron Microscopy (SEM)" and "Autoradiography in the Study of Olfactory Mucosa." The SEM micrographs included in this chapter are rewarding to view.

The cosmetic chemist might find chapter 1, which is entitled, "Instrumental Aspects of Olfactometry," as the most likely to prove useful in cosmetic science where, for example, odor measurement to determine the efficiency of deodorants might be needed. The perfumer might also find use for such techniques.

With its bibliography of 1492 authors, this volume is an impressive compendium of our knowledge about Olfactory research.—HARRY C. SAUNDERS—Shaw Mudge and Company.

SURFACTANT SCIENCE SERIES, VOLUME 7: ANIONIC SURFACTANTS, PART II, Ed. by Warner M. Linfield, Marcel Dekker, Inc., New York, 1976, XI + 360 Pages. Price $39.95.

Part II completes Volume 7 of the Surfactant Science Series. Part II picks up where Part I left off and deals with specific groups of surfactants. Chapter 9, the initial chapter in this book, deals with "Petroleum Sulfonates" followed by "Olefin Sulfonates," "Alpha-sulfomonocarboxylic Acids and Derivatives," "Sulfopolycarboxylic Acid Derivatives," "Sulfoalkyl Esters and Amides of Fatty Acids," "Alkyl Glyceryl Ether Sulfonates," "Phosphorus-containing Anionic Surfactants," and lastly, "N-Acylated Amino Acids as Surfactants."

Again, the same format is used in this book as is described for Part I, and the treatment for each chapter is as thorough and comprehensive as in the first section of the volume. The book concludes with an author and subject index which is cumulative for both parts of the volume. This practice is an unfortunate one if one chooses to buy only the first part of the volume since, as mentioned in the review of Part I, it does not contain either an author or subject index and would make it difficult to browse and search that part effectively. The same criticisms of the printing quality that were cited for Part I also apply, unfortunately, to Part II.—ROBERT MARCHISOTTO—Biosciences Information Service.

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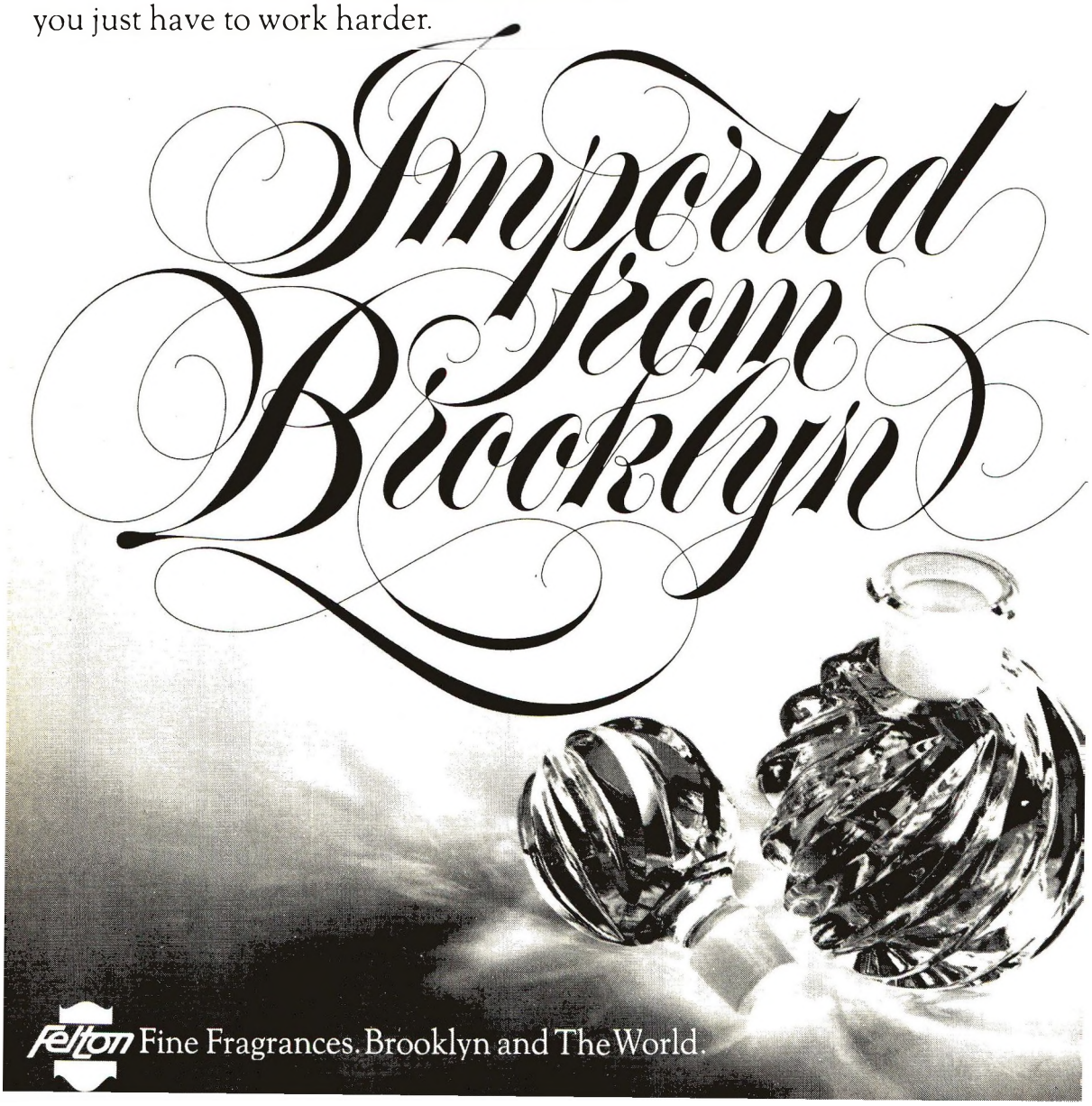

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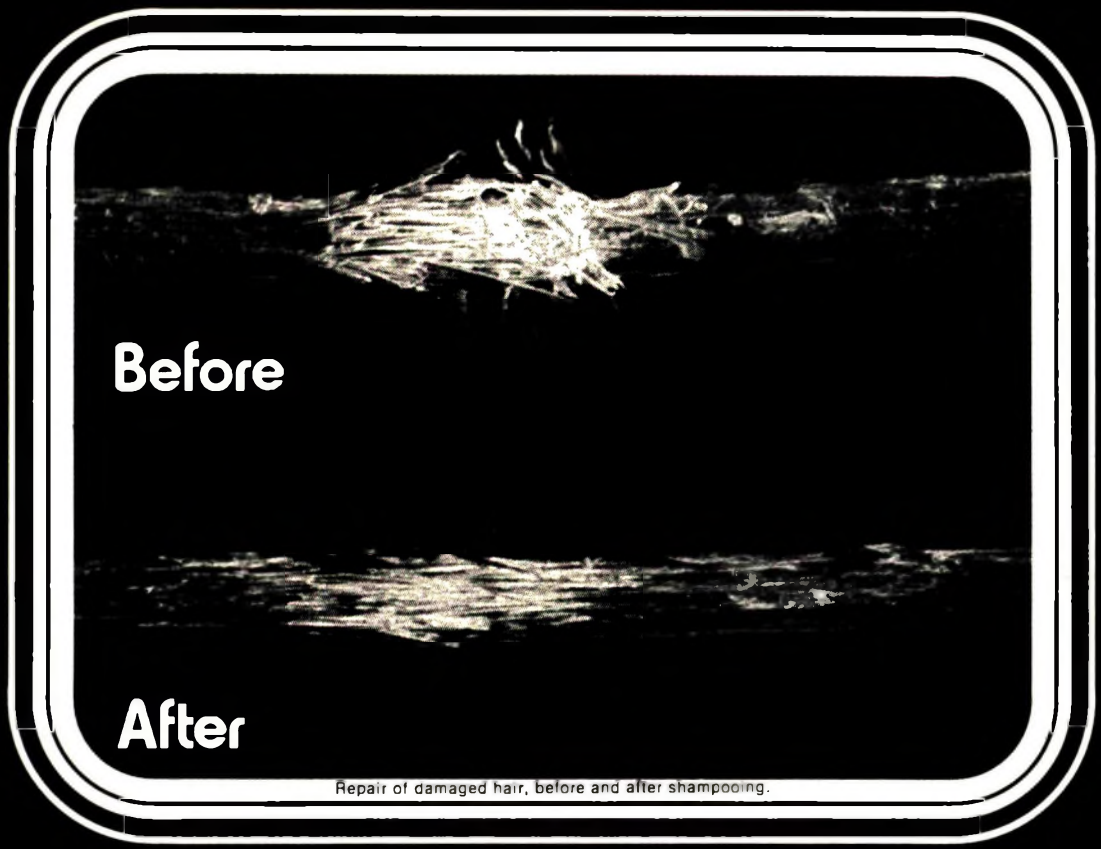

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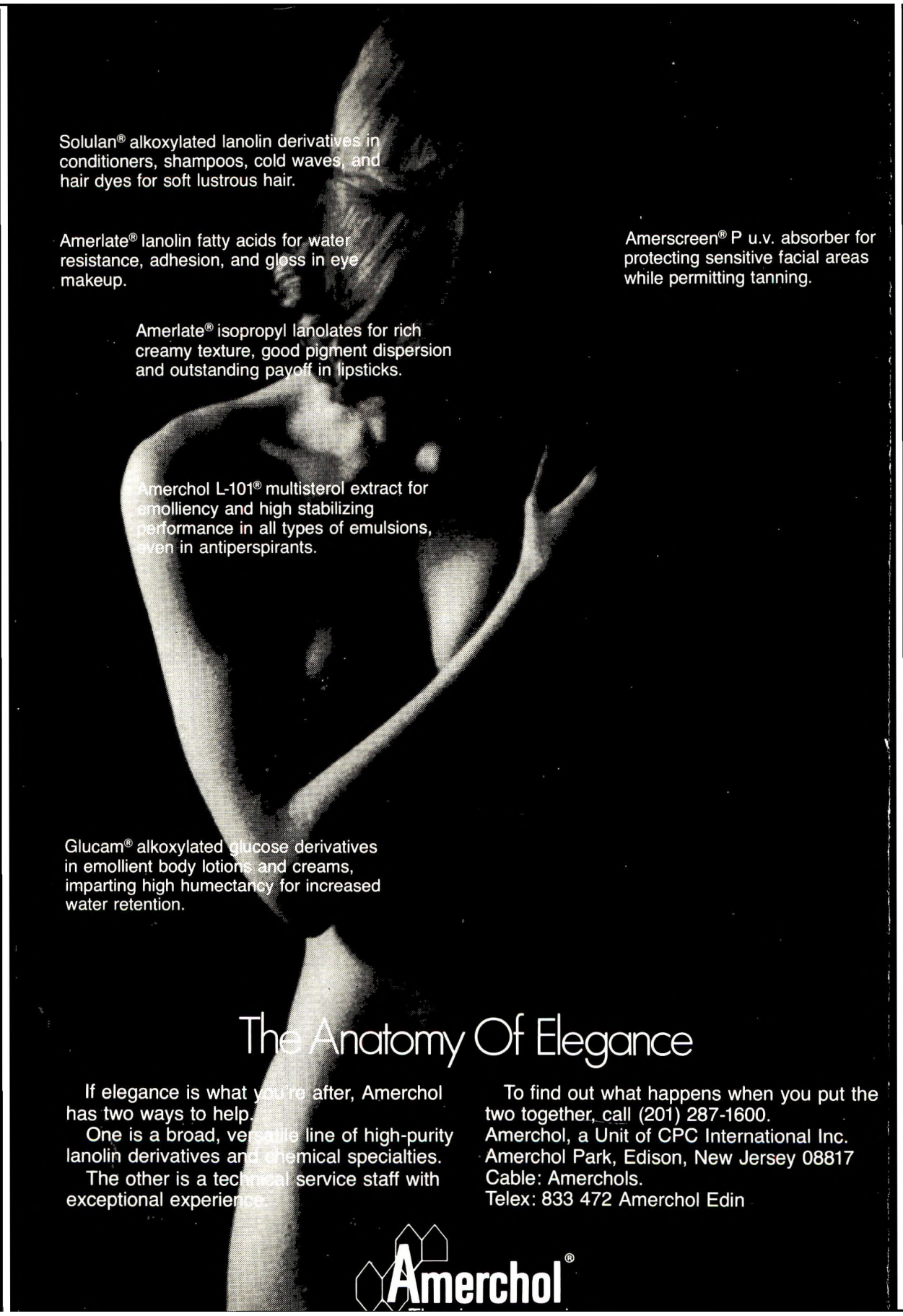
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